"For some must watch, while some must sleep"

HAMLET - Act. III, Sc. ii
The Middle East Journal of Anesthesiology is a publication of the Department of Anesthesiology of the American University of Beirut, founded in 1966 by Dr. Bernard Brandstater who coined its famous motto:

“For some must watch, while some must sleep” (Hamlet-Act. III, Sc. ii).

and gave it the symbol of the poppy flower (Papaver somniferum), it being the first cultivated flower in the Middle East which has given unique service to the suffering humanity for thousands of years. The Journal’s cover design depicts The Lebanese Cedar Tree, with’s Lebanon unique geographical location between East and West. Graphic designer Rabi Moukalled

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“For some must watch, while some must sleep”
(Hamlet-Act. III, Sc. ii)
BRIDION—*for optimal neuromuscular blockade management* and improved recovery

### Predictable and complete reversal
- 98% of BRIDION patients recovered to a TOF* ratio of 0.9 from reappearance of T2 † within 5 minutes‡
- 97% of BRIDION patients recovered to a TOF* ratio of 0.9 from 1 to 2 PTcs † within 5 minutes§

### Rapid reversal
- BRIDION rapidly reversed patients from reappearance of T2 † in 1.4 minutes
- BRIDION rapidly reversed patients from 1 to 2 PTcs † in 2.7 minutes

BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. In children and adolescents (aged 2-17 years), BRIDION is only recommended for routine reversal of moderate rocuronium-induced neuromuscular blockade.

**Important safety information**
BRIDION is not recommended in patients with severe renal impairment. Studies in patients with hepatic impairment have not been conducted and, therefore, patients with severe hepatic impairment should be treated with great caution. Caution should be exercised when administering BRIDION to pregnant women as no clinical data on exposed pregnancies are available.

BRIDION has not been investigated in patients receiving rocuronium or vecuronium in the Intensive Care Unit (ICU) setting.

If neuromuscular blockade is required within 24 hours of BRIDION administration, a nondepolarizing neuromuscular blocking agent should be used instead of rocuronium or vecuronium. The most commonly reported adverse reactions were dysgeusia (metal or bitter taste) and anesthetic complications (movement, coughing, grimacing, or suffocation on the endotracheal tube). In patients treated with BRIDION, a few cases of awareness were reported. The relation to BRIDION was uncertain. In a few individuals, allergic-like reactions (ie, flushing, erythematous rash) following BRIDION were reported. Clinicians should be prepared for the possibility of allergic reactions and take the necessary precautions. In a trial of patients with a history of pulmonary complications, bronchospasm was reported in 2 patients and a causal relationship could not be fully excluded.

Volunteer studies have demonstrated a slight (13%–22%) and transient (<30 minutes) prolongation of the prothrombin time/activated partial thromboplastin time (PT/aPTT) with BRIDION; however, clinical studies have demonstrated no clinically relevant effect on peri- or postoperative bleeding complications with BRIDION alone or in combination with anticoagulants. As BRIDION has demonstrated an in vitro pharmacodynamic interaction with anticoagulants, caution should be exercised in patients on anticoagulation for a pre-existing or comorbid condition. This pharmacodynamic interaction is not clinically relevant for patients receiving routine postoperative prophylactic anticoagulation. Although formal interaction studies have not been conducted, no drug interactions were observed in clinical trials. Pooled data suggest that clinically significant drug interactions are unlikely with the possible exceptions of ondansetron, fusidic acid, and hormonal contraceptives.

† Train-of-four
‡ Post tetanic count
§ Second twitch


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**SIMULATION LAB: “A CONTEMPORARY MEDICAL ESSENTIAL”**

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There are multiple causes of cardiac arrest during pregnancy. Some causes are pregnancy-associated such as hemorrhage, amniotic fluid embolism, and preeclampsia, or anesthesia-related such as anaphylactic reactions. Also, it may be traumatic in origin (Fig 1).

If the cardiac arrest occurs in the first half of gestation, the purpose of cardiopulmonary resuscitation (CPR) is to resuscitate the mother, emergency delivery of the fetus is not likely to improve the efforts of resuscitation. However, beyond the threshold of fetal viability (24 weeks of gestation or greater). These are data to suggest that delivery may actually improve maternal survival. Delivery of the fetus will decrease aortocaval compression, with a consequent increase of the venous return and cardiac output. An additional benefit is that chest compression will be more effective once the gravid uterus is evacuated1-3).

The time interval from cardiac arrest to delivery is probably the single most important factor for fetal survival. If the fetus is delivered within 5 minutes of maternal cardiac arrest, intact neurological survival is markedly increased for both the mother and the newborn.
Traumatized pregnant patient

The general principle of management of traumatized patients during the tragic war in Lebanon was similar to that suggested by the Pittsburgh group:

1. Total support: Normal brain function in brain failure with potential reversibility + irreversible vital organ failure.
2. All but CPR: Normal brain function, in brain failure with potential reversibility + irreversible vital organ failure.
3. No extraordinary measures: severe irreversible brain function with only minimal neurological activity + irreversible other vital organ failure.

In nonpregnant patients, active resuscitation is usually limited to the first two categories having normal brain function, or brain failure with potential reversibility. However, in the pregnant traumatized patient, with a viable fetus aged 24 weeks of gestation or greater, perimortem Cesarean section may be performed in the four categories to save the fetus, and may improve the chances of maternal resuscitation.

In the pregnant patient, drug-induced hypersensitivity reactions are usually a classic anaphylactic-type sensitivity with IgE involvement. The placenta plays an important role in protecting the fetus since the placental barrier will prevent crossing the high molecular weight IgE antibodies across the placenta to the fetal circulation.

Maternal cardiac arrest can also follow amniotic fluid embolism (AFE). The current management of the parturient with AFE is supportive. It is based on attempts at maintaining oxygenation, optimizing the hemodynamic status, and correcting the coagulopathy. In an effort to improve the outcome of the newborn, continuous fetal monitoring should be instituted. In undelivered women suffering cardiac arrest, consideration should be given to emergency perimortem Cesarean delivery. However, for the mother who is hemodynamically unstable, but has not suffered cardiac arrest, such decision becomes complex, and will depend on the status of the fetus.

In the pregnant cardiac patient undergoing cardiopulmonary bypass, the patient may develop severe hemodynamic deterioration following failure attempts to wean off bypass. An emergency Cesarean section may be followed by dramatic improvement of the patient’s hemodynamics which facilitates a successful weaning from bypass.

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References

CONTINUOUS NON-INVASIVE ARTERIAL PRESSURE DEVICE AS AN ADJUNCT TO RECOGNIZE FLUCTUATING BLOOD PRESSURES DURING ELECTIVE CESAREAN SECTION UNDER SUBARACHNOID BLOCKADE (SAB)


Background: Measuring non-invasive blood pressure (NIBP) in less than one minute intervals (STAT NIBP measurements) is not always feasible. Therefore, large number of undetectable hypotension episodes can only be recognized with continuous beat to beat monitoring of blood pressure, for example, by continuous non-invasive arterial pressure monitor (CNAP).

Objective: The purpose of the current study was to investigate whether CNAP correlates well with conventional intermittent oscillometric NIBP during elective cesarean sections under subarachnoid blockade (SAB) and whether CNAP based patient management results in improved immediate maternal vasopressor requirements and improved immediate fetal/neonatal outcomes compared with NIBP based patient management.

Materials and Methods: The CNAP finger cuff together with the CNAP arm cuff were placed on the same arm which also had the peripheral intravenous access. On the contralateral arm the conventional NIBP arm cuff was placed. Study Group: The patients were managed by the anesthesia provider based on the CNAP monitor readings. Control Group: The patients were managed by the anesthesia provider based on the NIBP monitor readings.

Results: The CNAP-based treatment (study) group had a statistically significant lower use of oxytocin and lower estimated blood loss than the NIBP-based treatment (control) group. The differences in incidences of vasopressors use and peri-operative nausea vomiting between study group and control group did not reach statistical significance. CNAP readings were more likely to be in systolic hypotensive phases (<100mmHg) and diastolic hypertensive phases (>80mmHg) as compared to NIBP readings.

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**Conclusion:** Continuous non-invasive arterial pressure (CNAP) device may ONLY act as an adjunct to recognize fluctuating blood pressures during elective cesarean section under subarachnoid blockade (SAB).

**Introduction**

Neuraxial anesthesia including epidural anesthesia and subarachnoid blockade (SAB) is preferred over general anesthesia for cesarean section for the sake of comparative significant decline in the maternal mortality. The major side-effect of neuraxial anesthesia is hypotension that is evident in 95% cases. Even though the fetal consequences of maternal hypotension during cesarean section are unclear, maternal hypotension can be presumably deleterious because maternal blood pressure sustains placento-fetal oxygen exchange-delivery. Therefore close monitoring for maternal blood pressure and when needed, immediate treatment for hypotension is crucial. The exact blood pressure monitoring can only be done with intra-arterial blood pressure monitoring utilizing an intra-arterial catheter. Due to inherent side-effects of invasive intra-arterial catheters, blood pressure is routinely monitored intermittently with non-invasive blood pressure (NIBP) device. However, more than one-in-five hypotensive episodes during surgery can be missed and another one-in-five hypotensive episodes may be detected with a delay by NIBP. Consequently, immediate intervention may be delayed. Moreover, in every other patient, hypotension occurs within 3 minutes of SAB administration. There are no guidelines for optimal NIBP cycle interval during cesarean section. Measuring NIBP in less than one minute intervals (STAT NIBP measurements) is not always feasible. Therefore, large number of undetectable hypotension episodes can only be recognized with continuous beat to beat monitoring of blood pressure. Based on principle of volume-clamped method first described by Penaz and colleagues, a continuous non-invasive arterial pressure monitor (CNAP Monitor 500, CNSystems Medizintechnik AG, Graz, Austria) may be a good alternative. In the past, CNAP has been evaluated and shown acceptable results.

The purpose of the current study was to investigate whether CNAP correlates well with conventional intermittent oscillometric NIBP measurement (and correspondingly recognizes undetectable hypotension episodes) in our patient population who present for elective cesarean sections under SAB and whether CNAP based patient management results in improved immediate maternal vasopressor requirements and improved immediate fetal/neonatal outcomes compared with NIBP based patient management.

**Materials and Methods**

After institutional review board approval for prospective, randomized research study, a written and informed consent for inclusion in the study was taken from the pregnant patients aged 18 years and above who presented for elective cesarean section under SAB. Exclusion criteria for the study were: ASA class IV and V pregnant patients, age less than 18 years, patients with cardiac arrhythmia, vascular pathologies of the upper limbs (recent vascular surgery, Raynaud’s disease, vascular stenosis), any contraindication for SAB and emergency cesarean sections. After admission to the operation room, patients were monitored using a five-lead electrocardiogram, NIBP, and pulse oximetry. A note was made of total infused volume of preload received by the patient before the institution of SAB and of co-load being received by the patient while instituting SAB. The CNAP (CNAP Monitor 500, CNSystems Medizintechnik AG) device’s finger cuff measurement was calibrated with CNAP arm cuff before the first measurement, thereafter calibration with CNAP arm cuff was repeated every 15 min and additionally after patient’s repositioning. Before institution of the SAB, the baseline differences in CNAP arm cuff pressures and NIBP arm cuff
pressures were measured. Patients with arm-to-arm differences of more than 10mmHg in systolic and/or diastolic pressures at baseline (right arm pressures vs. left arm pressures) were excluded from the study. The baseline measurements for blood pressure were recorded in the sitting position when the patient was being prepared for SAB. Thereafter, the patients were randomized and divided into two groups based on the computer generated random number list.

**Study Group:** The patients were managed by the anesthesia provider based on the CNAP monitor readings.

**Control Group:** The patients were managed by the anesthesia provider based on the NIBP monitor readings.

SAB was performed in the sitting position using a 25 gauge Whitcare spinal needle with 12 mg hyperbaric bupivacaine mixed with 150 mcg preservative free morphine. After application of SAB, the patients were immediately turned supine with at least 10 degree left tilt. The success of the sensory block was tested for adequacy of surgical anesthesia. Standard anesthesia monitoring ensued. The management of hypotension was to maintain a systolic blood pressure above 100 mm Hg or mean arterial pressure within 20% of baseline mean arterial pressure with incremental boluses doses of 80 mcg phenylepherine. Total amount of boluses given were recorded. If needed, ephedrine boluses were supplemented as rescues for blood pressure unresponsive to phenylepherine. Total volume of infused intravenous solutions (crystalloid, colloid or blood products) were recorded. Neonatal birth weight and maternal blood loss estimate were recorded. APGAR score after 1 and 5 min, and first umbilical (cord) vein/arterial blood gas analyses at birth were noted for all newborns. Pre-fetal delivery, NIBP was cycled every 1 minute and post-fetal delivery, NIBP was cycled every 2.5 minutes.

The CNAP system consists of a double finger cuff, a pressure transducer mounted on the forearm, and an upper arm oscillometric cuff for calibration. The principle of the CNAP is to keep the blood volume of the finger arteries constant by applying an exterior pressure to the vessel wall. This is done by an electronic system controlling the pressure inside a cuff around the finger. The pressure in the cuff, which is needed to keep the volume constant during arterial pulsation, corresponds to the BP. We used the middle finger and the index finger for the finger cuffs. The system can be pre-set to average 0, 5, 10, or 20 beats. For this investigation, all CNAP values presented as a moving median over the last 10 beats.

**Statistical Analysis**

To determine a sample size for the study a F-test (ANOVA- Analysis of Variance: fixed effects, special main effects and interactions) power analysis was done to obtain an alpha error probability of 0.05 and a 1 minus beta error probability of 0.8. A sample size of 130 cases were chosen to give the study sufficient power to determine differences between the continuous variables and the categorical variables of the two groups viz. CNAP monitor readings based treatment group vs. NIBP monitor readings based treatment group.

An ANOVA (Analysis of Variance) and a repeated measures ANOVA (balanced model) where appropriate were used to compare the continuous data. Chi square analysis and Fisher exact tests were used to compare categorical data and proportions. Pearson correlation coefficients, regression analysis and Bland-Altman plots (for all the pooled comparative readings across all the patients) were used to correlate the CNAP vs. NIBP readings. P-value <0.05 was considered significant.

**Results**

Due to logistic limitations, only 53 patients were consented for the study. Sixteen patients were included due to erroneous zeroing methods utilized while zeroing CNAP monitor. Two patients were excluded due to technical difficulties with CNAP and two patients were excluded due to failed SAB. Henceforth, data from 33 patients were included for the final analysis of all variables except fetal/cord blood gas analyses wherein four more patients were excluded due to non-availability of that data.

The demographic characteristics and baseline pre-operative vital parameters were statistically similar.
in both groups (Table 1). The CNAP-based treatment group showed statistically significant reductions in estimated blood loss (P=0.04) and oxytocin used (P=0.02) as compared to the NIBP-based treatment group. Additionally, pre-fetal delivery periods required more phenylephrine and ephedrine administrations on an average when maternal blood pressures were being treated based on CNAP readings (Table 2) and consequently, clinically less patients reported intraoperative nausea-vomiting in the study group (53%) as compared to control group (69%); however, these values did not reach statistical significance. Cord blood gas variables were similar between the two groups (Table 3).

For subsequent analysis, the blood pressure data points were pooled together for comparative correlations irrespective of their treatment groups (study group or control group). For the study period, 33 patients were cumulatively monitored for 14hrs 44minutes during pre-fetal delivery periods and 25hrs 8minutes during post-fetal delivery periods. As pre-fetal delivery, NIBP was cycled every 1 minute and post-fetal delivery, NIBP was cycled every 2.5 minutes, cumulatively comparative data points for CNAP readings vs. NIBP readings that should have been available were 884 for pre-fetal delivery period and 603 for post-fetal delivery period. However, only 555 data points were eventually compared pre-fetal delivery and only 398 data points were eventually compared post-fetal delivery because CNAP-NIBP-readings’ simultaneous captures in S5 Collect Data Software for appropriate comparison were 63% and 66% (less than 100% due to artifacts and/or incomplete readings) for pre-fetal delivery periods and post-fetal delivery periods respectively. Eventually, all 33 patients included in the final analysis had at least 15 data-points each (cumulative pre- and post-fetal delivery) inclusive of some hypotensive and hypertensive phases.

As elicited in Table 4 and Figures 1&2 and assuming the normal ranges for systolic blood pressures (100-120mmHg), diastolic blood pressures (40-80mmHg) and mean arterial pressures (60-93mmHg), CNAP overall readings were less often within normal range during pre-fetal delivery periods with more likelihood for systolic hypotension and diastolic-mean arterial hypertension as compared to

| Table 1 |
|-----------------------|-----------------------|-----------------------|
| **Baseline Characteristics** | **Treatment based on CNAP (n=17)** | **Treatment based on NIBP (n=16)** | **P-value** |
| Age (in years) | 28.2 ± 6.1 | 29.9 ± 6.1 | 0.43 |
| Height (in inches) | 63.6 ± 3.1 | 63.1 ± 2.8 | 0.58 |
| Weight (in pounds) | 216.8 ± 32.8 | 214.8 ± 43.7 | 0.88 |
| CNAP ARMS | | | |
| Arm on which CNAP placed | 10Left/7Right | 12Left/4Right | 0.46 |
| Baseline Systolic Blood Pressure (mmHg) | 132.8 ± 14.5 | 144 ± 18.2 | 0.06 |
| Baseline Diastolic Blood Pressure (mmHg) | 83.1 ± 12.2 | 88.9 ± 14.8 | 0.23 |
| Baseline Mean Arterial Pressure (mmHg) | 99.8 ± 12.3 | 108.2 ± 15.2 | 0.09 |
| Baseline Heart Rate (per minute) | 88.1 ± 9.7 | 96.3 ± 14.3 | 0.06 |
| NIBP ARMS | | | |
| Arm on which NIBP placed | 7Left/10Right | 4Left/12Right | 0.46 |
| Baseline Systolic Blood Pressure (mmHg) | 134.6 ± 15 | 143.5 ± 16.8 | 0.12 |
| Baseline Diastolic Blood Pressure (mmHg) | 81.5 ± 10.6 | 87.1 ± 14.2 | 0.21 |
| Baseline Mean Arterial Pressure (mmHg) | 98.5 ± 12.1 | 108 ± 16.2 | 0.06 |
| Baseline Heart Rate (per minute) | 88.2 ± 11.3 | 95.9 ± 14.5 | 0.1 |

CNAP: Continuous Non-invasive Arterial Pressure
NIBP: Non-Invasive Blood Pressure (Intermittent)
Table 2

Peri-operative Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment based on CNAP (n=17)</th>
<th>Treatment based on NIBP (n=16)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Injection-to-Fetal Delivery Time (in minutes)</td>
<td>27 ± 7</td>
<td>25 ± 7</td>
<td>0.37</td>
</tr>
<tr>
<td>Fetal Delivery-to-Surgery End Time (in minutes)</td>
<td>41 ± 16</td>
<td>50 ± 22</td>
<td>0.2</td>
</tr>
<tr>
<td>Intravenous Fluids prior to spinal injection (ml)</td>
<td>691.2 ± 272.9</td>
<td>678.1 ± 266.4</td>
<td>0.89</td>
</tr>
<tr>
<td>Intravenous Fluids pre-delivery (ml)</td>
<td>720.6 ± 277.9</td>
<td>671.9 ± 236.6</td>
<td>0.59</td>
</tr>
<tr>
<td>Intravenous Fluids post-delivery (ml)</td>
<td>1147.1 ± 293.9</td>
<td>1043.8 ± 222</td>
<td>0.27</td>
</tr>
<tr>
<td>Phenylepherine pre-delivery (mcg)</td>
<td>447.1 ± 323.5</td>
<td>352.5 ± 272.2</td>
<td>0.37</td>
</tr>
<tr>
<td>Phenylepherine post-delivery (mcg)</td>
<td>171.8 ± 232.7</td>
<td>160 ± 354.2</td>
<td>0.91</td>
</tr>
<tr>
<td>Ephedrine pre-delivery (mg)</td>
<td>5.3 ± 13.3</td>
<td>1.6 ± 4.4</td>
<td>0.29</td>
</tr>
<tr>
<td>Ephedrine post-delivery (mg)</td>
<td>2.4 ± 4.4</td>
<td>1.9 ± 5.4</td>
<td>0.78</td>
</tr>
<tr>
<td>Estimated Blood Loss (ml)</td>
<td>617.6 ± 174.1</td>
<td>758.4 ± 208.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Oxytocin (units)</td>
<td>4.2 ± 1.4</td>
<td>5.7 ± 2.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Baby’s Sex</td>
<td>3 Female/14 Male</td>
<td>7 Female/9 Male</td>
<td>0.14</td>
</tr>
<tr>
<td>Baby’s Weight (gm)</td>
<td>3316.5 ± 404.3</td>
<td>3474.3 ± 463.4</td>
<td>0.3</td>
</tr>
<tr>
<td>APGAR @ 1 min</td>
<td>6.9 ± 2.5</td>
<td>7.8 ± 1.6</td>
<td>0.24</td>
</tr>
<tr>
<td>APGAR @ 5 min</td>
<td>8.9 ± 0.3</td>
<td>8.8 ± 0.5</td>
<td>0.66</td>
</tr>
<tr>
<td>Intra-operative Nausea Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8 (47%)</td>
<td>5 (31%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Nausea Only</td>
<td>5 (29%)</td>
<td>5 (31%)</td>
<td></td>
</tr>
<tr>
<td>One Vomiting</td>
<td>1 (6%)</td>
<td>1 (7%)</td>
<td></td>
</tr>
<tr>
<td>Multiple Vomiting</td>
<td>3 (18%)</td>
<td>5 (31%)</td>
<td></td>
</tr>
<tr>
<td>Post-operative Nausea Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14 (82%)</td>
<td>12 (75%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Nausea Only</td>
<td>1 (6%)</td>
<td>2 (13%)</td>
<td></td>
</tr>
<tr>
<td>One Vomiting</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Multiple Vomiting</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

CNAP: Continuous Non-invasive Arterial Pressure
NIBP: Non-Invasive Blood Pressure (Intermittent)

NIBP readings (P<0.01). Contrastingly, CNAP systolic (not diastolic or mean arterial) readings were more often within normal range during post-fetal delivery periods but with persistent more likelihood for systolic hypotension and diastolic hypertension as compared to NIBP readings (P<0.01).

For individual data-point comparisons, correlation coefficients for CNAP readings vs. NIBP readings for systolic-diastolic-mean arterial pressures ranged from 0.36-0.51 in pre-fetal delivery period and 0.47-0.57 in post-fetal delivery period (Table 5); however, on Bland-Altman analysis/plotting, it was noticed that as compared to NIBP readings, CNAP readings most frequently (=Mode) underestimates systolic blood pressure and overestimates both diastolic blood pressure-mean arterial pressure during pre-fetal delivery periods whereas CNAP readings most frequently (=Mode) underestimates both systolic blood pressure-mean arterial pressure and overestimates only diastolic blood pressure during post-fetal delivery periods (Table 6). The graphical representations of correlation between CNAP readings
Table 3

<table>
<thead>
<tr>
<th>Blood Gas Variable</th>
<th>Treatment based on CNAP (n=14)</th>
<th>Treatment based on NIBP (n=15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CORD ARTERIAL BLOOD GAS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methemoglobin (%)</td>
<td>1.6 ± 0.3</td>
<td>1.7 ± 0.3</td>
<td>0.36</td>
</tr>
<tr>
<td>Carboxyhemoglobin (%)</td>
<td>1.2 ± 1.2</td>
<td>0.6 ± 0.8</td>
<td>0.16</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.5 ± 0.9</td>
<td>14.6 ± 1.2</td>
<td>0.86</td>
</tr>
<tr>
<td>pH</td>
<td>7.25 ± 0.07</td>
<td>7.26 ± 0.04</td>
<td>0.81</td>
</tr>
<tr>
<td>p Carbon dioxide (mmHg)</td>
<td>55.2 ± 9.3</td>
<td>55.7 ± 6.8</td>
<td>0.87</td>
</tr>
<tr>
<td>p Oxygen (mmHg)</td>
<td>18.7 ± 6.9</td>
<td>17.2 ± 5.4</td>
<td>0.51</td>
</tr>
<tr>
<td>Base Excess</td>
<td>-4.2 ± 2.5</td>
<td>-3.6 ± 1.7</td>
<td>0.47</td>
</tr>
<tr>
<td>Oxygen-Hemoglobin Sat (%)</td>
<td>31 ± 17.3</td>
<td>27.6 ± 13.6</td>
<td>0.36</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>23.4 ± 2.1</td>
<td>24 ± 1.8</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>CORD VENOUS BLOOD GAS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methemoglobin (%)</td>
<td>1.6 ± 0.4</td>
<td>1.7 ± 0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Carboxyhemoglobin (%)</td>
<td>2.4 ± 1.6</td>
<td>1.8 ± 1.3</td>
<td>0.28</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.6 ± 1</td>
<td>14.6 ± 1.1</td>
<td>0.97</td>
</tr>
<tr>
<td>pH</td>
<td>7.31 ± 0.04</td>
<td>7.31 ± 0.06</td>
<td>0.88</td>
</tr>
<tr>
<td>p Carbon dioxide (mmHg)</td>
<td>45.8 ± 6.5</td>
<td>47.7 ± 8.9</td>
<td>0.51</td>
</tr>
<tr>
<td>p Oxygen (mmHg)</td>
<td>29.3 ± 6.7</td>
<td>27.7 ± 8.1</td>
<td>0.58</td>
</tr>
<tr>
<td>Base Excess</td>
<td>-3.9 ± 1.9</td>
<td>-3.5 ± 1.6</td>
<td>0.55</td>
</tr>
<tr>
<td>Oxygen-Hemoglobin Sat (%)</td>
<td>58.7 ± 14.2</td>
<td>54.8 ± 21</td>
<td>0.57</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>22.1 ± 2.1</td>
<td>22.8 ± 1.5</td>
<td>0.32</td>
</tr>
</tbody>
</table>

CNAP: Continuous Non-invasive Arterial Pressure
NIBP: Non-Invasive Blood Pressure (Intermittent)

Discussion

The results of our study can be summarized as follows: (a) all 33 patients included in the final analysis had at least 15 data-points each (cumulative pre- and post-fetal delivery) inclusive of some hypotensive and hypertensive phases that met the criteria of Association for the Advancement of Medical Instrumentation (AAMI) 81060 standard which was historically meant for beat-to-beat comparison between CNAP monitoring and invasive arterial line-based continuous blood pressure monitoring; (b) the CNAP-based treatment (study) group had a statistically significant
Table 4
Frequency Distribution of Blood Pressure Readings

<table>
<thead>
<tr>
<th>Range of Parameter</th>
<th>Pre-Fetal Delivery Comparative Datapoints' (n=555) frequency</th>
<th>Post-Fetal Delivery Comparative Datapoints' (n=398) frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CNAP</td>
<td>NIBP</td>
</tr>
<tr>
<td>SYSTOLIC BLOOD PRESSURE READINGS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤80 mmHg</td>
<td>16 (3%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>81-89 mmHg</td>
<td>19 (3%)</td>
<td>13 (2%)</td>
</tr>
<tr>
<td>90-99 mmHg</td>
<td>47 (8%)</td>
<td>27 (5%)</td>
</tr>
<tr>
<td>100-120 mmHg</td>
<td>208 (37%)</td>
<td>230 (41%)</td>
</tr>
<tr>
<td>121-139 mmHg</td>
<td>158 (28%)</td>
<td>193 (35%)</td>
</tr>
<tr>
<td>140-159 mmHg</td>
<td>74 (13%)</td>
<td>79 (14%)</td>
</tr>
<tr>
<td>160-179 mmHg</td>
<td>13 (2%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>≥180 mmHg</td>
<td>20 (4%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>DIASTOLIC BLOOD PRESSURE READINGS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤35 mmHg</td>
<td>4 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>36-39 mmHg</td>
<td>2 (0%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>40-80 mmHg</td>
<td>363 (65%)</td>
<td>476 (86%)</td>
</tr>
<tr>
<td>81-89 mmHg</td>
<td>106 (19%)</td>
<td>50 (9%)</td>
</tr>
<tr>
<td>90-99 mmHg</td>
<td>49 (9%)</td>
<td>15 (3%)</td>
</tr>
<tr>
<td>100-109 mmHg</td>
<td>24 (4%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>≥110 mmHg</td>
<td>7 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>MEAN ARTERIAL PRESSURE READINGS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50 mmHg</td>
<td>3 (1%)</td>
<td>2 (0%)</td>
</tr>
<tr>
<td>51-59 mmHg</td>
<td>5 (1%)</td>
<td>16 (3%)</td>
</tr>
<tr>
<td>60-93 mmHg</td>
<td>349 (63%)</td>
<td>407 (73%)</td>
</tr>
<tr>
<td>94-106 mmHg</td>
<td>116 (21%)</td>
<td>100 (18%)</td>
</tr>
<tr>
<td>107-119 mmHg</td>
<td>59 (11%)</td>
<td>25 (5%)</td>
</tr>
<tr>
<td>120-132 mmHg</td>
<td>13 (2%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>≥133 mmHg</td>
<td>10 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

CNAP: Continuous Non-invasive Arterial Pressure
NIBP: Non-Invasive Blood Pressure (Intermittent)

lower use of oxytocin and lower estimated blood loss than the NIBP-based treatment (control) group; (c) differences in incidences of vasopressors use and peri-operative nausea vomiting between study group and control group did not reach statistical significance most likely because of lack of statistical power; (d) only 64% simultaneous CNAP and NIBP comparative data-points were captured during the entire study period but those pooled 953 out of potential 1487 data-points provided sufficient data for differential analyses between pooled CNAP readings and pooled NIBP readings irrespective of patients being in a study group or in a control group; (e) CNAP readings were more likely to be in systolic hypotensive phases (<100mmHg) and diastolic hypertensive phases (>80mmHg) as compared to NIBP readings; (f) as expected CNAP readings and NIBP readings correlated well, but 95% confidence limits for CNAP-NIBP differences were clinically unacceptable that ranged from -48 to 49 mmHg for systolic blood pressures, -24 to 42 mmHg for diastolic blood pressures, and -22 to 31 mmHg for diastolic blood pressures, and
-24 to 27 mmHg for mean arterial pressures in post-fetal delivery periods (Table 6) because in spite of being mired in controversies and debate, currently followed AAMI’s guidelines recommend clinical acceptability of bias (CNAP-NIBP mean difference) ≤5mmHg and standard deviation (SD) ≤8mmHg\(^{20,22}\); and (g) left uterine displacement during the pre-fetal delivery period may have some role in the significant overestimations of diastolic blood pressures and mean arterial pressures by CNAP when CNAP arm cuff and finger cuff were placed in the left arm of the patients.

In regards to technical details about CNAP use during this study, only two out of 33 patients required small size finger cuffs with medium size finger cuffs good for the remaining patients; however ten out of 33 patients required large adult size arm cuffs as compared to medium adult size arm cuffs for the remaining patients. Only one out of 33 patients reported minimal skin changes in relation to finger cuffs that spontaneously resolved by the time patient was transferred from operating room to recovery unit.

<table>
<thead>
<tr>
<th>Statistical Variable for Difference in Blood Pressure Readings by Two Methods (CNAP and NIBP)</th>
<th>Magnitude of Difference in Systolic Blood Pressure Readings (CNAP-NIBP) (in mmHg)</th>
<th>Magnitude of Difference in Diastolic Blood Pressure Readings (CNAP-NIBP) (in mmHg)</th>
<th>Magnitude of Difference in Mean Arterial Pressure Readings (CNAP-NIBP) (in mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-Fetal Delivery Comparative Datapoints (n=555)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>1 ± 24.4</td>
<td>9 ± 16.7</td>
<td>6 ± 15.1</td>
</tr>
<tr>
<td>Median</td>
<td>-1</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Mode</td>
<td>-10</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Upper Limit of Agreement (Mean+2SD)</td>
<td>49</td>
<td>42</td>
<td>36</td>
</tr>
<tr>
<td>Lower Limit of Agreement (Mean-2SD)</td>
<td>-48</td>
<td>-24</td>
<td>-24</td>
</tr>
<tr>
<td><strong>Post-Fetal Delivery Comparative Datapoints (n=398)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>-4 ± 20.9</td>
<td>5 ± 13.2</td>
<td>2 ± 12.7</td>
</tr>
<tr>
<td>Median</td>
<td>-7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Mode</td>
<td>-9</td>
<td>2</td>
<td>-3</td>
</tr>
<tr>
<td>Upper Limit of Agreement (Mean+2SD)</td>
<td>37</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>Lower Limit of Agreement (Mean-2SD)</td>
<td>-46</td>
<td>-22</td>
<td>-24</td>
</tr>
</tbody>
</table>

CNAP: Continuous Non-invasive Arterial Pressure  
NIBP: Non-Invasive Blood Pressure (Intermittent)
As all patients were awake during the procedures and effectively tolerated the arm cuffs and finger cuffs for the entire duration of cesarean section, subjective patient satisfaction scores were not analyzed. Besides the left tilt’s effects on CNAP-NIBP differences, it cannot be ruled out whether the use of forced air-warming blankets (depending on if the awake patients requested for them and were able to tolerate them intraoperatively to counter perceived temperature changes) and routine practice of pressurized non-warmed (cold) intravenous fluids boluses/infusions especially during immediate post-SAB pre-fetal delivery periods have any role to play in finger cuff based beat-to-beat CNAP readings’ under/overestimations.

During our study, it was our observation that CNAP controller, power supply cord, and medium size finger cuffs needed replacements despite dedicated/single operator-use suggesting the possibilities for CNAP components being delicate/vulnerable to breakage requiring cautious usage especially during rapid turnover of operating rooms. Another major

<table>
<thead>
<tr>
<th>APGAR Variable correlated with Pre-Fetal Delivery Time</th>
<th>Group wherein Treatment was based on CNAP readings (n=17)</th>
<th>Group wherein Treatment was based on NIBP readings (n=16)</th>
<th>Cumulative Group Irrespective of Treatment Basis (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APGAR @ 1minute</td>
<td>-0.21 (0.42)</td>
<td>0.21 (0.43)</td>
<td>-0.1 (0.59)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Gas Variable correlated with Pre-Fetal Delivery Time</th>
<th>Group wherein Treatment was based on CNAP readings (n=14)</th>
<th>Group wherein Treatment was based on NIBP readings (n=15)</th>
<th>Cumulative Group Irrespective of Treatment Basis (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORD ARTERIAL BLOOD GAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methemoglobin</td>
<td>0.11 (0.71)</td>
<td>-0.14 (0.62)</td>
<td>-0.02 (0.94)</td>
</tr>
<tr>
<td>Carboxyhemoglobin</td>
<td>-0.17 (0.57)</td>
<td>0.08 (0.77)</td>
<td>-0.05 (0.78)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>-0.3 (0.29)</td>
<td>0.22 (0.43)</td>
<td>-0.01 (0.95)</td>
</tr>
<tr>
<td>pH</td>
<td>-0.45 (0.11)</td>
<td>-0.18 (0.53)</td>
<td>-0.34 (0.07)</td>
</tr>
<tr>
<td>p Carbon dioxide</td>
<td>0.49 (0.07)</td>
<td>-0.21 (0.44)</td>
<td>0.19 (0.31)</td>
</tr>
<tr>
<td>p Oxygen</td>
<td>-0.18 (0.54)</td>
<td>0.43 (0.11)</td>
<td>0.09 (0.64)</td>
</tr>
<tr>
<td>Base Excess</td>
<td>-0.16 (0.58)</td>
<td>-0.52 (0.04)</td>
<td>-0.31 (0.11)</td>
</tr>
<tr>
<td>Oxy-Hemoglobin Sat</td>
<td>-0.26 (0.36)</td>
<td>0.35 (0.21)</td>
<td>0.01 (0.97)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>0.19 (0.51)</td>
<td>-0.5 (0.06)</td>
<td>-0.13 (0.49)</td>
</tr>
<tr>
<td>CORD VENOUS BLOOD GAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methemoglobin</td>
<td>0.46 (0.1)</td>
<td>-0.19 (0.5)</td>
<td>0.12 (0.54)</td>
</tr>
<tr>
<td>Carboxyhemoglobin</td>
<td>0.21 (0.46)</td>
<td>-0.15 (0.61)</td>
<td>0.06 (0.74)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>-0.05 (0.87)</td>
<td>0.43 (0.11)</td>
<td>0.2 (0.31)</td>
</tr>
<tr>
<td>pH</td>
<td>-0.41 (0.15)</td>
<td>-0.4 (0.14)</td>
<td>-0.39 (0.03)</td>
</tr>
<tr>
<td>p Carbon dioxide</td>
<td>0.42 (0.13)</td>
<td>0.38 (0.17)</td>
<td>0.38 (0.04)</td>
</tr>
<tr>
<td>p Oxygen</td>
<td>0.07 (0.8)</td>
<td>-0.03 (0.9)</td>
<td>0.02 (0.92)</td>
</tr>
<tr>
<td>Base Excess</td>
<td>-0.03 (0.91)</td>
<td>-0.42 (0.12)</td>
<td>-0.22 (0.26)</td>
</tr>
<tr>
<td>Oxy-Hemoglobin Sat</td>
<td>-0.01 (0.96)</td>
<td>-0.13 (0.64)</td>
<td>-0.08 (0.69)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>0.21 (0.47)</td>
<td>0 (&gt;0.99)</td>
<td>0.12 (0.55)</td>
</tr>
</tbody>
</table>

CNAP: Continuous Non-invasive Arterial Pressure
NIBP: Non-Invasive Blood Pressure (Intermittent)
r: Correlation Coefficient with P-Value in parentheses (significant if <0.05)
S5 Data Collect Software was required with appropriate connected cables to ensure transfer and recording of data (this step might be overridden in the future if the CNAP monitor becomes incorporated in the anesthesia machine itself). Additionally, due to paucity of recorded channels in S5 Data Collect Software, only four variables per time point were auto-recorded (CNAP systolic, CNAP diastolic, NIBP systolic and NIBP diastolic) and both mean arterial pressures (CNAP or NIBP) were calculated as equal to \([2\times \text{Diastolic} + \text{Systolic}]/3\) based on corresponding auto-recorded pressures.

In regards to calibration cycle, currently

**Table 8**

*Differences elicited when Patients had CNAP measurements in Left Arm vs. when Patients had CNAP measurements in Right Arm*

<table>
<thead>
<tr>
<th>Statistical Variable for Difference in Blood Pressure Readings by Two Methods (CNAP and NIBP)</th>
<th>Magnitude of Difference in Systolic Blood Pressure Readings (CNAP-NIBP) (in mmHg)</th>
<th>Magnitude of Difference in Diastolic Blood Pressure Readings (CNAP-NIBP) (in mmHg)</th>
<th>Magnitude of Difference in Mean Arterial Pressure Readings (CNAP-NIBP) (in mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Fetal Delivery Comparative Datapoints</td>
<td>CNAP measured in Left Arm (n=371)</td>
<td>CNAP measured in Right Arm (n=184)</td>
<td>CNAP measured in Left Arm (n=371)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1 ± 23.6</td>
<td>0 ± 26.2</td>
<td>11 ± 17.1</td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
<td>-5</td>
<td>11</td>
</tr>
<tr>
<td>Mode</td>
<td>9</td>
<td>-7</td>
<td>15</td>
</tr>
<tr>
<td>Upper Limit of Agreement (Mean±2SD)</td>
<td>48</td>
<td>53</td>
<td>45</td>
</tr>
<tr>
<td>Lower Limit of Agreement (Mean-2SD)</td>
<td>-46</td>
<td>-52</td>
<td>-23</td>
</tr>
<tr>
<td>Post-Fetal Delivery Comparative Datapoints</td>
<td>CNAP measured in Left Arm (n=287)</td>
<td>CNAP measured in Right Arm (n=111)</td>
<td>CNAP measured in Left Arm (n=287)</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>-5 ± 21.7</td>
<td>-2 ± 18.3</td>
<td>4 ± 13.2</td>
</tr>
<tr>
<td>Median</td>
<td>-7</td>
<td>-6</td>
<td>4</td>
</tr>
<tr>
<td>Mode</td>
<td>-14</td>
<td>-9</td>
<td>4</td>
</tr>
<tr>
<td>Upper Limit of Agreement (Mean±2SD)</td>
<td>38</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Lower Limit of Agreement (Mean-2SD)</td>
<td>-49</td>
<td>-39</td>
<td>-22</td>
</tr>
</tbody>
</table>

CNAP: Continuous Non-invasive Arterial Pressure  
NIBP: Non-Invasive Blood Pressure (Intermittent)  
The Comparative Values indicated in **BOLD** were statistically significant (P<0.01)
Fig. 1
Pre-Fetal Delivery Distribution of CNAP vs. NIBP readings in various blood pressure ranges
(graphical methodology as inspired from Benes et al\textsuperscript{23})
Fig. 2
Post- Fetal Delivery Distribution of CNAP vs. NIBP readings in various blood pressure ranges
(graphical methodology as inspired from Benes et al23)
Fig. 3
Pre-Fetal Delivery Comparison of CNAP vs. NIBP readings and their corresponding Bland-Altman Plots

Fig. 4
Post-Fetal Delivery Comparison of CNAP vs. NIBP readings and their corresponding Bland-Altman Plots
would have been possible only if CNAP was being compared with invasive arterial line pressures). Target control infusion based phenylepherine administrations rather than its total dose would have been better estimations because otherwise under/overestimations can happen depending on the fluidity of hemodynamics and catching up by the operator-administered doses intermittently.

In summary, beat-to-beat CNAP can only act as an enhancement for NIBP because it is just preempting the providers to recalibrate/zero with NIBP during the time-period when they are not measuring NIBP, for example, during the 1-minute interval of NIBP or during the lowest possible 5-minute calibration cycle interval of CNAP. Three simple steps when using CNAP for enhancing NIBP could be as follows: (a) if low beat-to-beat CNAP pressures, immediately check NIBP (recycle for zero/recalibration); (b) if high beat-to-beat CNAP pressures, immediately check NIBP (recycle for zero/recalibration); and (c) if normal ranged beat-to-beat CNAP pressures, ensure high vigilance because CNAP pressures may be lower or higher than the standard NIBP readings at that time because CNAP numbers are as good as last calibration of arm cuff readings (especially if it was an extremely SUBNORMAL/hypotensive number or an extremely SUPRANORMAL/hypertensive number) which can be auto-repeated no less than 5minutes (although manual calibration can be done any number of times).

**Conclusion**

Continuous non-invasive arterial pressure (CNAP) device may ONLY act as an adjunct to recognize fluctuating blood pressures that may need confirmation with intermittent oscillometric non-invasive blood pressure (NIBP) measurements during elective cesarean section under subarachnoid blockade (SAB).

**Acknowledgements**

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along with the cables for connection with the S5/ADU anesthesia monitor along with the configured S/5 Data Collect Software licensed from the GE Healthcare was provided for the study time-period by the CNSystems Medizintechnik AG, Graz, Austria. Austrian Contact Person was Katja Maier (Lerche), Head of Business Development, and Local Contact Person in United States was Ron Borgschulte, Partners in Medicine LLC, St. Louis, Missouri. George Mckelvey, PhD, Department of Anesthesiology, Detroit Medical Center helped with statistical analysis of our data.
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COMPARISON OF INDIRECT VIDEO LARYNGOSCOPES IN CHILDREN YOUNGER THAN TWO YEARS OF AGE: A RANDOMIZED TRAINEE EVALUATION STUDY

Marissa G. Vadi*, Elizabeth A. Ghazal**, Bryan Halverson** and Richard L. Applegate II**

Background: Gaining proficiency with various airway management tools is an important goal for anesthesiology training. Indirect video laryngoscopes facilitate tracheal intubation in adults, but it is not clear whether these findings translate to children. This study evaluates the total time to successful intubation when performed by anesthesiology trainees using GlideScope Cobalt® video laryngoscopy (GlideScope), Storz DCI® video laryngoscopy (Storz), or direct laryngoscopy (Direct) in children <2 years old with normal airway anatomy.

Methods: Sixty-five children presenting for elective surgery were randomly assigned to undergo tracheal intubation using GlideScope, Storz, or Direct. Laryngoscopists were anesthesiology trainees in clinical anesthesia year ≥2 who had proven basic proficiency with each laryngoscope on an infant airway manikin. Total time to successful intubation (TTSI, seconds), rate of successful intubation on first laryngoscopy attempt, and the change in intubation time from manikin to clinical settings were recorded. An intubation time difference >10 seconds was defined as clinically significant.

Results: TTSI was longer for Storz (42.1; 34.0 to 59.0) than for Direct (21.5; 17.0 to 34.3; p=0.002). We were not able to demonstrate a difference >10 seconds between the GlideScope and the other laryngoscopes. Median manikin intubation time was <10 seconds and increased significantly in the clinical setting for all laryngoscopes (all p <0.0001).

Conclusions: Anesthesiology trainees completed manikin tracheal intubation rapidly with all laryngoscopes studied, but required a clinically significant longer time to tracheally intubate children <2 years. Our findings suggest in vivo training should be included to facilitate proficiency with device-specific intubation techniques.

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Introduction

Tracheal intubation is a central component of competency-based curricula in anesthesiology training programs, and includes gaining proficiency with a number of airway management tools. Failed or prolonged tracheal intubation attempts constitute major causes of anesthetic morbidity and mortality. Development of technical proficiency in pediatric airway management poses unique challenges for anesthesiology trainees. The neonate or infant has a large occiput and tongue, a more cephalad larynx, a long and floppy epiglottis, and a shorter trachea and neck when compared to an older child or adult. These anatomical differences may increase the difficulty of obtaining optimal glottic views in small children. Pediatric patients tolerate apnea for a shorter time than adults and may especially benefit from atraumatic, single-attempt laryngoscopy and tracheal intubation.

Indirect video laryngoscopes, designed to allow a view of the glottis without requiring alignment of the oral, pharyngeal, and tracheal axes, have become accepted as effective tools for airway management. These laryngoscopes have been shown in adults to improve glottic view and facilitate guidance to novice laryngoscopists, though it remains unclear whether these advantages translate to pediatric airways. The GlideScope Cobalt® (Verathon Medical, Bothell, WA) and Storz DCI® video laryngoscopes (Karl Storz, Tuttlingen, Germany) are both available for pediatric use. The GlideScope Cobalt® video laryngoscope features a reusable video baton and single-use curved laryngoscopy blades while the pediatric Storz DCI® video laryngoscope allows use of Miller-like laryngoscope blades equipped with a video lens in the blade tip to provide high-resolution images on a video monitor. Dynamic video feedback allows supervising physicians to appropriately guide trainees and confirm proper tracheal tube placement.

Trainee proficiency can be judged based on the rate of successful tracheal intubation. For example, anesthesia trainees were found to need at least 57 intubation procedures to achieve first or second attempt tracheal intubation success using direct laryngoscopy in 90% of adult patients. Time to successful tracheal intubation is another marker of trainee proficiency. Investigations of indirect video laryngoscopy use by trainees in the pediatric clinical setting yield variable intubation times and success rates. Much of the literature on pediatric indirect video laryngoscopy use focuses on older children, manikin studies, small case series, or use by expert laryngoscopists. It remains unclear whether indirect video laryngoscopy improves tracheal intubation proficiency among more novice laryngoscopists when used in small children. Thus, the primary aim of this study was to compare tracheal intubation times by anesthesiology trainees in children under age 2 years with expected normal airway anatomy using the GlideScope Cobalt® video laryngoscope, the Storz DCI® video laryngoscope, or standard direct laryngoscopy.

Methods

This single-center, prospective randomized non-blinded parallel group study received Institutional Review Board approval, and was registered at ClinicalTrials.gov. Written informed consent was obtained from parents or legal guardians of children under the age of 2 years scheduled for elective surgery requiring tracheal intubation at our tertiary care hospital in the United States. Children with a known or predicted difficult airway, corrected gestational age less than 37 weeks, severe bronchopulmonary dysplasia, elevated intracranial pressure, or increased aspiration risk were excluded.

Subjects were randomly assigned to undergo tracheal intubation with the GlideScope Cobalt® video laryngoscope (size 2 blade; GlideScope), the Storz DCI® video laryngoscope (Miller 1 video blade; Storz), or direct laryngoscopy (Miller 1 blade; Direct). Randomization was carried out using computer-generated random numbers in blocks of 21 and allocation concealment was performed with sealed opaque envelopes until after informed consent for study participation was obtained. Tracheal intubations were performed by anesthesiology trainees in clinical anesthesia year 2 or above who had completed at least one month of pediatric anesthesiology at our hospital. Laryngoscopists proved basic proficiency with each laryngoscope before study participation by performing at least 3 consecutive tracheal intubations in less
than 30 seconds each on an infant airway manikin (Laerdal® Infant Airway Management Trainer, Stavanger, Norway). Manikin tracheal intubation times were recorded for each laryngoscopist. Prior in vivo video laryngoscope experience as reported by all laryngoscopists was recorded. All intubations were performed using styletted conventional tracheal tubes. Tracheal tubes for GlideScope intubations were shaped to approximate the curve of the size 2 Cobalt® blade while tracheal tubes for Storz or Direct intubations were shaped with a hockey-stick bend at the tip. Laryngoscopists were reminded to intubate safely, were aware they would be timed, and were instructed to direct their view to the video monitor during tracheal intubation when using GlideScope or Storz.

Anesthesia care included routine perioperative monitors per American Society of Anesthesiologists guidelines. Anesthesia induction was standardized to either inhalation of 70% nitrous oxide / 30% oxygen mixture and 4-8% sevoflurane followed by intravenous catheter placement; or by intravenous induction with propofol 3 mg.kg⁻¹ if intravenous access was established prior to induction of anesthesia. All patients received rocuronium 0.6 mg.kg⁻¹ IV followed by a saline flush to ensure administration; the first laryngoscopy attempt was not allowed to start for 90 seconds after administration as timed by a stopwatch.

An un-blinded research assistant announced intubation “start” (tip of laryngoscope passing the lips) and “stop” (removal of tip of laryngoscope past the lips) times to a second research assistant who was kept blinded to the laryngoscope in use and who recorded the time interval using a handheld stopwatch while facing the wall of the operating room. An intubation attempt was recorded each time the randomized laryngoscope was removed past the lips. If more than one intubation attempt was required, the patient was mask ventilated with 4-8% sevoflurane in 100% oxygen between attempts and the sum of the individual intubation times determined the total time to successful tracheal intubation (TTSI). The use of external laryngeal manipulation or shoulder rolls was recorded. The best Cormack-Lehane glottic view as reported by the laryngoscopist was recorded. An un-blinded member of the research team recorded technical factors complicating intubation which included visualization difficulty related to obscured view from fogging, secretions or blood in the airway; difficulty passing the tracheal tube past the vocal cords; inappropriate endotracheal tube size for the patient; or difficulty controlling the direction of the tracheal tube using the video display. The laryngoscope blade was inspected for the presence of blood and the mouth was inspected for signs of trauma following tracheal intubation. The lowest pulse oxygen saturation and lowest heart rate during intubation were recorded. Proper tracheal tube placement was confirmed by direct visualization, chest auscultation, and detection of end-tidal carbon dioxide.

**Statistical Analysis**

A 10 second difference in TTSI was considered clinically significant as previously published. Sample size calculation yielded 60 patients needed to complete study participation to show a greater than 10 second intergroup difference was statistically significant, with power of 0.8 and an alpha value of 0.05. Anthropometric data were determined by World Health Organization child growth standards (WHO Anthro for PC 3.2.2, World Health Organization, Geneva, Switzerland). Groups were compared for patient characteristic similarity. The primary outcome measure was intergroup difference in TTSI. Intubation attempts in which the attending anesthesiologist performed the final intubation were excluded from analysis of the primary outcome measure, but were included in analysis of appropriate secondary outcome measures. Secondary outcome measures included intergroup differences in: the number of first attempt successful tracheal intubations; TTSI for tracheal intubations completed on the first attempt; the total number of intubation attempts needed to successfully intubate the trachea; best Cormack-Lehane glottic view; and technical factors complicating intubation. Time to manikin tracheal intubation, change in tracheal intubation time from manikin to clinical settings and relationships of tracheal intubation times to laryngoscopist characteristics were also analyzed.

Data distribution was analyzed by Shapiro-Wilk, with p <0.05 indicating the distribution was not normal. Normally distributed continuous data were expressed as mean and 95% confidence interval and analyzed by
univariate ANOVA with Tukey’s method to compare means. Continuous data that were not normally distributed were expressed as median and 95% confidence interval and analyzed using Kruskal-Wallis test, with differences between medians compared by the Hodges Lehman method assuming data symmetry. Changes in time to successful intubation from the manikin to clinical settings were compared by paired Wilcoxon. Categorical data were analyzed by Chi-square. Statistical significance was taken at p < 0.05 (JMP 10.0.0, SAS Institute, Cary, NC, USA).

Results

Seventy-seven children were screened and sixty-five aged 3 weeks to 23 months of age were enrolled during an 8 month period. One subject was excluded for intubation timing error and one additional subject was excluded for lack of video laryngoscope availability after randomization (Figure 1). There were no significant intergroup differences in patient characteristics (Table 1). The attending anesthesiologist completed the intubation in one Storz and two GlideScope patients, thus these were excluded from TTSI analysis. Intubation times were not normally distributed (Shapiro-Wilk, all p <0.01). TTSI was significantly different between groups, longer for Storz (42.1; 34.0 to 59.0 seconds) than for Direct (21.5; 17.0 to 34.3 seconds; p = 0.002; Table 2). The 95% confidence intervals of median TTSI were narrower in Direct (Figure 2). We were not able to demonstrate a TTSI difference of at least 10 seconds between GlideScope (30.8; 24.1 to 46.4 seconds) and either Direct or Storz. Analysis limited to intubations successfully completed on the first attempt showed TTSI was longer in 16 Storz patients (34.3; 27.8 to 42.3 seconds) than in 17 Direct patients (19.3; 15.6 to 26.1 seconds; p=0.003), and 16 GlideScope patients (25.0; 19.4 to 31.9 seconds; p=0.04).

Manikin intubation time was not different based on year of training overall or within laryngoscope groups (all p >0.40). Similarly, TTSI was not different

---

**Fig. 1**

CONSORT flow diagram

**Assessed for eligibility (n = 77)**

- Excluded (n = 12)
  - Refused to participate n = 12

**Randomized (n = 65)**

- Allocated to Direct n = 20
  - Received allocated intervention (n = 19)
  - Did not receive allocated intervention (n = 1) (Timing error n = 1)

- Allocated to GlideScope n = 22
  - Received allocated intervention (n = 22)
  - Did not receive allocated intervention (n = 0)

- Allocated to Storz n = 23
  - Received allocated intervention (n = 22)
  - Did not receive allocated intervention (n = 1) (Assigned laryngoscope not available for use n = 1)

**Analysis**

- Analyzed n = 19
  - Excluded from analysis (n = 0)

- Analyzed n = 22
  - Excluded from analysis (n = 2) (Attending anesthesiologist completed intubation n = 2)

- Analyzed n = 21
  - Excluded from analysis (n = 1) (Attending anesthesiologist completed intubation n = 1)

Consolidated Standards of Reporting Trials (CONSORT) flow diagram. TTSI = Total time to successful tracheal intubation.
Total time to successful tracheal intubation performed by anesthesiology trainees in children <2 years old was different for patients intubated using direct laryngoscopy, GlideScope or Storz video laryngoscopes in the clinical setting (p=0.006 Kruskall-Wallis). Intergroup comparison of medians by Hodges Lehman is shown. Median and 95% confidence interval are indicated for each group.

Total time to successful tracheal intubation plotted for individual anesthesiology trainees in manikin and clinical settings, with median times indicated by solid lines. Dotted lines connect manikin and clinical tracheal intubation times for individual laryngoscopists using assigned laryngoscopes. Tracheal intubation time increased significantly from the manikin to clinical setting within each laryngoscope group (paired Wilcoxon, all p <0.0001).
based on year of training overall (p = 0.27), or within laryngoscope groups (all p >0.20). TTSI increased from the manikin to the clinical setting for individual laryngoscopists within all groups (all p <0.0001; Figure 3). The magnitude of this increase was larger in Storz than Direct (p = 0.01; Table 2).

Only 3 pulse oxygen desaturations to <92% were reported: Storz to 76% (n=1), which was felt to be secondary to bronchospasm; GlideScope to 85% (n=1) and Direct to 77% (n=1) due to prolonged intubation attempts. There were no bradycardias reported in any group, even in the setting of pulse oxygen desaturation. Atropine was given to 1 Direct and 1 GlideScope patient before laryngoscopy. Exclusion of these patients did not change results of lowest heart rate analysis. Blood was found on the laryngoscope blade after intubation in 2 Storz patients, but no major upper airway trauma was noted in any patient. Technical factors other than inappropriate endotracheal tube size were more likely to complicate tracheal intubation in Storz (p=0.04). There were no significant differences in other secondary outcome markers (Table 3).

Discussion

It is prudent to investigate the clinical efficacy of newly developed airway devices marketed for use in small children prior to recommendations for widespread use, as these devices are often miniature versions of adult equipment. Indirect video laryngoscopy has been previously shown to improve the rate of successful intubation by novice laryngoscopists in patients age >12 years33. However, in this study of anesthesiology trainees intubating younger children (age <2 years) with normal airway anatomy, TTSI was longer for Storz than for Direct. TTSI was nearly 10 seconds longer for GlideScope than Direct, although we did not find statistical significance for this difference. Tracheal intubation time using Direct or GlideScope by pediatric anesthesiologists who had performed >50 GlideScope intubations in infants were similar to what we found when intubations were performed by anesthesiology trainees10. These findings suggest the intergroup difference we found in time to intubate children <2 years of age was likely not based solely on longer TTSI when intubation is performed by anesthesiology trainees.

In addition to TTSI, it is reasonable to consider differences in first attempt success rates, total number of intubation attempts, and vital sign variability as important markers of laryngoscopist proficiency and device safety. We found no statistically significant difference in first attempt success rates or total number of intubation attempts between laryngoscope groups. The absence of vital sign variability and the minimal airway trauma observed during intubation are evidence that our trainees exercised appropriate caution during intubation attempts, even if measuring TTSI may have motivated them to intubate as rapidly as possible.

Table 1

Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Direct N = 19</th>
<th>GlideScope N = 22</th>
<th>Storz N = 22</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age (months); median (95% confidence interval)</td>
<td>8.1 (5.7-13.1)</td>
<td>7.6 (4.8-10.8)</td>
<td>8.5 (6.3-10.5)</td>
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<td>Gender (F; M)</td>
<td>6; 13</td>
<td>11; 11</td>
<td>9; 13</td>
<td>0.49</td>
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<td>ASA status (1; 2; 3; 4)</td>
<td>4; 9; 6; 0</td>
<td>6; 13; 3; 0</td>
<td>3; 12; 5; 2</td>
<td>0.37</td>
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<tr>
<td>Weight (kg); mean (95% confidence interval)</td>
<td>8.0 (6.9-9.2)</td>
<td>8.2 (7.1-9.3)</td>
<td>8.0 (6.0-9.1)</td>
<td>0.96</td>
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<tr>
<td>Weight for length percentile; median (95% confidence interval)</td>
<td>72.1 (47.6-84.0)</td>
<td>71.9 (49.2-84.6)</td>
<td>58.5 (31.3-76.7)</td>
<td>0.74</td>
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Continuous data were not normally distributed (Shapiro-Wilk p <0.05) and were expressed as median (95% confidence interval) and analyzed by Kruskal-Wallis except for weight, which is expressed as mean (95% confidence interval) and analyzed by ANOVA; categorical data were analysed by Chi square. There were no significant intergroup differences.
The reasons for our findings are likely multifactorial. The Storz fiberoptic camera is positioned close to the tip of the laryngoscope, providing a magnified and detailed image of the glottis, but a narrow angle of view. Oral secretions may obscure the fiberoptic camera lens and the narrow angle of view may lead to difficulty placing the tracheal tube after obtaining a view of the glottis. Laryngoscopists reported the least prior experience with Storz when compared to the other laryngoscopes in this study thus these trainees might have lacked the hand-eye coordination necessary for rapid Storz intubation. While this study was not specifically designed to investigate this difference, technical factors complicated intubation in over one-third of video laryngoscope tracheal intubations compared to approximately one-fifth of Direct tracheal intubations. Several Storz required more than one intubation attempt due to inability to maneuver the tracheal tube past the vocal cords despite a grade I or II glottic view (n=6), or oral secretions obscuring the glottic view (n=2). The tracheal tube could not be maneuvered past the glottis in 3 GlideScope patients, but oral secretions complicated no GlideScope intubations. Use of the GlideScope Cobalt video laryngoscope size 2 blade has been reported to be occasionally complicated by a reflected image of the vocal cords. Such an optical illusion could lead the laryngoscopist to advance the tracheal tube towards a false view of the glottis, resulting in multiple intubation attempts.

Multiple studies of indirect video laryngoscopes in the pediatric population derive their data from manikin evaluations that our results suggest may not accurately predict human results. In our study, intergroup differences in manikin intubation times, while statistically significant, were only a few seconds and not clinically significant. Trainees were rapidly able to intubate the manikin but TTSI in the clinical setting was significantly longer (Table 2). This suggests that manikin training may not be equivalent to in vivo training and thus perhaps should be seen as a precursor to, but not a replacement for clinical experience in

<table>
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<tr>
<th>Table 2</th>
<th>Tracheal intubation times</th>
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</thead>
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<tr>
<td></td>
<td>Direct N = 19</td>
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<tr>
<td>Time to successful tracheal intubation (seconds)</td>
<td>21.5(17.0-34.3)</td>
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<td>Differences</td>
<td>Direct to Storz</td>
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<td></td>
<td>Direct to GlideScope</td>
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<td>Storz to GlideScope</td>
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<td>Time to intubate manikin seconds</td>
<td>6.8(5.2-8.1)</td>
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<td>Direct to GlideScope</td>
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<td></td>
<td>Storz to GlideScope</td>
</tr>
<tr>
<td>Change in time manikin to clinical seconds</td>
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<td>Direct to GlideScope</td>
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<tr>
<td></td>
<td>Storz to GlideScope</td>
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</table>

Intergroup comparisons of tracheal intubation times when performed by anesthesiology trainees in an infant airway manikin or in children <2 years. Data were not normally distributed (Shapiro-Wilk all p <0.05) so are expressed as median (95% confidence interval) and were analyzed by Kruskal-Wallis; differences in medians were analyzed using Hodges Lehman assuming data symmetry. Total time to successful tracheal intubation in the clinical setting was longer in Storz than in Direct. Tracheal intubation time increased from the manikin to clinical setting within all groups (all p <0.0001); this difference was larger in Storz than Direct.
Several factors limit generalizing the findings of this study. Trainees reported more prior intubation experience using DL than the other laryngoscopes. This is expected since we studied trainees who had completed at least one year of anesthesiology residency. Because of this we were unable to equalize prior clinical experience with DL to that with the other laryngoscopes. We studied anesthesiology trainees, leading to a limited number of laryngoscopists at different stages of training. This limits assessment of any learning effect that may have occurred, since none of the 22 individuals studied performed more than 3 intubations with one type of laryngoscope within the study. We did not obtain a measure of neuromuscular relaxation such as train of four prior to intubation as this is not part of our standard practice in children <2 years old. As no intubation was associated with coughing or patient movement it is unlikely that a difference in neuromuscular blockade contributed to differences in time to successful intubation.

Conclusion

Mastery of multiple intubation techniques is a key goal of anesthesiology training. Anesthesiology trainees completed manikin tracheal intubation rapidly with all laryngoscopes studied, but required a clinically significant longer time to tracheally intubate children <2 years. Our findings suggest that adequate in vivo training should be included to facilitate achieving expert level with device-specific techniques including the required hand-eye coordination needed to pass the endotracheal tube beyond the vocal cords.
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PERIPHERAL INTRAVENOUS CATHETER PROBLEMS IN INFANTS AND CHILDREN PRESENTING FOR ANESTHESIA AND SURGERY

PAUL A. TRIPÍ*, SUSAN THOMAS**, ANNA CLEBONE***, MARK M. GOLDFINGER*** AND JOSEPH D. TOBIAS****

Background: Anesthesia providers frequently rely upon in-situ peripheral intravenous catheters (IVs) during the perioperative care of pediatric patients. IV dysfunction can result in complications including inability to administer medications for resuscitation, extravasation of tissue-toxic medications, and incomplete induction of anesthesia. This study was performed to prospectively assess the frequency of IV dysfunction in children presenting for anesthesia care.

Methods: A survey of IV patency and integrity was completed in patients less than 18 years of age arriving at the preoperative holding area for anesthesia evaluation. Prior to the induction of anesthesia, an anesthesiologist examined the IV for patency and evidence of infiltration. Demographic information, catheter site and size, condition of skin, elapsed time since insertion, and hospital site of catheter insertion were recorded.

Results: Over a 14-month period, 108 IVs were evaluated in 106 patients. One or more problems were identified with 35% of the IVs. Problems included erythema or pain to palpation at insertion site (29%), difficulty with injection of saline (45%), pain on injection of saline (50%), infiltrate at insertion site (13%), no flow or poor flow to gravity (42%), and kinked catheter (11%). The frequency of IV dysfunction was higher in infants (50%), with 24 gauge catheters (59%), with lower extremity IVs (50%), and with IVs in place for more than 3 days (75%).

Conclusions: Approximately one-third of pre-existing IVs were dysfunctional in children presenting for anesthesia and surgery. Inspection for the integrity of the IV should occur prior to and during use, and a plan should be in place for readily replacing the IV in cases of dysfunction or for using an alternative route for the induction of anesthesia.

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Conflicts of interest: None of the authors have any conflicts of interest.
Introduction

Anesthesiologists may rely upon a pre-existing peripheral intravenous catheter (IVs) in the perioperative period. Dysfunction of these catheters can result in complications including pain on injection, the inability to administer medications for resuscitation, incomplete induction of anesthesia, and extravasation of medications and fluids leading to tissue injury. Along with compromising patient safety, complications relating to IVs have an economic impact. In the United States, IV dysfunction which is not promptly rectified may be considered a hospital acquired condition and cause for Medicare nonpayment under future Department of Health and Human Services directives.

Pediatric patients may be particularly vulnerable to IV dysfunction due to the fragility of their vasculature, smaller veins, smaller size of the IV catheters, and increased subcutaneous tissue. Although there are no data on the frequency of IV-related dysfunction in infants and children in the perioperative setting, other clinical settings have been examined. In a large population of children receiving intravenous infusions, Brown et al. reported an 11% incidence of extravasation and a 0.25% incidence of significant skin and tissue damage with sloughing. In a pediatric intensive care unit (PICU), the frequency of phlebitis was 13% and extravasation was 28%. The incidence has been noted to be particularly high in younger patients especially neonates with an incidence of IV complications, including infiltrates, as high as 80%. Devastating complications have occurred, particularly in neonates, resulting in compartment syndrome, full thickness injury requiring skin grafting, and associated mortality. Numerous medications that may be administered in the perioperative setting are associated with extravasation morbidities, including vasoactive medications (epinephrine, vasopressin), hyperosmolar infusions (calcium chloride, sodium bicarbonate, total peripheral nutrition, mannitol), and medications containing propylene glycol (etomidate, diazepam). Additional studies have demonstrated that the frequency of IV complications is increased in infants and patients with long in-situ catheter times.

The current study prospectively evaluated the incidence of IV catheter dysfunction and occlusion in pediatric patients presenting for anesthesia and attempted to determine risk factors for such problems.

Methods

After institutional review board approval, a survey of IV patency and integrity was completed in patients less than 18 years of age arriving in the preoperative holding area for anesthesia evaluation prior to their surgical procedure. The inclusion criterion was that a patient had one or more IV catheters in place. Data collected included patient demographics, as well as IV function, site condition, and problems related to its use during anesthesia. Patient demographic information included age, weight, and gender. Description of the IV included catheter gauge, anatomic location of the insertion site, presence or absence of kinking, hospital site of catheter placement, and elapsed time since insertion. An anesthesiologist evaluated the IV function by examining the flow of an intravenous solution delivered by gravity and by flushing the IV with 0.1 mL/kg of normal saline (NS). Flow was recorded as good versus poor/absent. Injection was recorded as easy versus impossible/difficult, and the patient’s response to injection was recorded as pain/response versus no pain/no response. The skin was evaluated for presence or absence of erythema, edema, and pain to palpation. Finally, the anesthesiologist noted whether there were problems related to the use of the IV during anesthesia. The evaluation and flushing of the IV was performed by the anesthesiologist assigned to the case. All of the data was collected and recorded by a research associated not involved with the care of the patient. Data were analyzed and descriptive statistics generated using the program, Statistical Package for the Social Sciences (SPSS, Chicago, IL).

Results

The study cohort included 108 IVs that were evaluated in 106 patients over a 14-month period. The distribution of the patients’ ages, location of the catheters, size (gauge of the catheters, the hospital location where they were placed, and their duration of use are listed in table 1. One or more problems were identified with 38 of the IVs (35% of total IVs). In
these 38 IVs, problems included erythema or pain to palpation at insertion site (11), difficulty with injection of NS (17), pain with injection of NS (19), infiltrate at insertion site (5), poor flow or no flow to gravity (16), and kinked catheter (4).

The frequency of IV dysfunction, which was considered to be present when one or more of the problems was identified, was evaluated against several variables. Findings included a frequency of dysfunction that was 50% (9/18) in infants, 59% (13/22) in 24 gauge catheters, 50% (5/10) in lower extremity IVs, and 75% (9/12) in IVs greater than three days old. The anesthesiologist used 68 of the 70 IVs scored as having no problems and 19 of the 38 IVs scored as dysfunctional. In the group in which the IV catheter was judged as dysfunctional, in some patients, the problems were able to be resolved by taking down the dressing, reapplying tape or flushing the IV catheter. No complications occurred with use in either group.

Discussion

Hospitalized children requiring surgery frequently present to the preoperative holding area with one or more IVs in place. Anesthesiologists often rely upon these IVs for the induction of anesthesia and the administration of fluids intraoperatively. In this study, approximately one-third of in-situ IVs were found to be dysfunctional, with evidence of inflammation at the insertion site, obstruction to flow, or both.

IV failure can lead to serious consequences. Incomplete induction of anesthesia in a patient with a “full-stomach” may lead to gastric insufflation, delays in tracheal intubation, and aspiration of gastric contents. Infiltration of the IV site can lead to tissue injury resulting from direct chemical effects of medications (e.g. vasoactive substances and concentrated electrolytes) or by increased local pressure. The extent of damage may be more severe in infants who have decreased peripheral circulation, lower mean arterial pressure, a small body mass, and may not be able to communicate discomfort effectively. Extravasation that occurs in the perioperative period may be undetected as the extremities are under surgical drapes and may have devastating consequences, including skin necrosis requiring surgical debridement and skin grafting. Finally, the inability to administer medications for resuscitation can result in critical delays in correcting hemodynamic instability and restoring perfusion to vital organs.

Despite these significant potential complications of a dysfunctional IV, placement of a new IV prior to the induction of anesthesia in an awake child can be difficult for a variety of reasons. Children are afraid of needles and will not cooperate with insertion. Their lack of cooperation may disrupt the preoperative holding area environment, causing anxiety in other children waiting for surgery. Insertion of the IV may be technically difficult, especially in infants or children with chronic illnesses with prolonged hospital stays. Repeated attempts may make the post-induction insertion of an IV more difficult due to elimination of many potential sites. Such factors often compel an anesthesiologist to utilize an in-situ IV unless it is entirely non-functional. In our study, 50% of the IVs scored as dysfunctional were utilized by the anesthesiologist without complication, but only after

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (total cohort = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (years)</td>
<td></td>
</tr>
<tr>
<td>Infants (0-1)</td>
<td>18 (9)</td>
</tr>
<tr>
<td>Preschoolers (1-5)</td>
<td>31 (7)</td>
</tr>
<tr>
<td>School age (5-12)</td>
<td>34 (13)</td>
</tr>
<tr>
<td>Teenagers (more than 12)</td>
<td>25 (9)</td>
</tr>
<tr>
<td>Location of IV catheters</td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>45 (17)</td>
</tr>
<tr>
<td>Forearm</td>
<td>24 (7)</td>
</tr>
<tr>
<td>Antecubital fossa</td>
<td>29 (9)</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Catheter size</td>
<td></td>
</tr>
<tr>
<td>24 gauge</td>
<td>22 (13)</td>
</tr>
<tr>
<td>22 gauge</td>
<td>54 (13)</td>
</tr>
<tr>
<td>20 gauge</td>
<td>24 (10)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>8</td>
</tr>
<tr>
<td>Location placed</td>
<td></td>
</tr>
<tr>
<td>Inpatient ward</td>
<td>59 (22)</td>
</tr>
<tr>
<td>ICU</td>
<td>4 (2)</td>
</tr>
<tr>
<td>ED</td>
<td>20 (6)</td>
</tr>
<tr>
<td>Outside hospital/other</td>
<td>25 (8)</td>
</tr>
<tr>
<td>Catheter age</td>
<td></td>
</tr>
<tr>
<td>Less than 1 day</td>
<td>64 (19)</td>
</tr>
<tr>
<td>1-2 days</td>
<td>20 (6)</td>
</tr>
<tr>
<td>2-3 days</td>
<td>12 (4)</td>
</tr>
<tr>
<td>More than 3 days</td>
<td>12 (9)</td>
</tr>
</tbody>
</table>

The total number of IVs is listed followed by the number that were judged as dysfunctional in parenthesis.

ED = emergency department; ICU = intensive care unit
correcting the obstruction to flow or ascertaining that fluid and medications were properly reaching the circulation. When necessary, a new IV was then placed after the induction of general anesthesia.

This study identified factors that were associated with a higher frequency of IV dysfunction in children presenting for anesthesia and surgery. The frequency of dysfunction was ≥ 50% in younger patients (less than 1 year of age), with smaller catheters (24 gauge), when the IV was in the lower extremity, and when the IV was in place for more than 3 days. The potential for a high incidence of a dysfunctional IV in younger children and infants is particularly worrisome as this population may be challenging when it comes to vascular access.

Anesthesiologists should be aware that pre-existing IVs in hospitalized children presenting for surgery are frequently dysfunctional. As noted in our study, it may be feasible to resolve problems of a dysfunctional IV catheter with simple maneuvers such as removing the dressing, eliminating a kink in the IV catheter or simply administering a normal saline flush. However, if such maneuvers fail, the IV catheter should not be used for anesthetic care. The frequency of dysfunction may be particularly high in infants, who are also more susceptible to injury with infiltration and extravasation of medications. The correct functioning of the IV should be established prior to its use. Inadequate free flowing of the IV or problems with flushing the IV with saline may be addressed and the IV used for anesthetic care once function has been restored. However, dysfunctional IVs should be used with caution or not at all and the site monitored throughout the case.

References

COMPARISON OF INTRAOPERATIVE KETAMINE VS. FENTANYL USE DECREASES POSTOPERATIVE OPIOID REQUIREMENTS IN TRAUMA PATIENTS UNDERGOING CERVICAL SPINE SURGERY

AVIVA C. BERKOWITZ*, ARYEH M. GINSBURG**, RAYMOND M. PESSO*, GEORGE L.D. ANGUS***, AMIEE KANG**** AND DOV B. GINSBURG*****

Background: Postoperative airway compromise following cervical spine surgery is a potentially serious adverse event. Residual effects of anesthesia and perioperative opioids that can cause both sedation and respiratory depression further increase this risk. Ketamine is an N-methyl-d-aspartate (NMDA) receptor antagonist that provides potent analgesia without noticeable respiratory depression. We investigated whether intraoperative ketamine administration could decrease perioperative opioid requirements in trauma patients undergoing cervical spine surgery.

Methods: We retrospectively reviewed anesthesia records identifying cervical spine surgeries performed between March 2014 and February 2015. All patients received a balanced anesthetic technique utilizing sevoflurane 0.5 minimum alveolar concentration (MAC) and propofol infusion (50-100 mcg/kg/min). For intraoperative analgesia, one group of patients received ketamine (N=25) and a second group received fentanyl (N=27). Cumulative opioid doses in the recovery room and until 24 hours postoperatively were recorded.

Results: Fewer patients in the ketamine group (11/25 [44%] vs. 20/27 [74%], respectively; p = 0.03) required analgesics in the recovery room. Additionally, the total cumulative opioid requirements in the ketamine group decreased postoperatively at both 3 and 6 hours (p = 0.01).

Conclusion: Ketamine use during cervical spine surgery decreased opioid requirements in both the recovery room and in the first 6 hours postoperatively. This may have the potential to minimize opioid induced respiratory depression in a population at increased risk of airway complications related to the surgical procedure.

Keywords: Ketamine, Opioids, Postoperative Analgesia, Fentanyl, Cervical Spine Surgery

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Introduction

Cervical spine surgery is associated with the potential for postoperative airway compromise due to laryngopharyngeal edema, hematoma, and abscess formation1-6. Patients are especially vulnerable to this highly dangerous complication in the acute postoperative period due to the residual effects of anesthesia, as well as due to perioperative opioid use, which can cause both sedation and respiratory depression7-9. Ketamine is an N-methyl-d-aspartate (NMDA) receptor antagonist that has potent analgesic properties even at small sub-anesthetic doses. It is postulated that by blocking the NMDA receptor, ketamine decreases nociceptive pain pathways and may prevent the development of hyperalgesia as well as opioid tolerance, which is a common problem with this class of medications10. Ketamine also has a significant benefit over other analgesics, such as opioids, in that it does not cause respiratory depression11. In contrast, the group of drugs that most significantly depresses ventilation is the opioids, which include both natural derivatives (opiates such as morphine) and semi-synthetic opioids (such as fentanyl, remifentanil, oxycodone, and methadone)8.

Several clinical studies have been conducted to test whether intraoperative ketamine administration can minimize perioperative opioid requirements in a variety of surgical procedures and have produced conflicting results12-19. However, the consequence of intraoperative use of ketamine as the primary analgesic during cervical spine surgery is largely unknown, and patients may stand to benefit much from elucidation of this issue. We hypothesized that intraoperative ketamine administration can minimize perioperative opioid requirements while still providing effective analgesia, thereby minimizing the risk of airway compromise in a class of patients who are already at particularly increased risk of this complication.

Materials and Methods

After obtaining institutional review board approval, we retrospectively reviewed anesthesia records identifying cervical spine surgeries in trauma patients performed between March 2014 and February 2015. These cases were cross-referenced with the electronic medical records of our institution to determine opioid consumption in the postoperative period.

Basic patient information including age, height, weight, body mass index (BMI), sex, American Society of Anesthesiology Health Classification Status (ASA status), presence of diabetes and hypertension, as well as operative and perioperative data including number of spinal levels, repair with or without instrumentation, surgical duration, hospital length of stay, and incidence of postoperative nausea or postoperative mechanical ventilation were collected for analysis. Patients were divided into two groups based on those that exclusively received either intraoperative ketamine or fentanyl.

All patients had received a relatively standardized anesthesia induction that included 2 mg midazolam, either 0.5 mg/kg ketamine (ketamine group) or approximately 1.5 mcg/kg fentanyl (fentanyl group), 2 mg/kg propofol, and neuromuscular blocking agents (typically succinylcholine or cisatracurium) to facilitate intubation and surgical exposure as requested by the surgeon. After induction, all patients received a balanced anesthetic technique for anesthesia maintenance utilizing sevoflurane 0.5 MAC and propofol infusion (50-100 mcg/kg/min). Patients who received ketamine (N=25) were placed on a continuous intraoperative infusion of 10 mcg/kg/min (ketamine group) and the patients who received fentanyl (N=27) were placed on a continuous infusion of approximately 2 mcg/kg/hr (fentanyl group). All anesthesia providers were asked by the surgeon to administer 10 mg of dexamethasone intravenously upon anesthesia induction to all patients. All patients in the study had intraoperative neuromonitoring analyzing somatosensory evoked potentials (SSEPs) by a trained neurophysiologist. The cumulative doses of opioids in the recovery room and up to 24 hours postoperatively were recorded.

Statistical Analysis

Descriptive statistics were performed on all variables in this study. Categorical variables were described as frequency distributions and percentages of the study population. Continuous variables were
summarized as means ± standard deviations. Chi-square test and Fisher exact test were used to compare categorical binary outcomes when appropriate. The total cumulative morphine equivalents at different time intervals were compared using an unpaired Student t test. A p-value of <0.05 was considered significant. SAS version 9.4 (SAS Institute Inc. Cary, NC) was used as the statistical tool in this study.

Results

Fifty-two patients undergoing cervical spine surgery were included in this study. Patient characteristics were similar in both the ketamine and fentanyl groups (Table 1), and there was no significant difference found between the two groups in terms of the number of spine levels involved, duration of surgery, and hospital length of stay (Table 2).

In evaluating the opioid requirements in the recovery room (post anesthesia care unit [PACU]; Table 3) for each patient, we found that there were significantly fewer patients in the ketamine group than in the fentanyl group who required pain medication (44% vs. 74%, p = 0.03). Similarly, the average cumulative morphine consumption in the PACU was lower in the ketamine group (3.4 mg ± 4.6 mg vs. 8.6 mg ± 7.1 mg, p = 0.01).

We also recorded the average cumulative morphine requirements of each patient during the first 24 hours after surgery (Table 4). The average cumulative morphine consumption was significantly decreased in the ketamine group at 3 hours (5.8 mg ± 5.8 mg vs. 11.0 mg ± 8.5 mg, p = 0.01) and at 6 hours (8.9 mg ± 7.1 mg vs. 17.4 mg ± 8.3 mg, p = 0.01). The significant difference between the two groups did not appear at 24 hours.

Differences in the incidence of post-operative nausea and/or vomiting (PONV) and the number

<table>
<thead>
<tr>
<th>Table 1: Patient Characteristics by Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ketamine</strong></td>
</tr>
<tr>
<td>Patients, No.</td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Female, %</td>
</tr>
<tr>
<td>ASA Status</td>
</tr>
<tr>
<td>I-II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>Comorbidity</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or as a percentage.

<table>
<thead>
<tr>
<th>Table 2: Operative and Perioperative Details by Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spinal Levels, No. %</strong></td>
</tr>
<tr>
<td>One</td>
</tr>
<tr>
<td>Two</td>
</tr>
<tr>
<td>Duration of Surgery, min</td>
</tr>
<tr>
<td>Hospital LOS, days</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or as a percentage. LOS = length of stay.

<table>
<thead>
<tr>
<th>Table 3: Analgesic Requirements in the Post-anesthesia Care Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients Requiring Analgesia, %</strong></td>
</tr>
<tr>
<td>11 (44.0%)</td>
</tr>
</tbody>
</table>

Data are presented as a percentage or as mean ± SD. PACU = post-anesthesia care unit.

<table>
<thead>
<tr>
<th>Table 4: Postoperative Analgesic Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cumulative Morphine, mg</strong></td>
</tr>
<tr>
<td>3 hr</td>
</tr>
<tr>
<td>6 hr</td>
</tr>
<tr>
<td>24 hr</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.
of patients requiring post-operative mechanical ventilation were also evaluated. No significant difference was found in either parameter up to 24 hours after surgery (Table 5).

### Table 5

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Ketamine</th>
<th>Fentanyl</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV</td>
<td>1 (4%)</td>
<td>3 (11.1%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Post-operative Mechanical Ventilation</td>
<td>0 (0%)</td>
<td>1 (3.7%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Data are presented as number and percentages.

PONV = post-operative nausea and/or vomiting.

### Discussion

The intraoperative use of ketamine as the primary analgesic in trauma patients undergoing cervical spine surgery and its effects on postoperative opioid requirement has not been previously studied. We have demonstrated that intraoperative ketamine use can reduce both the number of patients requiring pain medication during recovery in the PACU, as well as decrease the cumulative morphine requirements up to 6 hours following surgery (Tables 3 and 4).

The benefit of an intraoperative opioid sparing anesthetic technique is especially valuable because due to the increasing use of intraoperative neuromonitoring to monitor spinal cord function, patients often receive larger than typical total opioid dosages. Anesthetic agents typically employed during surgery can affect the ability to effectively monitor and record signal responses. In particular, inhalational anesthetic agents are known to have a significant effect on the neuromonitoring signal responses\(^{20}\). In contrast, intravenous anesthetic agents such as propofol, ketamine, and opioids have a significantly lesser effect\(^{21}\). A typical balanced anesthetic technique for spine surgery will often incorporate infusions of propofol and opioids, resulting in larger than typical total intraoperative opioid administration. As mentioned previously, all patients in this study had intraoperative neuromonitoring recordings (SSEPs) throughout the surgical procedure.

It is well known that opioids are the class of drugs that most significantly depresses ventilation through their actions at the μ-opioid receptors on respiratory neurons in the brainstem [8]. Opioid-induced respiratory depression is potentially life threatening and has been the cause of substantial morbidity and mortality\(^{22-23}\). It is of clinical importance to note that patients with risk of airway obstruction, such as obstructive sleep apnea may be more sensitive to the respiratory depressant effect of opioids and thus should have their doses adjusted accordingly\(^{24}\). In light of the above, the use of intraoperative ketamine in patients undergoing cervical spine surgery to minimize perioperative opioid requirements while still providing effective analgesia is particularly beneficial. This is of particular clinical importance in this class of patients, as they are already at increased risk of airway compromise due to surgical manipulation of the cervical spine.

Previous studies have shown that the use of intraoperative ketamine not only decreases pain acutely but has also demonstrated a reduction in pain intensity at 6 weeks\(^{25-26}\). In our study, ketamine use demonstrated a significant decrease of cumulative opioid requirements up to 6 hours, but there did not appear to be any significant decrease at 24 hours. This may be attributed to our smaller sample size, and requires further evaluation. Based on the findings of the present study, the next logical step is to systematically evaluate the use of ketamine as a primary analgesic in patients undergoing surgery where opioids should be minimized, such as patients who may be susceptible specifically to the adverse effects of opioids and those who are opioid tolerant or are at risk of potential airway compromise either due to inherent patient characteristics or surgical manipulation. Among these, ketamine may be particularly beneficial in chronic pain patients who consume large amounts of opioid medications and who may be somewhat resistant to the analgesic effects of opioids in the acute postoperative setting.

The benefit of intraoperative low dose ketamine in our study was without an apparent increase in side effects such as hallucinations, PONV, and need for postoperative mechanical ventilation (Table 5). Although the literature has mentioned cases of
hallucinations following ketamine administration, the use of hypnotic doses of propofol has been shown to block ketamine-induced hallucinations\textsuperscript{27}. One patient in the fentanyl group did require postoperative mechanical ventilation as they did not meet extubation criteria, which was presumed to be due to opioid induced respiratory depression and sedation. Of note, this patient did not receive any further opioids for several hours until they were safely extubated. For these reasons, low dose ketamine administration can be considered as a useful primary analgesic for patients undergoing surgery with potential for airway compromise.

The findings of this study substantially add to the existing body of literature regarding the efficacy of intraoperative ketamine in comparison to opioid administration during cervical spine surgery with the goal of improving patient safety and satisfaction. A limitation to our study was that it relied on the use of retrospective data collection and analysis and we were not able to study if ketamine specifically caused a reduction in respiratory depression. Future prospective studies will hopefully determine if intraoperative ketamine administration can reduce opioid induced respiratory depression and airway compromise in patients undergoing cervical spine surgery.
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COMBINED BLOCK OF THE FEMORAL AND LATERAL FEMORAL CUTANEOUS NERVES UNDER ULTRASOUND FOR POST-OPERATIVE ANALGESIA IN PATIENTS UNDERGOING HIP SURGERY: A DOUBLE BLIND RANDOMIZED TRIAL

MAROUN BADWI GHABACH¹, JAMIL MARWAN ELMAWIEH², MAY SEMAAN MATTAN³ AND MAY RADY HELOU⁴

Background: Inadequate pain management of post-operative pain of patients undergoing hip surgery can result in morbidity and mortality complications. Anatomically, pain resulted from the incision site innervation (Lateral femoral cutaneous nerve) and the hip joint innervation mainly the femoral nerve. Adding femoral nerve blockade to the multimodal regimen for postoperative pain control after hip surgery has been described.

Methods: all 31 patients included in the study received preoperatively combined FN and LFCN block with Normal Saline 0, 9% (group I) or bupivacaine 0.5% (group II) randomly by using a previously generated continuous randomization list kept in a closed envelope. Pain control regimen consisted of Perfalgan 1g IV every 6 hours systematically and Dolosal 50 mg IM every 6 hours if needed (i.e. VAS > 4). Pain level was measured by using Visual Analogue Scale (VAS) for the first 24 hours.Time to the first request of analgesia and the total dose of dolosal were calculated.

Results: The number of patients who requested narcotics was significantly higher in group I (8) than group II (3), P=0,044; the total dose of dolosal used was significantly higher in group I (50 mg) than group II (9,375mg), P=0,0058. Time to the first request for analgesia was significantly lower in group I (6hrs ± 5,12) as compared to Group II (21.3 hrs ± 23.1), P =0,043.

Conclusion: In conclusion, FN and LFCN block when added to the standard regimen for postoperative pain management after hip surgery had a benefit in decreasing pain scores as well as opioid consumption.

Keywords: Femoral Nerve, Lateral Femoral Cutaneous Nerve, Nerve Block, Postoperative Analgesia, Ultrasound.

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Conflict of interest: None of the authors declare any personal, professional or business conflict of interest.
Introduction

Post-operative pain of hip surgery is a significant issue; it affects early mobilization, joint range of motion and length of hospital stay. An inadequate pain management can lead to secondary medical morbidities as venous thromboembolism and cardiac events.

Post-operative analgesia, depending on the institution regimen for pain treatment, is either parenteral opioids, epidural or multimodal analgesia with or without peripheral nerve block. Opioids provide efficient pain relief but are associated with serious side effects especially in the elderly including respiratory depression, sedation, hallucination, nausea, bladder dysfunction and pruritus. Epidural analgesia is efficient but also had side effects including hypotension, bladder dysfunction and epidural hematoma. Femoral nerve, lumbar plexus and fascia iliaca blocks had been demonstrated to improve pain scores and to reduce morphine consumption in the post-operative period. Posterior lumbar plexus block is more effective than femoral nerve block but its use is limited because of more serious complications as epidural hematoma, total spinal, renal puncture and others. The clinical success rate of fascia iliaca block is variable due to highly variable anatomical course of the lateral femoral cutaneous nerve besides the need of high volume of local anesthetic.

In our study we tested the hypothesis that a combined block of the femoral nerve (FN) and lateral femoral cutaneous nerve (LFCN) under ultrasound preoperatively has a positive impact on the post-operative analgesia. The end-point was the decrease in the percentage of patient who rescue narcotics in the first 24 hours period post-operatively and the total dose of narcotics needed.

Patients and Methods

The clinical study was performed after receiving institutional review board and informed consent from the patients. Thirty one consecutive patients scheduled for unilateral hip arthroplasty or osteosynthesis between September 1st and December 30th 2014, were included in the study. Inclusion criteria were age above 18 years, ASA I-III, and weight above 50 kg. Exclusion criteria were peripheral neuropathy, communication failure, bleeding disorders, allergy to local anesthetics, and use of chronic pain medications.

The surgical procedure was performed with a standardized spinal anesthesia regimen. The patients presented to the operating room without premedication. The monitoring consisted of noninvasive blood pressure measurements, electrocardiography, pulse oximetry, and qualitative ETCO2. An infusion of Ringer’s solution was started, O2 was supplied via a face mask (6L/min) and 5 µg sufentanil (Janssen-Cilag, Switzerland) was given intravenously. All patients received combined FN and LFCN block with Normal Saline 0, 9% (group I) or bupivacaine 0.5% (group II) randomly by using a previously generated continuous randomization list kept in a closed envelope. This envelope handed to an anesthesia technician not involved in the study who prepared identical syringes either containing 20 mL of NaCl 0.9% or 20 mL of bupivacaine (Astra-Zeneca, USA) 0.5% according to the randomization number on the list. In the supine position and at the side of surgery, the block area was disinfected. With a linear array probe (4-12 MHZ, GE LOGIC e ultrasound), the FN block was performed at the inguinal cease level, the LFCN blocked immediately inferior to the anterior superior iliac spine. 15 mL of the solution (bupivacaine or NaCl 0.9%) were injected around the FN, while 5mL around the LFCN. Standard spinal anesthesia was then performed to all patients in the sitting position by intrathecal injection of 13 mg of heavy bupivacaine 0.5% at the L3-L4 or L4-L5 level. Postoperatively, pain level was measured by using Visual Analogue Scale (VAS), no pain = 0 and worst pain = 10, at rest and at lower limb spontaneous movement of the operated side every six hours after spinal anesthesia has resolved (spontaneous lower limb movement in the recovery room) for the first 24 hours (H0, H6, H12, H18, H24). Pain control regimen consisted of Perfalgan 1g IV every 6 hours systematically and Dolosal 50 mg IM every 6 hours if needed (i.e. VAS > 4). Time to the first request of analgesia, and the total dose of dolosal used for every patient in the first 24 hours postoperatively were calculated. Demographic data were collected for all patients including age, sex, physical status classification according to the American Society of Anesthesiologists (ASA), type of
surgery and operative time.

Main postoperative anesthesia related complications including nausea, vomiting and drowsiness were measured.

Parametric variables were described as ± SD, qualitative variables were described as number (percentage) and as median range. Student’s t-test, chi square test or Fisher exact test was used as appropriate to compare the two groups. P < 0.05 was considered statistically significant.

Results

Demographic according to the patient age, sex, ASA physical status, operating time and type of surgery were not significantly different between the two groups (Table 1), as well as postoperative anesthesia related complications (Table 2).

In the first 24 hours postoperatively: The number of patients who requested narcotics was significantly higher in group I (8/15) than group II (3/16), P=0.044;

| Table 1 | Demographic characteristics of patients and type of surgery in Group I (Normal Saline) and Group II (Femoral nerve and Lateral Femoral cutaneous Nerve Block). |
|-----------------|-----------------|-----------------|-----------------|
| Age, y, mean ± SD | Normal Saline Group I, n=15 | 77.5 ±11 | 75 ±13.5 | 0.28 (NS) |
| Sex, male/female | 4/11 | 8/8 | 0.18 (NS) |
| ASA physical Status, number of patients, I/II/III | 1/5/9 | 3/7/6 | 0.38 (NS) |
| Operation Time in min, (mean ± SD) | 107.33 ± 28.4 | 118.437 ± 28.7 | 0.288 (NS) |
| Arthrosis/fracture | 1/14 | 2/14 | 0.58 (NS) |

Abbreviations: y = years, m = minutes, NS = Non-Significant.

| Table 2 | Comparison of anesthesia related complications in the 2 groups. |
|-----------------|-----------------|-----------------|-----------------|
| | Normal Saline Group I, n=15 | FN+LFCN Block Group II, n=16 | P value |
| Nausea | 2 | 3 | 0.68 (NS) |
| Vomiting | 1 | 0 | 0.29 (NS) |
| Drowsiness | 2 | 1 | 0.5 (NS) |

Abbreviations: NS = Non-Significant.

| Table 3 | Dolosal consumption and time to first request for analgesia in the 2 groups. |
|-----------------|-----------------|-----------------|-----------------|
| | Normal Saline Group I, n=15 | FN+LFCN Block Group II, n=16 | P value |
| Nbr of patients who requested recue dolosal in first 48 hrs post-op | 8 (53%) | 3 (18.75%) | 0.044 (S) |
| Dolosal consumption in 48 hours, mg, average | 50 mg ± 14.46 | 9.375 mg ± 5.0 | 0.0058 (S) |
| Time to the first request for analgesia when needed | 6 hrs ± 5.127 | 21.3 hrs ± 13.1 | 0.043 (S) |

Abbreviation: hrs=hours, S=Significant.
The total dose of dolosal used was significantly higher in group I (50 mg) than group II (9,375 mg), P=0.0058. Time to the first request for analgesia was significantly lower in group I (6hrs ± 5.12) as compared to Group II (21.3 hrs ± 23.1), P =0.043. (Table 3).

The visual analogue pain score in Group I (Normal Saline) at rest and at movement of the operated lower limb shows a sea-saw shape (Figure I). In group II (FN+LFCN Block) the visual analogue pain score graphs at rest and at movement of the operated limb shows a stable level of analgesia. (Figure I).

**Discussion**

Pain after hip surgery consists of pain located at the site of the incision, the femoral shaft and pain due to a reflexogenic contracture of the quadriceps musculature\(^1\). Patients characterize this pain as moderate to severe during the first day after surgery. Improvement in management of this pain had a major impact on morbidity and mortality\(^3,11\). Anatomically, the hip joint is innervated by several nerves, including the femoral nerve, the obturator nerve, the sciatic nerve and the superior gluteal nerve; also to note that the incisional site is innervated by the lateral femoral cutaneous nerve. As a result, performing peripheral nerve blockades for anaesthesia in hip surgery is complex\(^12,13\). However, femoral nerve blockade alone have been shown to reduce postoperative pain and morphine consumption in previous studies\(^14,15\). Its blockade had attracted interest based on the fact of the high success rate, its simplicity and the low risk of complications. The advantage of LFCN blockade to cover the surgical site-incision inducing pain added to the FN block blockade has not been examined before in a prospective randomized study.

One retrospective study, reported by Vanderbroek et al with multiple limitations\(^16\) concluded that patients undergoing primary hip arthroplasty had lower pain scores and consequently less opioid use when they have received FN and LFCN block added to the standard protocol for postoperative pain control regimen.

In our double blind randomized study, a combined single shot FN block (15 mL of bupivacaine 0.5%) with LFCN block (5 ml of bupivacaine 0.5 %) was added to a standard protocol of postoperative analgesia

---

**Fig. 1**

*Visual analogue pain score in Group I (Normal Saline) and Group II (Femoral nerve and Lateral Femoral cutaneous Nerve Block) in the first 24 hours postoperatively at rest and on moving the operated lower limb.*

Abbreviation: VAS=Visual Analogue Score.
(Perfalgan 1g IV every 6 hours systematically and Dolosal 50 mg IM every 6 hours if needed). It resulted in a significant decrease in the number of patients who requested narcotics (dolosal) by 65% (8 patients versus 3) as well as the consumption of dolosal in the first 24 hours postoperatively by 80% (50mg versus 9,375mg) as compared to the control group. The time to the first request for a rescue narcotic is significantly prolonged in block group (6hrs versus 21 hrs) as compared to the control group. The results demonstrated the efficacy of FN and LFCN blockade in improving postoperative analgesia.

The VAS pain score was evaluated at rest and at movement of the surgical lower limb. At rest, patients of block group had a stable VAS score over the time, in contrast to the control group who showed a sea-saw profile due to the need for rescue analgesia over the time. This demonstrated the efficacy of LFCN blockade in providing postoperative analgesia of the incisional area.

In our standard protocol, the single shot regimen and not the continuous nerve block with catheter, was adopted to permit an early rehabilitation without possible falls due to muscle weakness secondary to FN block. Moreover, the use of ultrasound guidance allows a precise block with an amount of anesthetic solution (bupivacaine 0.5%, total of 20 mL) that does not produce systemic toxicity. To note that the type of hip surgery (osteosynthesis or arthroplasty) had no influence on the pain score or the total amount of narcotics used.

A limitation of this study was the performance of the block in the preoperative period and an impossibility to evaluate the success of the block due to the shortness of the time to start the surgery in the operating theater.

In conclusion, FN and LFCN block when added to the standard regimen for postoperative pain management after hip surgery had a benefit in decreasing pain scores as well as opioid consumption.
References:


COMPARISON OF POSTOPERATIVE ANALGESIC EFFECT OF INTRATHECAL KETAMINE AND FENTANYL ADDED TO BUPIVACAINE IN PATIENTS UNDERGOING CESAREAN SECTION: A PROSPECTIVE RANDOMIZED DOUBLE-BLIND STUDY

MARZIEH BEIGOM KHEZRI*, ELHAM TAHAEI** AND AMIR HOSSEIN ATLASBAF***

Objectives: To compare the analgesic efficacy of intrathecal Ketamine and fentanyl added to bupivacaine in patients undergoing cesarean section.

Methods: Ninety patients 18-40 years old were recruited in a prospective double-blinded, randomized way. Spinal anesthesia was performed in the three groups by using bupivacaine 10mg combined with 0.1mg/kg ketamine in group K, bupivacaine 10mg combined with 25 µg fentanyl in group F and bupivacaine 10mg combined 0.5 ml distilled water in group P. The time to first analgesic request, analgesic requirement in the first 24 hours after surgery, sensory and motor blockade onset time, duration of sensory and motor blockade, the incidence of adverse effects were recorded.

Results: The mean time to first analgesic request was longer in group K (296.80 ± 32.46) compared to group F (277.87 ± 94.25) and group P (235.43 ± 22.35). The difference between group K and F (P = 0.504) was not significant but the difference between group K and group P (P <0.001) and group F and group P (P = 0.042) was significant.

Conclusion

Addition of ketamine or fentanyl to spinal bupivacaine were equally effective in pain control after cesarean section and therefore, based on the specific conditions of patients, ketamine at concentrations mentioned earlier, could be a proper alternative to achieve postoperative analgesia

Keywords: Ketamine, fentanyl, intrathecal, cesarean, Pain

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Introduction

Spinal anesthesia has been introduced as an alternative anesthetic technique to general anesthesia in obstetric setting with many advantages such as dulling of the stress response, reducing amount of blood loss, and enhancing the postoperative analgesia and satisfaction of patient leading to improvement in the final outcomes. Decreasing the dose of bupivacaine used in spinal anesthesia helps to achieve rapid anesthetic recovery with minimal adverse effect, but may result in anesthetic failure.

Pain control after cesarean delivery is associated with improved breastfeeding and infant rooming in. However, in parturient women, we must balance the benefits of analgesia and known fetal and maternal side effects induced, including bradycardia, respiratory depression, arterial hypotension, emetogenesis, and pruritus.

Many drugs have been adjusted to local anesthetics to provide optimal analgesia with lower side effects such as opioids, midazolam, clonidine, ketamine, magnesium, and neostigmine.

Currently, opioids are widely used for pain relief, but they often provide sub-optimal analgesia with occasional serious side effects. Fentanyl is the most frequently intrathecal lipophilic opioid used as an analgesic agent with minimal cephalad spread making it the least likely of all the intrathecal opioids to cause delayed respiratory depression. However, it is reported that only a single administration of an opioid may also induce a long lasting reduction of threshold of pain sensitivity, leading to delayed hyperalgesia. Ketamine is an anesthetic agent with potent analgesic properties used as an adjunct in spinal anesthesia. It has a local anesthetic effect and a noncompetitive antagonistic effect on N-methyl d-aspartate receptors. Ketamine binds to opiate receptors and interacts with cholinergic, adrenergic and 5-hydroxytryptamine systems. It can block the N-methyl-d-aspartate excitation of central neurons. However, despite extensive discourses, there is still controversy in the literature as to the safety and analgesic efficacy of ketamine through the intrathecal route.

Preservative-free racemic ketamine was shown to be devoid of neurotoxic effects after both single and repeated administration in animals.

Yu et al reported that ketamine provided potent protective effects against the ischemic reperfusion induced spinal cord injuries. Furthermore, in obstetrics, ketamine has no detrimental effect on uterine blood flow, and maternal or fetal hemodynamics. Moreover, Horacek et al reported that a subanesthetic dose of ketamine infusion induced changes similar to those by monoaminergic-based antidepressants. We hypothesized that ketamine might provide better pain relief after cesarean section than fentanyl without pruritus, respiratory depression, hemodynamic instability, or hyperalgesia. In order to test our hypothesis, we designed a randomized, double-blind, placebo-controlled study to compare the postoperative analgesic effects of ketamine and fentanyl added to spinal bupivacaine in patients undergoing cesarean section.

Methods

Following the approval by the Ethics Committee of Medical School, Qazvin University of Medical Sciences, and obtaining informed patient consent, ninety patients 18-40 years old, with American Society of Anesthesiologists (ASA) physical status I or II, scheduled for cesarean section under spinal anesthesia, were recruited in a prospective, double-blinded, randomized way. The Consolidated Standards of Reporting Trials (CONSORT) recommendations for reporting the randomized, controlled clinical trials were followed. Exclusion criteria included significant coexistence of conditions such as cardiovascular and hepatorenal diseases, allergy to bupivacaine or ketamine, long-term opioid use, or a history of chronic pain or any contraindication to regional anesthesia such as local infection or bleeding disorders. The patients were randomly allocated to one of the three groups of 30 patients each by using the computer-generated randomization list. Three syringes were labeled as A, B, and C and were filled with equal amounts of drugs (2.5 ml). All of the syringes prepared by the personnel who were not involved in the study, and were randomly handed to the anesthetist who was unaware of the drugs. The ketamine group received bupivacaine...
10mg combined with 0.1mg/kg ketamine, the fentanyl group received bupivacaine 10mg combined with 25 µg fentanyl, and the placebo group received bupivacaine 10mg combined with 0.5ml distilled water, intrathecally. All patients received 5-7 ml/kg lactated Ringer’s solution before spinal anesthesia. After using an aseptic technique, a 25-gauge Quincke needle was inserted intrathecally via a midline approach into the L4-5 interspaces while the patient was in sitting position. The primary outcomes of this study are to evaluate the time to first requirement of analgesic supplement and total analgesic consumption in the first 24h postoperative period. The secondary outcomes included the assessment of sensory block onset time, onset of motor block, duration of blockade, hemodynamic variables, the incidence of hypotension, ephedrine requirements, bradycardia, hypoxemia (saturation of peripheral oxygen (SpO₂) <90), and adverse events such as sedation, dizziness, pruritus, and postoperative nausea and vomiting.

In this study, the postoperative analgesia was defined as the time to first requirement of analgesic supplement from the time of injection. No additional analgesic was administered unless requested by the patient. Sensory block was assessed by a pinprick test. The onset of sensory block was defined as the time between the end of injection of the intrathecal anesthetic and the absence of pain at the T10 dermatome; the duration of sensory block was defined as the time for regression of the sensory from the maximum block height to the T10 dermatome as evaluated by pinprick. The maximum level of sensory block was evaluated by pinprick after 20 min after injection. Motor block was assessed by the modified Bromage score (0, no motor loss; 1, inability to flex the hip; 2, inability to flex the knee; and 3, inability to flex the ankle); the onset of
motor block was defined as the time from intrathecal injection to Bromage block 1, and the duration of motor block was assumed when the modified Bromage score was zero. The duration of spinal anesthesia was defined as the period from spinal injection to the first occasion when the patient complained of pain in the postoperative period.

Patients were preoperatively elucidated to use the verbal rating scale (VRS) from 0 to 10 (0: no pain, 10: maximum pain) for pain assessment. If the VRS exceeded four and the patient requested a supplement analgesic, diclofenac Na Supp 100 mg every 8 hours was given to post-operative pain as needed (q8h PRN). If the time course following the administration of diclofenac Na decreased to less than 8h and the patient made another request for supplement analgesic, pethidine 25 mg IV was given.

The mean arterial pressure (MAP), heart rate (HR), and (SpO2) were recorded by an anesthetist blinded to the patient group 5 min before the intrathecal injection and also at 2, 4, 6, 8, 10, 15, and 20 min after injection. If systolic blood pressure (SBP) was 20% below the baseline or less than 90 mmHg, ephedrine 5mg was administered intravenously. Also, if HR was less than 50 beats/min, 0.5mg of atropine sulfate was administered intravenously.

A follow up telephone call was done 24 hours after the surgery and again 1 month and 6 months later, which the patients were asked about the dysesthesia of the lower limbs or buttocks and the other side effects.

To calculate the sample size, data from previous similar studies were taken into consideration. A sample size of 25 patients per group was required to detect a 20-min difference in the mean duration of analgesia between the groups using the Mann-Whitney U-test, with a power of 0.9 and an α equal to 0.05. We included 30 patients in each group to allow for dropouts and protocol violations. Data were analyzed using SPSS (SPSS 15.0, SPSS Inc, Chicago, IL, USA). Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Parametric data were expressed as mean and standard deviation (SD) and analyzed by independent T test. The X2 test was used to analyze the incidence of side effects. A p-value <0.05 was considered as significant, statistically.

**Results**

A total of 95 patients were initially enrolled in the study and 5 patients had to be excluded because of logistical reasons or other violations of the study protocol. Ninety patients were included and randomly assigned to their treatment groups [Fig. 1].

There were no significant differences in age, height, and weight among the three groups. The duration of surgery was also similar [Table 1].

Table 2 shows the mean onset of sensory block was longer in group F (95.33 ± 39.17 sec) than group P (78.5 ± 26.00 sec) and group K (89.33 ± 22.03 sec). The difference between group K versus group F (P = 0.44) and group P (P = 0.165) was insignificant, while this difference between group F and P was significant (P = 0.032) through LSD post hoc test. However the overall difference among three groups were not significant through Anova test (P = 0.094).

The mean duration of sensory block in group K

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group K (n = 30)</th>
<th>Group F (n = 30)</th>
<th>Group P (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.43 ± 3.70</td>
<td>30.20 ± 5.41</td>
<td>29.16 ± 5.11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.5 ± 15.4</td>
<td>88.5 ± 13.6</td>
<td>89.7 ± 11.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 ± 4.6</td>
<td>160 ± 8.4</td>
<td>162 ± 6.1</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>85.63 ± 15.70</td>
<td>79.16 ± 20.11</td>
<td>81.70 ± 18.76</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, K = ketamin, F = fentanyl, P = placebo. There are no significant differences among the three groups.
The median value for the maximum height of block was T6 for all three groups.

The mean duration of motor blockade time was significantly longer in group K (170.43 ± 22.70 min) than P (136.76 ± 28.85 min) and F groups (143.16 ± 33.94). The difference in mean duration of motor blockade time between group K versus P (P <0.000) was longer than group P (122.23 ± 32.78 min) and group F (133.53 ± 32.68 min) (Table 2). The difference between group K and P (P = 0.013) was statistically significant but the difference between group K and F (P = 0.356) and between group F and P (P = 0.283) was not significant through LSD post hoc test.

As shown Table2, the mean onset of motor block was (86.00 ± 33.15) in group K, (80.00 ± 30.62) in group P, and (81.83 ± 27.21) sec in group F. The difference between group K versus F (P = 0.597) and P (P = 0.447) was insignificant. Similarly, the difference in group F and P was insignificant (P = 0.816).

Data are presented as number of patients(%). K = ketamin; F = fentanyl; P = placebo. * p <0.05 compared to the placebo group. ** p <0.05 compared to the other two groups.

Table 2
Characteristics of spinal anesthesia

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group K (n = 30)</th>
<th>Group F (n = 30)</th>
<th>Group P (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset time of Sensory block (second)</td>
<td>89.33 ± 22.03</td>
<td>95.33 ± 39.17*</td>
<td>78.5 ± 26.00</td>
<td>0.094</td>
</tr>
<tr>
<td>Duration of sensory block (min)</td>
<td>143.73 ± 17.77*</td>
<td>133.53 ± 32.68</td>
<td>122.23 ± 32.78</td>
<td>&lt;0.018</td>
</tr>
<tr>
<td>Onset time of Motor block (second)</td>
<td>86.00 ± 33.15</td>
<td>81.83 ± 27.21</td>
<td>80.00 ± 30.62</td>
<td>0.737</td>
</tr>
<tr>
<td>Duration of motor block (min)</td>
<td>170.43 ± 22.70**</td>
<td>143.16 ± 33.94</td>
<td>136.76 ± 28.85</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Time to first request of analgesic (min)</td>
<td>296.80 ± 32.64*</td>
<td>277.88 ± 94.25*</td>
<td>235.43 ± 22.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of spinal Anesthesia</td>
<td>211.73 ± 74.80</td>
<td>208.50 ± 35.45</td>
<td>192.33 ± 30.36</td>
<td>0.291</td>
</tr>
<tr>
<td>Total ephedrine requirement</td>
<td>1.83 ± 3.82</td>
<td>5.52 ± 2.16</td>
<td>5.58 ± 4.16</td>
<td>0.159</td>
</tr>
<tr>
<td>Total analgesic consumption in 24 h (number of analgesic request)</td>
<td>2(2-2)*</td>
<td>2(1-3)</td>
<td>3(2-3)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or median IQR, K = ketamin; F = fentanyl; P = placebo. * p <0.05 compared to the placebo group. ** p <0.05 compared to the other two groups.

Table 3
Side effects observed in three study groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group K</th>
<th>Group F</th>
<th>Group P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>1 (%33)</td>
<td>1 (%3.3)</td>
<td>0</td>
<td>0.60</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypotension</td>
<td>7 (%23.3)</td>
<td>4 (%13.3)</td>
<td>8 (%26.7)</td>
<td>0.420</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Dryness</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (%3.3)</td>
<td>6 (%20)</td>
<td>3 (%10)</td>
<td>0.118</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1 (%3.3)</td>
<td>1 (%3.3)</td>
<td>.600</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1 (%3.3)</td>
<td>0</td>
<td>0.364</td>
</tr>
<tr>
<td>Shivering</td>
<td>2(6.7)</td>
<td>1(3.3)</td>
<td>4(13.3)</td>
<td>0.328</td>
</tr>
</tbody>
</table>

Data are presented as number of patients(%). K = ketamin, F = fentanyl, P = placebo.
Fig. 2 Blood pressure changes in the three groups

Data are presented as mean ± SD, K = ketamin, F = fentanyl, P = placebo. MAP = mean arterial blood pressure (mm Hg), SA = spinal anesthesia. * p <0.05 compared to the other groups.

Fig. 3
Heart rate changes in three groups

Data are presented as mean ± SD, K = ketamin, F = fentanyl, P = placebo, HR = heart rate (bpm), SA = spinal anesthesia
and F groups (P < 0.001) were significant whereas no significant difference in duration of motor block between F and P groups was found (P = 0.668).

The duration of anesthesia in ketamine group (211.73 ± 74.80) was longer compared to the fentanyl group (208.50 ± 35.45) and placebo (192.33 ± 30.36) groups. However the difference among three groups was not significant through Anova test (P = 0.291). (Table 2).

The mean time to first analgesic request was longer in group K (296.80 ± 32.46) compared to groups F (277.88 ± 94.25) and P (235.43 ± 22.35 min). There were no difference between group K and F (P = 0.504) but the difference between group K and P (P < 0.001) and group F and P (P = 0.042) was significant (Table 2).

The total number of analgesic request by patients during 24 hours after surgery in ketamine group was significantly smaller than placebo group (P = 0.002) but this difference in group K versus F (P = 0.538) and group F versus P (P = 0.071) was not significant.

Transient hypotension occurred at various time points in three groups, despite pre-block volume loading (Fig. 2).

The mean variation of mean arterial pressure, heart rate was defined as the difference between the highest and the lowest mean arterial pressure and heart rate in each patient. The mean variation of MAP was 25.78 ± 11.64 in group K, 33.73 ± 10.73 in group P, and 50.00 ± 76.14 in group F. The difference between group K and P was significant (P = 0.040) whereas no significant difference between P versus group K (P = 0.495) and group F (P = 0.164).

The overall difference in ephedrine requirement between the three groups was not statistically significant.

The mean variation of HR was 33.9 ± 11.62 in group K, 33.43 ± 12.79 in group F, and 32.86 ± 10.17 in group P. As shown Fig. 3, the difference between group K and group F (P = 0.876) and group P (P = 0.730) groups was not significant as it was for the difference between groups F and P (P = 0.850).

The three groups were found to have no significant difference in terms of other intraoperative and postoperative side effects including pruritus, nausea, vomiting, headache, shivering, and respiratory depression. No patient in either group showed any sensory or motor complications within the next six months follow up after surgery (Table 3). All newborns in our study were free of any adverse effect.

Discussion

Addition of ketamine or fentanyl to spinal bupivacaine results in prolonged analgesia after cesarean delivery compared with the placebo group. The total analgesic consumption within the first 24h postoperative was similar in fentanyl and ketamine groups following cesarean section. These results are in accordance with previous research but contradict other studies. However, it is reported that NMDA receptor antagonists such as ketamine have a preventive and also therapeutic effect on postoperative pain. Furthermore, ketamine blocks the voltage-sensitive calcium channels, depresses sodium channels, and alters cholinergic neurotransmission, which is responsible for pain mechanisms; it acts as a noradrenergic and serotonergic uptake inhibitor, which is implicated in descending antinociceptive pathways.

Our current findings suggest that ketamine significantly enhances the pethidine effects on postoperative pain management, thereby preventing the subsequent NMDA activation. The NMDA receptor antagonist potentiates the opioid antinociception by blocking the spinal C-fiber stimulation. Analgesic consumptions known to be related to primary hyperalgesia caused by the augmentation of the sensitivity of primary afferent receptors rather than by central sensitization.

The discrepancy of the results may be due to different methodologies and populations. For example, Kathirvel et al used a higher dose (10 mg) of bupivacaine in the control group than in the ketamine group (7.5 mg). In the current study, we used 10 mg bupivacaine in both groups.

Another finding which should be noted is that the onset of sensory and motor block was similar in three groups. This finding is consistent with the results of study by Murali Krishna et al. However the results
by Unlugenc et al [28] and Yanli and Eren34 suggested that the addition of intrathecal ketamine to spinal bupivacaine shortened the onset of both sensory and motor blockades. Results of the clinical study by Galindo35 suggested that the pH-adjusted solutions of local anesthetics produced a more rapid onset of blockade with better quality and longer duration than the unmodified commercial preparations, a finding in agreement with our finding. The addition of ketamine decreases the pH of bupivacaine and therefore, the onset of the sensory block is prolonged compared to control group. We used distilled water in the placebo group and ketamine 0.1 mg/kg in the ketamine group combined with spinal bupivacaine. We speculate that the pH of the solution is a possible reason why ketamine prolongs the onset of sensory block. The pH of ketamine hydrochloride is slightly acidic (3.5-5.5), whereas the pH of distilled water used in the placebo group is neutral (pH 7-7.4), and also the PH of fentanyl is 4-7.5.

The addition of intrathecal ketamine 0.1 mg/kg or fentanyl 25 µg to spinal bupivacaine prolonged the duration of motor and sensory block similarly. These findings are contrary to the findings of Unlugenc et al[28] and Shrestha et al[29]. They reported that motor and sensory duration was significantly longer in Group F than in Groups K. However, the discrepancy of the results may be due to different methodologies.

Transient hypotension episodes and vasopressor requirement in ketamine group were less than fentanyl and placebo groups, a finding in agreement with previous studies32,33,36. The overall results of our study are consistent with studies by Bion36 Murali Krishna et al33, and Kathirvel et al32, who reported that the use of intrathecal ketamine was associated with minimal hemodynamic changes. Bion36 suggested that the transmission of ketamine into the venous system (azygos vein) of the spinal cord leads to hemodynamic stability during spinal anesthesia.

The selection of intrathecal ketamine dose of 0.1 mg/kg and fentanyl was based on the fact that several previous studies showed that the use of such dose could prolong the duration of analgesia without additional side effects.32,33,36

In the present study, we did not find any incidence of behavioral, psycho-mimetic, or neurological complications and delayed respiratory depression in the patients receiving ketamine or fentanyl intrathecally. This result is in accordance with the findings by Bion et al36, who reported that intrathecal ketamine acts locally on the spinal cord nociceptors and does not act systemically after being absorbed into the circulation.38 However, it seems that the incidence of complications with intrathecal ketamine or fentanyl is a dose-dependent phenomenon and thus the routine use of such drugs at high doses in clinical practice should be postponed until its safety is proved by further studies.

In conclusion, both fentanyl and ketamine when added to spinal bupivacaine were equally effective in pain control after cesarean section and therefore, based on the specific conditions of patients, if the administration of fentanyl cannot be justified due to some possible complications, ketamine at concentrations of 0.1 mg/Kg could be a proper alternative to achieve postoperative analgesia.
## References


33. MURALI KRISHNA T, PANDA NB, BAJRA YK, RAJEEV S: Combination of intrathecal ketamine and fentanyl plus bupivacaine in cesarean section.


EFFECT OF PREOPERATIVE INTRAVENOUS OXYCODONE ON LOW-DOSE ROPIVACAINE SPINAL ANESTHESIA COMBINED WITH INTRATHECAL FENTANYL

Na Wang*, Songling Zhang**, Yaowen Fu*** and Jinguo Wang****

Background: Low-dose ropivacaine combined with intrathecal fentanyl can provide adequate anaesthesia with minimal haemodynamic variation. Preemptive analgesia can enhance analgesic effect of spinal anaesthesia without obvious side effects.

Aims: To assess the efficacy of preoperative intravenous oxycodone on transurethral resection of prostate (TURP) under 10 mg ropivacaine spinal anaesthesia combined with intrathecal 25 μg fentanyl.

Methods: Sixty patients undergoing TURP were randomly divided into two groups: Group O (n=30), in which the patients were administered 0.1 mg·kg⁻¹ oxycodone intravenously 10 min prior to the operation for 2 min, and Group C (n=30) in which the patients were administered intravenously a similar volume of 0.9% saline. The participants were injected with hyperbaric 10 mg ropivacaine and 25 μg fentanyl intrathecally. The block characteristics, hemodynamic values, the tramadol consumption and adverse effects were analyzed.

Results: The peak level of sensory block was lower in Group C. Time to the first analgesic request and time to two-segment regression of sensory block were shorter in Group C. Fewer patients in Group O were given postoperative analgesics.

Conclusion: Preoperative intravenous oxycodone can prolong analgesic effect of this method and postoperative analgesia.

Keywords: Preemptive analgesia; Spinal anaesthesia; Oxycodone; Ropivacaine; Fentanyl

Introduction

Intrathecal anesthesia which can maintain patients awake during the surgery to detect early symptom of transurethral resection syndrome is a widely used anesthetic method for transurethral resection of the prostate (TURP). Hyperbaric 10 mg ropivacaine plus intrathecal 25 μg fentanyl can yield an adequate anesthetic condition for TURP, restrict the spread of the sensory block, and provide a rapid regain of motor function, but may not produce a satisfactory postoperative

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Preemptive analgesia can not only prolong the duration of spinal analgesia, but also improve the quality it produced, without causing an increase in the incidence of side effects. Preemptive analgesia is defined as an antinociceptive treatment that prevents the establishment of central sensitization, which amplifies pain.

Previous researches reveal that preoperative oral oxycodone can reduce intraoperative stress reaction, postoperative pain and analgesic requirements in patients under general anesthesia without an increase of side effects. So far, no studies have been found associated with the preemptive analgesia of preoperative oxycodone on ropivacaine-fentanyl spinal anesthesia.

We designed this clinical research to test the hypothesis that preoperative oxycodone could enhance ropivacaine-fentanyl spinal anesthesia in patients undergoing TURP.

**Methods and materials**

The International Clinical Trials Registry number of this clinic trial is ChiCTR-IPR-15006998. After approval of the Institutional Ethics Committee (NO. 2014-271) and obtaining written informed consent from all of the patients, 60 patients with American Society of Anesthesiologists (ASA) I to II undergoing elective TURP were recruited for this study. Patients having histories of substance abuse, mental disturbance and neurological disease, and allergic reactions to opioids were excluded from the clinical trial. With a sequence of numbers generated by computers and sealed envelopes, we divided the patients into two groups: Group O and Group C with 30 patients in each group. The study drug solution was prepared before spinal puncture. The anesthetist was unaware of the grouping situation.

Electrocardiogram, noninvasive blood pressure and oxygen oximeter were monitored. Venous access was obtained with a 16 gauge cannula. Before spinal injection, all patients received 5 ml·kg⁻¹ normal saline over 20 min. In order to prevent fluid overload resulting from absorption of irrigation fluid, the intravenous infusion was kept under minimal maintenance during the surgery.

All patients received ropivacaine 1.0 ml (10 mg) (Naropin, Astra Zeneca AB, Sodertalje, Sweden), fentanyl 0.5 ml (25 µg) (Fentanyl, Yichang Humanwell Pharmaceutical CO, LTD, Yichang, China) and 10 % glucose 0.5 ml (Keli, Sichuan Kelun Pharmaceutical CO, LTD, Chengdu, China)—in total, hyperbaric ropivacaine 0.5% (2 ml) intrathecally. Intrathecal puncture was implemented at L3-4 using a 22 G Quincke needle. After spinal puncture was successful, the patients were administered intrathecally with the drug solution for 10 s with the needle bevel cephalad orientating. Then all patients were placed in a supine position with head tilted up 30°. Ten minutes after spinal injection, 0.1mg·kg⁻¹ oxycodone (oxycodone, HAMOL LIMITED, Nottingham, U.K.) diluted with 0.9% saline to achieve a concentration of 1 mg·ml⁻¹ was given intravenously slowly for 2 min in Group O, or 0.1 ml·kg⁻¹ normal saline as placebo was administrated intravenously for 2 min in Group C. The operation began 10 min later. Mean arterial pressure (MAP) and heart rate (HR) were measured every 5 min. A bolus of 5 mg ephedrine which could be repeated every 3 min was used for treatment of hypotension defined as a reduction of more than 20 percent from the basic systolic blood pressure. Intravenous 0.5 mg atropine was used for the treatment of bradycardia which was defined as heart rate <45 beat per minute. The patients given ephedrine or atropine were recorded. Supplemental 100 µg fentanyl was given intravenously, once the patient felt pain. If another dose of fentanyl was needed, the induction of general anesthesia was performed and the patient was removed from this research. The patients were observed for the first postoperative 24 h.

The sensory block level was defined as the dermatomal segment without pain perception using a pin-prick test on both sides of the midthoracic line. The sensory block level was checked every 2 min till the peak level was achieved, and then every 10 min. The peak sensory block level was defined as the same block level which persisted for four consecutive tests. The degree of the motor block was measured using a Bromage scale which was graded as following: 1, complete motor block; 2, almost complete motor block: able only to move the feet; 3, partial motor block; 4, detectable weakness of hip flexion; 5, no detectable weakness of hip flexion; 6, no weakness at all.
The sedation score was assessed by an independent investigator using Ramsay sedation scale (1, anxious and agitated; 2, cooperative and tranquil; 3, drowsy but responds to command; 4, asleep but responds to tactile stimulation; and 5, asleep and no response). In the postoperative period, the surgeon would prescribe tramadol to the patient who declared his pain score was more than three. The participants who required tramadol, tramadol doses used and unwanted events were recorded in the first postoperative 24 h.

The time to the first analgesic request defined as the time period from the extubation of the patient to the time point when the first analgesic was required was the primary endpoint of this study. Presuming that preoperative intravenous oxycodone would prolong time to the first analgesic request by 30 min, 23 participants were needed in each group to discover the variance with 5% two-sided α and 10% β. Thirty patients were included in each group for possible dropouts.

The data analysis were conducted using SPSS 17.0 (SPSS Inc, Chicago, IL, USA). Inter-group differences in descriptive statistics were tested with Student’s t-test. Changes in MAP and HR at various time points within each group were analyzed using ANOVA for repeated measures. The peak sensory block and peak motor block were analyzed with Mann-Whitney U test between the two groups. Categorical data were compared using either chi-square or Fisher’s exact test. P values of <0.05 were accepted as statistically significant.

**Results**

No inter-group significant differences were found according to demographic data or surgical characteristics (Table 1).

**Table 1**

<table>
<thead>
<tr>
<th>Patient demographics and surgical data</th>
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<tbody>
<tr>
<td>Group O (n=30)</td>
</tr>
<tr>
<td>Age (yr)</td>
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<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>ASA I/Ⅱ (n)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
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<tr>
<td>Prostate volume (g)</td>
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</tbody>
</table>

Values are presented as mean ± standard deviation and number of patients. ASA: American Society of Anesthesiologists.

**Table 2**

<table>
<thead>
<tr>
<th>Postoperative analgesic use and spinal block characteristics</th>
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<tbody>
<tr>
<td>Group O (n=30)</td>
</tr>
<tr>
<td>Need for Tramadol analgesia</td>
</tr>
<tr>
<td>Time to first rescue (min)</td>
</tr>
<tr>
<td>Peak sensory block level</td>
</tr>
<tr>
<td>Time to peak Sensory block (min)</td>
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<tr>
<td>Time to two-segment regression of sensory block (min)</td>
</tr>
<tr>
<td>Peak motor block level</td>
</tr>
<tr>
<td>Time to peak motor block level (min)</td>
</tr>
<tr>
<td>Time to reach Bromage score six level (full recovery of motor block) (min)</td>
</tr>
</tbody>
</table>

Values are presented as number of patients, mean ± standard deviation, and median (range).
In the first postoperative 24 h, 9 patients in Group O (30%) vs 22 patients in Group C (73%) were given postoperative tramadol analgesia \((P = 0.001)\) and the time to the first analgesic request was longer in Group O \((P = 0.010)\). No significant difference was found between the two groups with respect to the time to peak sensory block, the peak motor block, the time to peak motor block and the time to Bromage score six. The peak sensory block was higher, and the time to two-segment regression was longer in Group O \((P = 0.040 \text{ and } 0.006)\). The motor blockade was detected in all patients in both groups (Table 2).

MAP and HR 5 min after lying on the operating bed \((T_1)\), 5 min \((T_2)\) and 10 min \((T_3)\) after spinal anesthesia, 5 min \((T_4)\), 10 min \((T_5)\), 30 min \((T_6)\) and 60 min \((T_7)\) after oxycodone or normal saline administration were shown in Figure 1 and Figure 2. MAP and HR decreased because of spinal anesthesia within each group, but not significantly, and were comparable at each time point between the two groups.

The use of ephedrine was similar between the two groups. All patients were observed with a sedation score <3 at all time points. There were no significant differences between the two groups for the supplemental fentanyl use or any of the adverse events (Table 3). The \(\text{SpO}_2\) and respiration rate were always within the normal range during the study period (93-100% for \(\text{SpO}_2\) and 12-16 breath·min\(^{-1}\) for respiration rate) in both groups. There was no vomit, respiratory depression perioperatively.

### Table 3

<table>
<thead>
<tr>
<th>Ephedrine use and side effects</th>
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<tbody>
<tr>
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<td>--------------------------------</td>
</tr>
<tr>
<td>Ephedrine 3(10%)</td>
</tr>
<tr>
<td>Supplemental fentanyl 0(0%)</td>
</tr>
<tr>
<td>Hypotension 3(10%)</td>
</tr>
<tr>
<td>Bradycardia 4(13%)</td>
</tr>
<tr>
<td>Nausea 8(27%)</td>
</tr>
<tr>
<td>Dizziness 2(7%)</td>
</tr>
<tr>
<td>Pruritus 3(10%)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation and number of patients (%).

In the first postoperative 24 h, 9 patients in Group O (30%) vs 22 patients in Group C (73%) were given postoperative tramadol analgesia \((P = 0.001)\) and the time to the first analgesic request was longer in Group O \((P = 0.010)\). No significant difference was found between the two groups with respect to the time to peak sensory block, the peak motor block, the time to peak motor block and the time to Bromage score six. The peak sensory block was higher, and the time to two-segment regression was longer in Group O \((P = 0.040 \text{ and } 0.006)\). The motor blockade was detected in all patients in both groups (Table 2).

### Discussion

The present study demonstrates that small-dose ropivacaine-fentanyl spinal anesthesia provides adequate anesthetic condition for TURP, but it doesn’t provide satisfactory postoperative analgesia. When the opioid addition to local anesthetics is
not sufficient, another intravenous or intramuscular opioid or nonopioid drug usage may be considered to improve the anesthesia and analgesia\(^8\). Therefore, in this study, preoperative intravenous oxycodone was chosen to improve the effect of spinal anesthesia. In the oxycodone group, the time to the first analgesic request is prolonged without an influence on motor block. The result of this study may attribute to blunt perception of pain in central nervous system resulting from preoperative oxycodone which is not associated with motor block. Fast recovery of motor block can contribute to fewer complications\(^9\).

The role of preoperative oral oxycodone has been previously reported on general anesthesia\(^7,10\). The advantage of controlled-release oxycodone given 1 h prior to operation is proved in laparoscopic cholecystectomy and liposuction\(^7,10\). Konstantatos et al. do not find any analgesic benefit of preoperative controlled-release oxycodone for uterine artery embolization\(^6\). The result is at variance with ours. The reason could be the late administration of oral oxycodone which was given to the patients just prior to the start of operation in their trail. Enough interval of time between drug injection and the start of operation was essential for preemptive analgesia. It takes 5 min for intravenous oxycodone to reach its peak level, so 10 min before the operation is selected as the administration time in the present research.

MAP and HR are reduced due to spinal anesthesia within each group, but not significantly and are not significantly different at every time point between the two groups. This implies that neither 10 mg ropivacaine-25 µg fentanyl spinal anesthesia nor intravenous oxycodone is associated with significant hemodynamic variation which is a major concern for elderly patients.

Fentanyl and oxycodone are both opioids and have the same side effects, among which respiratory inhibition is the most unwanted adverse events, because it is sometimes life-threatening. However respiratory depression is not found in the present trial. The incidences of postoperative nausea and vomiting, pruritis, dizziness are low in this study and have no inter-group difference. The result is in line with the previous study that oxycodone has fewer adverse effects than morphine\(^6\). Intrathecal fentanyl also can result in these side effects. Pruritus is proved to be a common adverse effect of intrathecal fentanyl\(^11\), but it is not an issue in this research. Maybe elderly patients are not susceptible to pruritus\(^12\).

The limitations of this study are its small scale and the single type of the disease and the patients. Therefore, the protocol is not suitable for all patients.
Summary

In conclusion, preoperative intravenous oxycodone can prolong the effect of ropivacaine-fentanyl spinal anesthesia without causing an increase of side effects.

Conflict of interest: The authors have no financial conflicts of interest to disclose.

References

Abstract

Background: The unimodal approach of using pentazocine as post-cesarean section pain relief is inadequate, hence the need for a safer, easily available and more effective multimodal approach.

Aim: To evaluate the effectiveness of rectal diclofenac combined with intramuscular pentazocine for postoperative pain following cesarean section.

Methods: In this double blind clinical trial, 130 pregnant women scheduled for cesarean section under spinal anesthesia were randomly assigned to two groups. Group A received 100mg diclofenac suppository and group B received placebo suppository immediately following surgery, 12 and 24h later. Both groups also received intramuscular pentazocine 30mg immediately following surgery and 6 hourly postoperatively in the first 24 h. Postoperative pain was assessed by visual analogue scale at end of surgery and 2, 12 and 24 h after surgery. Patient satisfaction scores were also assessed.

Results: One hundred and sixteen patients completed the study. Combining diclofenac and pentazocine had statistically significant reduction in pain intensity at 2, 12, and 24 hours postoperatively compared to pentazocine alone (p <0.05). No significant side effects were noted in both groups. The combined group also had significantly better patient satisfaction scores.

Conclusion: The addition of diclofenac suppository to intramuscular pentazocine provides better pain relief after cesarean section and increased patient satisfaction.

Keywords: Pentazocine, diclofenac suppository, cesarean section, postoperative, analgesia
Introduction

Postoperative pain management is a common problem following cesarean section\(^1,2\). Effective pain relief promotes early mobilization and good mother-child interactions\(^1\). Established methods of postoperative pain relief include infiltration of surgical wound with local anesthetic agent, continuous epidural, oral, intramuscular, intravenous and rectal analgesia. Intramuscular pentazocine, a partial agonist opioid is widely used in low resources countries for postoperative analgesia with limited effect\(^3\). A multimodal approach has been proposed to be more effective\(^2\).

Non-steroidal anti-inflammatory drugs (NSAIDs) have beneficial effect on postoperative analgesia and are devoid of adverse effects associated with opioids such as sedation, respiratory depression, nausea and vomiting\(^4\). NSAIDs also reduce pain of uterine contraction by inhibiting prostaglandin synthesis. Diclofenac sodium, a NSAID, is readily available as an oral, intramuscular or rectal medication. Intramuscular diclofenac is painful and oral absorption unpredictable in the perioperative period\(^5\). The rectal route offers rapid absorption of low molecular weight drugs, partial avoidance of first pass metabolism leading to improvement in rate controlled drug delivery and absorption\(^6\). Rectal diclofenac also avoids rare but hazardous complications of intramuscular diclofenac which include necrotizing fasciitis\(^7\), upper limb gangrene\(^8\), and anaphylactic shock\(^9\). Although awareness and use of rectal diclofenac among Nigerian physician anesthetists is limited, its role in post cesarean section pain relief is recognized elsewhere\(^10\).

We explored multimodal approach to pain relief after cesarean section using two different drugs with different routes of administration and mechanisms of action. We therefore compared the analgesic and side effect profile of intramuscular pentazocine alone or in combination with rectal diclofenac.

Materials and Methods

This study was a prospective, hospital-based, double-blind randomized placebo controlled trial approved by the hospital ethics and research committee. One hundred and thirty patients of ASA (American Society of Anesthesiologists’ Classification) I and II status undergoing elective or emergency caesarean section were recruited and written informed consent obtained. Exclusion criteria included refusal to participate in the study, epigastic pain, known peptic ulcer, bleeding complications, excessive intraoperative blood loss (>1000mls), and previous history of hypersensitivity reaction to NSAIDS, pentazocine, or tramadol. Intravenous metochlopramide 10mg and ranitidine 50mg were given to all patients preoperatively. All patients had cesarean section under spinal anesthesia. The spinal was performed using a 25-gauge Quincke needle with hyperbaric bupivacaine 5mg/ml to reach the appropriate level of analgesia (T8 to T6). No other intraoperative analgesia was given. Time of spinal needle insertion, operation time and intraoperative blood loss were recorded. The patients were randomly allocated with envelope concealment to two groups A and B. Group A (diclofenac) received 100mg diclofenac suppository (Lofnac®, Green Pharmaceuticals) and group B (placebo) were given an identical-looking suppository containing the main vehicle in which diclofenac is normally dissolved named polyethylene glycol. The study drug was administered immediately after surgery on the operating table by the attending obstetrician and repeated 12 and 24 hours postoperatively by the ward nurse. Also, all patients received 30mg intramuscular pentazocine immediately after surgery and 6 hourly for 24 hours. The attending anesthetist, obstetrician, nurses and patients were blinded to the trial drugs received by both groups.

Pain at rest and movement estimated by a visual analogue scale (VAS, 0cm = no pain to 10cm = worst imaginable pain), the need for rescue analgesics (intramuscular tramadol) and side effects such as nausea alone, nausea and vomiting, epigastric pain, respiratory depression, dizziness, anal discomfort and diarrhea, were recorded. Pain assessment was done by an anesthetist blinded at 0, 2, 12, and 24 hours after surgery. Intramuscular tramadol(50 mg) was given as rescue analgesia if the VAS pain score was greater than 30mm. Likert scales for level of satisfaction with pain relief ranging from very satisfied to very dissatisfied and preferred route of drug administration (i.m or rectal) were also assessed.
Data obtained were entered into a predesigned sheet and analyzed using SPSS version 16 (SPSS Inc., Chicago, IL). Categorical data were analyzed using Chi-square test with Fisher’s exact test. Means and standard deviation (SD) were calculated for quantitative variables and the differences between two independent groups were compared using student’s t-test. The level of statistical significance was considered at p < 0.05.

Results

One hundred and sixteen patients completed the study (completion ratio 89.2%) out of 130. Six subjects were excluded because of postpartum hemorrhage. There were no significant differences between the two groups with reference to patients’ demographic and obstetric characteristics as shown in Tables 1 and 2.

<table>
<thead>
<tr>
<th>Patients’ baseline characteristics and duration of surgery in the two groups</th>
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<tbody>
<tr>
<td>Group A</td>
</tr>
<tr>
<td>Total number</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Height (m)</td>
</tr>
<tr>
<td>Body Mass Index (BMI) Kg/m²</td>
</tr>
<tr>
<td>Duration of surgery (mins)</td>
</tr>
</tbody>
</table>

Data is presented as mean ± standard deviation.

The pain score in the two groups was similar at zero minutes (while on the operating table) in the immediate postoperative period but there was a statistical significant difference in VAS scores between the two groups at 2, 12, and 24 h after surgery both at rest and with movement (Figure 2). Fifteen (28.8%) patients in placebo group compared to six in diclofenac group (9.4%) (p = 0.0001) required intramuscular tramadol as a rescue analgesia.

Only one case of nausea and vomiting was seen in both group A (1.6%) and group B (1.9%). There were two cases of epigastric pain in group B (3.8%) and none in group A. There were no melena stool,
respiratory depression, dizziness, anal discomfort and diarrhea in either group. There was statistical significant difference between the two groups in level of satisfaction as shown in Table 3. Comparison between preference for route of drug administration in diclofenac group and placebo group.

**Discussion**

In this study, the average level of postoperative pain as estimated by VAS was lower in the diclofenac suppository group than in the placebo group. A study done by Akhavanakbari et al compared the effects of indomethacin, diclofenac, and acetaminophen suppositories following cesarean section. Patients in the diclofenac group had the least pain intensity at 12 hour and 24 hour\(^1\). In their study, 50mg diclofenac suppository was administered hourly over 24h which was equivalent to 12 hourly 100mg diclofenac suppository used in our study. A maximum mean VAS pain score of 1.4 in our study was comparable to 2.0 in diclofenac group by Akhavanakbari et al where unimodal approach to pain relief was used\(^1\). The American Society of Anesthesiologists Task Force on Acute Pain Management however recommends the use of multimodal analgesia\(^1\). The addition of diclofenac suppository to parenteral pentazocine in our study accounted for a lower VAS and fewer patients required rescue analgesia compared to the placebo group.

Studies by Dahl et al\(^1\) and Munishankar et al\(^1\) using 200mg of diclofenac daily also demonstrated less rescue analgesia required. In another study, combination of diclofenac and tramadol or diclofenac with acetaminophen provided satisfactory postoperative pain control in parturients undergoing cesarean section\(^1\). The addition of piroxicam to pentazocine as a multimodal approach showed good effect at 12 hour post cesarean section\(^1\). The challenge however, was the intramuscular administration of both drugs. Intramuscular injection is painful and may predispose to adverse effects. Alternative routes are desirable other than oral. Oral diclofenac is one of most frequently implicated NSAIDs in upper gastrointestinal bleeding or ulceration\(^1\). In Akhavanakbari et al’s study, rectal diclofenac did not cause gastrointestinal bleeding complications\(^1\). Other previous studies also showed that diclofenac suppositories had been used successfully as postoperative pain relief after cholecystectomy\(^1\) and herniorrhaphy\(^1\) with no significant side effects\(^1\).

Samimi et al compared combination of rectal diclofenac with paracetamol and rectal diclofenac alone for postoperative pain relief for hysterectomy and found significant lower pain scale in the first 24 hours in the combination group\(^1\). Despite the use of rectal suppositories in our study, patients still experienced mild pain based on their VAS pain scores. It is possible that a more varied multimodal approach adding a mild analgesic such as acetaminophen, may further add to improved pain relief.
Inadequate analgesia has been found to reduce patients’ satisfaction\textsuperscript{22} and may cause unwanted physiologic and psychological effects\textsuperscript{23}. In a preliminary study by Pinto Pereira et al\textsuperscript{24}, patients in the diclofenac suppository group were discharged earlier than the patients in the intramuscular diclofenac group. There was a correlation between time of discharge and level of satisfaction in a study done by Marinsek et al where 60\% of patients were satisfied at discharge with their postoperative analgesia\textsuperscript{22}. Time of discharge was not measured in our study because financial constraint on the part of mother and neonatal admission for sick babies were important factors that affect discharge in our hospital. Nonetheless, level of satisfaction was statistically significant in the diclofenac group which was similar to a separate study done by Soroori et al\textsuperscript{25}.

Ortiz et al did a study on preoperative patient education and found a significant improvement in related questions about satisfaction with reference to options for pain management\textsuperscript{26}. Patient satisfaction is improved after adequate information is provided to patients about the perioperative process especially when unfamiliar technique or route of drug administration is being introduced. The addition of diclofenac suppository increased the significant level of satisfaction in the diclofenac group.

There may be a link between level of satisfaction and preference for a particular route of administration of drug for postoperative analgesia. Our study demonstrated a significant preference for suppository form than intramuscular route of administration. Suppository form was effective and well tolerated in the Vyvan and Hanafial study but patients wanted to be informed preoperatively\textsuperscript{27}. Our explanation to patients preoperatively may have contributed to improved acceptance.

**Conclusion**

In conclusion, the addition of diclofenac suppository to intramuscular pentazocine was found to be safe and efficacious, and increased patient satisfaction following cesarean section. The combination may be an ideal alternative in poor resource settings where more potent opioids and regional techniques are not routinely available.

**Acknowledgements**

The authors wish to thank the entire staff of Departments of Anaesthesia, Obstetric, Gynaecology and Perinatology of Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria for their assistance throughout the conduct of the study.

The drugs (lofnac suppository and placebo) used for this study were provided by Greenlife Pharmaceutical Company but there were no financial gains attached to it.
References

THE EFFECT OF A SINGLE DOSE OF MAGNESIUM SULPHATE AS AN ADJUVANT TO EPIDURAL BUPIVACAINE FOR INFRAUMBILICAL SURGERIES:
A PROSPECTIVE DOUBLE-BLIND, RANDOMIZED CONTROL TRIAL

SHRUTHI AH*, SUDHEESH K**, NETRA SS***, RAGHAVENDRA RAO RS**** AND DEVIKA RANI D*****

Context: Epidural anesthesia provides the advantage of segmental blockade and many adjuvants have been added to shorten the onset of action, improve the quality of analgesia and prolong the duration of analgesia. Magnesium sulphate (MgSO₄) by virtue of its anti-nociceptive property has been administered by various routes.

Aim: To assess the effect of MgSO₄ on the duration of onset of action of injection bupivacaine for epidural anesthesia in infraumbilical surgeries.

Materials and methods: A prospective, double-blind, randomized control study was conducted in 40 patients. Group M received 15 ml of bupivacaine 0.5% + 1 ml of 50 mg MgSO4 and Group C received 15 ml of bupivacaine 0.5% + 1 ml of normal saline via epidural route. Onset time of the sensory and motor blockade were the primary outcomes studied. Highest level of sensory block, time for two segment regression, hemodynamic parameters, side effects were the secondary parameters.

Results: There was a significant difference between the groups in the mean onset time of sensory blockade at T8, 12.85 ± 2.32 min in Group M and 16.75 ± 1.74 min in Group C. Median level of sensory blockade was comparable. Mean onset time of motor blockade was 13.85 ± 3.28 min in Group M and 23.25 ± 3.35 min in Group C which was clinically and statistically significant. Time for two segment regression of sensory blockade was 95.75 ± 11.84 min in Group M and 55.5 ± 8.57 min in Group C which was significant. Hemodynamic parameters and side effects were comparable.

Conclusion: Magnesium sulphate as an adjuvant provides rapid onset of epidural anesthesia and prolongs the duration of analgesia with minimal side effects.

Keywords: Magnesium sulphate, bupivacaine, epidural, infraumbilical surgeries

Introduction

Central neuraxial blockade is widely used for lower abdominal and lower limb surgeries. Epidural anesthesia being a safe technique, has a unique feature of segmental blockade and better control over hemodynamic variables and provision of prolonged post-operative analgesia. Effective
treatment of perioperative pain blunts autonomic, somatic and endocrine responses. It is a common practice to use polypharmacy approach for treatment of intra-and post-operative pain as no single agent has yet been identified to specifically inhibit nociception without associated side effects. Search for a drug that provides optimal intraoperative anesthesia and prolonged postoperative analgesia with minimal side effects still continues.

Various adjuvants have been used with local anaesthetics via epidural route with the objectives of shortening the onset of action, improving the quality and prolonging the duration of analgesia and minimising the adverse events.

Magnesium is the fourth most plentiful cation in the body and the second most prevalent intracellular cation after potassium. Its antinociceptive property has been shown in animal and human models of pain. The anti-nociceptive effects are primarily based on physiological calcium antagonism, that is voltage-dependent regulation of calcium influx into the cell, and non-competitive antagonism of N-methyl-D-aspartate (NMDA) receptors thereby preventing central sensitization induced by peripheral nociceptive stimuli. These effects have prompted the investigation of magnesium as an adjuvant agent for intra-and post-operative analgesia as it is an inexpensive, relatively harmless molecule. Most of the studies have used magnesium as a co-adjuvant to opioids for prolongation of post-operative analgesia, while few studies have investigated its effect as an adjuvant for surgical anesthesia, when used as sole agent.

We therefore conducted a prospective, double blind, randomised, controlled clinical study to assess the effect of magnesium as an adjuvant for epidural bupivacaine with respect to the onset time of sensory and motor blockade. Two segment regression, hemodynamic variables, respiratory rate and oxygen saturation were the secondary outcomes of the study.

**Materials and Methods**

A prospective double-blind, randomized study was conducted on 40 patients undergoing elective infraumbilical surgery at tertiary level medical college hospital, between January 2012 to December 2012.

Institutional ethical committee approval was taken. Patients belonging to American Society of Anesthesiology (ASA) physical status I and II, aged between 18 to 50 years of either gender and those with a BMI less than 30 kg/m² were included in the study. Those with contraindication to central neuraxial blockade like patient refusal, local site and systemic infections, patients on anti-coagulant therapy, those with spinal deformities, with neurological illness or cardiac failure; with history of adverse reaction to study medication and history of chronic pain syndrome and long term analgesic use were excluded.

Pre-anesthetic check up was done on the day prior to surgery. Written informed consent was obtained. Patients were advised fasting for 6-8 hours and premedicated with ranitidine 150 mg and alprazolam 0.5 mg per orally on the previous night of surgery. After shifting the patient to the operating room, standard monitors like pulse oximeter, noninvasive arterial blood pressure (NIBP) and electrocardiography were attached and baseline vital parameters recorded. An intravenous access was obtained and preloading done with 10 ml/kg of lactated ringer’s solution. Midazolam 0.03 mg/kg intravenous was the premedicant administered.

Patients were divided into 2 groups of 20 patients each based on software-derived random number sequence (www.random.org). The patient and the anesthesiologist administering the drug and collecting the data subsequently, were unaware of the group to which the patient was allotted. Group M (n=20) received 15 ml of bupivacaine 0.5%+ 50 mg of magnesium sulphate (MgSO₄) made up to 1 ml. Group C (n=20) received 15 ml of bupivacaine 0.5%+ 1 ml of normal saline (placebo). Both the solutions were prepared under sterile conditions by an anesthesia technician as per instructions of principal investigator, who was not assisting the monitoring anesthesiologist.

Patients were divided into 2 groups of 20 patients each based on software-derived random number sequence (www.random.org). The patient and the anesthesiologist administering the drug and collecting the data subsequently, were unaware of the group to which the patient was allotted. Group M (n=20) received 15 ml of bupivacaine 0.5%+ 50 mg of magnesium sulphate (MgSO₄) made up to 1 ml. Group C (n=20) received 15 ml of bupivacaine 0.5%+ 1 ml of normal saline (placebo). Both the solutions were prepared under sterile conditions by an anesthesia technician as per instructions of principal investigator, who was not assisting the monitoring anesthesiologist.

Under aseptic precautions and local anesthesia, epidural space was identified at L1-L2 or L2-L3 intervertebral space with a 16G Tuohy needle by loss of resistance technique to air and an 18G epidural catheter was threaded 3-4 cm into epidural space. A test dose of 3 ml of lignocaine 2% with adrenaline (1:2,00,000) was administered after negative aspiration
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for blood and cerebrospinal fluid (CSF) and patient was monitored for intravascular/intrathecal placement of catheter for 2 minutes, epidural catheter was fixed and secured with tapes. The patients then received epidural medications as per randomization.

Pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR), peripheral oxygen saturation (SpO₂) and level of sedation as per Ramsay Sedation Scale (RSS) were recorded preoperatively, every 5 minutes intraoperatively, postoperatively every 30 minutes for next 2 hours, and every 4th hour till 12 hours and at 24 hours.

Sensory block was assessed by loss of sensation to temperature (by cold swab method) bilaterally along the midclavicular line every minute. Onset time of sensory block was defined as the time interval between the injection of anesthetic to the loss of sensation at T8 dermatome. Sensory blockade was checked 15 minutes after attainment of T8 level to note the cephalad spread beyond T8 dermatome. This was continued till two segment regression from the cephalad level was reached. This was also taken as the time for the first epidural top up and a bolus of bupivacaine 0.5% (3 ml) was administered via epidural route with no supplemental dose of magnesium sulphate intraoperatively.

Motor blockade was assessed using ‘Modified Bromage Scale’¹⁰. The assessment was done every minute till Bromage Scale 3 was attained. Surgeons were allowed to proceed with surgery once level of sensory block reached T8 and motor block was complete. Complications or side effects, if any were noted.

Patients in whom there was a failure to achieve adequate level of sensory or motor blockade were managed with general anesthesia and excluded from the study.

Hypotension was defined as SBP <90 mmHg or >30% decrease from baseline values and was treated with ephedrine 6 mg IV. Bradycardia was defined as HR <60 beats per minute (bpm) and was treated with atropine 0.02 mg/kg intravenous. Respiratory depression was documented when RR <8 breaths per minute or SpO₂ <85% and was managed with mask ventilation, endotracheal intubation and intermittent positive pressure ventilation, if necessary. Vomiting was managed with injection ondansetron 0.1 mg/kg and shivering was managed with administration of warm intravenous fluids and warming blankets.

Postoperative analgesia was managed with epidural bolus of bupivacaine 0.125% 8 ml boluses and/or Paracetamol 1 gm infusion as per discretion of treating consultants.

With the power of study at 90%, keeping alpha error at 5%, a minimum of 20 patients in each group was needed to detect an intergroup difference of at least 20% with respect to time for onset of sensory block. We included 20 patients in each group. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 17.0. Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Student’s t-test was used for differences in hemodynamic variables between the groups and repeat measures of ANOVA for intergroup evaluation. Nominal data was analysed using the Chi-Square test or Fisher Exact test. P value <0.05 was considered statistically significant.

Results

Table 1 shows that the demographic data between the two groups were comparable. Epidural block was effective in all patients and none of the patients required additional supplementation.

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Group M (mean ± SD)</th>
<th>Group C (mean ± SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37 ± 7</td>
<td>37.15 ±/8</td>
<td>0.953</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>4/16</td>
<td>5/15</td>
<td>0.352</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.7 ± 2.9</td>
<td>23.2 ± 2.5</td>
<td>0.583</td>
</tr>
<tr>
<td>ASA(I/II)</td>
<td>15/5</td>
<td>16/4</td>
<td>0.705</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>95 ± 15.6</td>
<td>93.8 ± 16.9</td>
<td>0.809</td>
</tr>
<tr>
<td>Type of surgery (orthopedic/ gynecologic)</td>
<td>4/16</td>
<td>5/15</td>
<td>0.352</td>
</tr>
</tbody>
</table>
Mean time taken to achieve T8 dermatomal level sensory blockade was earlier in group M (12.85 ± 2.32 minutes) than group C (16.75 ± 1.74 min) (P <0.001). Similarly time for maximum motor block of Modified Bromage scale 3 was 13.85 ± 3.28 min in group M and 23.25 ± 3.35 min in group C which was clinically and statistically significant (P <0.001). The median height of sensory blockade (T8) though was similar in both the groups with group M showing higher level of blockade (T6) in few patients, but the comparison was not statistically significant (P = 0.358). Time for two segment regression was significantly prolonged in group M (95.75 ± 11.84 min) when compared to group C (55.5 ± 8.57 min) which was significant (P <0.001). Six patients in group M required additional top up, whereas 18 patients in group C required additional top up (P <0.001, odds ratio 0.09) (Table 2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group M (n=20)</th>
<th>Group C (n=20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset time for sensory block (min)</td>
<td>12.85 ± 2.32</td>
<td>16.75 ± 1.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Onset time for motor block (min)</td>
<td>13.85 ± 3.28</td>
<td>23.25 ± 3.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Two segment regression (min)</td>
<td>95.75 ± 11.84</td>
<td>55.5 ± 8.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of patients requiring additional top ups</td>
<td>6</td>
<td>18</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean baseline heart rate was comparable in both groups. There was no statistically significant difference in heart rate between the groups throughout the study period (P >0.05) (Fig 1). Systolic, diastolic and mean arterial blood pressures (SBP, DBP, MAP) were comparable between the two groups at all time intervals during the study (Fig 2).

None of the patients in either group had any episode of respiratory depression or desaturation.

Median sedation score was 2 in group M and group C intraoperatively and postoperatively in both groups.

There were no significant differences between the two groups with respect to hypotension, need for vasopressor or bradycardia (Table 3). Five patients in group C while none of the patients in group M had shivering, but this was statistically insignificant.

**Discussion**

The present study using magnesium sulphate (MgSO₄) 50 mg as an adjuvant to epidural bupivacaine showed that the time for the onset of sensory and motor blockade was significantly shortened and time for two segment regression was significantly prolonged with no clinically significant difference in hemodynamic parameters and adverse events.

Noxious stimulation leads to the release of glutamate and aspartate neurotransmitters which bind to various excitatory receptors like N-Methyl D-Aspartate (NMDA). Activation of NMDA receptors causes an influx of calcium and sodium ions into the cells and efflux of potassium ions, and initiation of central sensitization¹¹⁻¹⁴. Central sensitization has an important role in pain perception and is considered to be one of the mechanisms implicated in the persistence of postoperative pain¹⁵. NMDA receptor signalling may be important in determining the duration of acute pain¹². Hence NMDA receptor antagonists will be effective in prevention and treatment of pain. Magnesium is a non-competitive antagonist of NMDA receptor and causes voltage-dependent blockade of ion channels producing a dramatic reduction of NMDA-induced currents thereby preventing central sensitization resulting from peripheral nociceptive stimuli¹⁴,¹⁶.

Abdel-Halim JMK¹⁷ found that co-administration of magnesium sulphate 50 mg with epidural bupivacaine and morphine preoperatively as a
single bolus dose provides a profound decrease in intraoperative and postoperative narcotic consumption, and in VAS pain scores with no significant side effects. Co-administration of epidural magnesium for postoperative epidural analgesia provided a pronounced reduction in patient-controlled epidural fentanyl consumption without any side effects. In these studies supplementation of magnesium, a non-competitive NMDA receptor antagonist resulted in enhancement of analgesic effect of opioids and by delaying development of tolerance probably caused a significant reduction in postoperative opioid consumption. However, the studies evaluating the effect of co-administration of magnesium alone with local anaesthetic in surgeries done under epidural anesthesia are very few.

Shahi V and colleagues showed that the time to achieve T6 block was 15.4 ± 2.1 minutes in epidural magnesium adjuvant group and 19.7 ± 2.1 minutes in control group, which is comparable with the observations of the present study.

There was statistically significant prolongation of time for two segment regression in patients receiving magnesium sulphate. This is in contrast with observations of Ghatak T and colleagues who found no statistically significant difference between the two groups. This was probably due to the volume of local anesthetic used, variations in performance of the block, drug preparations and patient characteristics.

Studies by Koinig H et al and Tramer MR et al have shown that systemic administration of magnesium is associated with smaller analgesic requirement and less discomfort in the postoperative period. A limitation to the parenteral application of magnesium for modulation of antinociception via NMDA channel antagonism is insufficient blood-brain barrier penetration to achieve effective cerebrospinal fluid concentrations. Similar finding was observed by
Ko SH et al and no postoperative analgesic effect of magnesium was seen\(^4\).

The clinical efficacy of magnesium and its safety in humans by intrathecal route has been shown by Buvanendran and colleagues\(^{25}\). Shoeibi G et al\(^{26}\) demonstrated that magnesium sulphate administered intrathecally with lignocaine, prolongs the duration of spinal analgesia in those undergoing caesarean section. Similarly in our study, magnesium as an epidural adjuvant resulted in prolongation of analgesia. It is possible that the analgesic effect occurs at the supra-spinal level and may be related to its systemic absorption. The epidural dose of magnesium in our study was too low for the systemic effect. The probable mechanism may have been diffusion of magnesium from the dura\(^{18}\).

Shivering occurred in five (20\%) patients in the control group whereas none of the patients of the magnesium group developed shivering. Though this was not of statistical significance, it may have clinical significance since it has been proven that hypomagnesemia can occur in patients under anesthesia and perioperative magnesium supplementation can prevent postoperative hypomagnesemia and decreases the incidence of postoperative shivering\(^1\).

In two cases reported by Goodman and colleagues\(^{27}\) larger doses (8.7 g and 9.6 g) of magnesium inadvertently administered into the epidural space did not cause any neurologic injury. However, we preferred to use a smaller dose of magnesium that would not cause any side-effects.

The present study has limitations. The overall 24 hour post-operative analgesic consumption was not studied and hence its effect on post-operative analgesia could not be ascertained. However, a study done with single dose of MgSO\(_4\) in labour analgesia has shown to reduce the need of top ups and hence, the epidural bupivacaine and fentanyl consumption\(^{28}\). Also, further studies are needed to evaluate the efficacy and safety of higher doses of magnesium sulphate with larger sample sizes and in different surgical settings and in patients with ASA physical status 3 and beyond.

**Conclusion**

Magnesium sulphate a NMDA receptor antagonist when used in a dose of 50 mg as an adjuvant to epidural bupivacaine not only hastens the onset of sensory and motor blockade but also prolongs the time for two segment regression thereby necessitating lesser need for top ups.
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References

EFFECT OF DEXMEDETOMIDINE ON HEMODYNAMIC PARAMETERS DURING EXTUBATION. A PROSPECTIVE RANDOMIZED DOUBLE BLIND STUDY


Background: Extubation is known to produce significant hemodynamic disturbances. There is a need to avoid increase in heart rate and blood pressure in hypertensive and cardiac patients and in vascular, neuro and intraocular surgeries.

Aims: To study the ability of dexmedetomidine to attenuate the hemodynamic responses during extubation.

Materials and methods: 80 patients of ASA Grade I-II aged 18-50 years received standard anesthesia. At the closure of skin incision, patients were randomly allocated to receive either dexmedetomidine 0.5 µg/kg (Group D) or saline placebo (Group C) intravenously over 10 minutes in a double-blind design. Heart rate (HR), systolic, diastolic and mean arterial pressures (SBP, DBP, MAP) were assessed before, during and after extubation. Time to eye opening and extubation, sedation, complications such as coughing, laryngospasm, bronchospasm and desaturation were recorded.

Results: HR, SBP, DBP and MAP were comparable to basal values in group D at extubation and lower than baseline values post-extubation but significant increase was noted in group C (P <0.001). Time to extubation and eye opening were prolonged in Group D (P <0.001). Incidence of hypotension was more in group D (22%) but was transient. Incidence of coughing was lower in Group D than in group C (P <0.001). Patients in group D were more sedated for 30 minutes post extubation.

Conclusion: Dexmedetomidine 0.5 µg/kg given before extubation attenuates hemodynamic reflexes during emergence from anesthesia without causing undue sedation, but prolongs time to extubation.

Keywords: Dexmedetomidine, general anesthesia, extubation, hemodynamic responses.

Introduction

Tracheal intubation and extubation are accompanied by raised sympathoadrenal activity with an increased plasma catecholamine levels which cause an increase in heart rate, myocardial contractility and systemic vascular resistance1,2. Majority of patients tolerate these changes without any significant consequences1 but patients with co-existing diseases like hypertension and diabetes may not be able to tolerate these responses.

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***** Professor and Head, Department of Anesthesiology, Bangalore Medical College and Research Institute, Bangalore, India. Financial support-Nil. Conflicts of interest- Nil.
An increase in heart rate is more likely to produce signs of myocardial ischemia due to the increased myocardial oxygen demand than hypertension. A recommendation is to maintain heart rate and blood pressure during intubation and extubation within 20% of normal awake value of that patient.

Various options in vogue to attenuate extubation response include: deeper planes of anesthesia, topical anesthesia, use of intravenous local anesthetics, calcium channel blockers, opioids, and sympathetic blockers etc. Alpha₂-agonists simultaneously potentiate the effects of general anesthetics, reduce their dose requirements, and attenuate sympathoadrenal responses to noxious stimuli encountered during anesthesia and surgery, thus providing improved hemodynamic, metabolic, and hormonal stability. Dexmedetomidine, is a highly selective alpha₂-adrenergic agonist that has sedative, anxiolytic and analgesic actions. It is known to exhibit dose dependent attenuation of the stress response to intubation. However not enough literature is available with regard to its effect on hemodynamic response to extubation. The aim of the current study is to assess the effect of dexmedetomidine when given at a dose of 0.5 µg/kg just before extubation on hemodynamic responses to emergence from anesthesia. Its effect on recovery was the secondary aim of the study.

Materials and Methods

A prospective, randomized, double blind case controlled study was conducted on 80 patients undergoing various elective surgeries under general anesthesia with endotracheal intubation at a tertiary level medical college hospital during the period between September 2010 to 2012. Institutional ethical committee approval was obtained.

Patients aged between 18 to 50 years belonging to American Society of Anesthesiology (ASA) physical status I and II were included in the study. Patient refusal, those with cardiac or pulmonary disease or any endocrinological disorder, head and neck surgeries, those with history of drug abuse or psychological disorder and obese patients, with difficult airway or history of sleep apnoea were excluded from the study.

Preanesthetic evaluation was done on the day prior to the surgery. A detailed history of present and past medical illnesses and history of drug allergies if any was recorded. Patients were advised overnight fasting and premedicated with oral ranitidine 150 mg and oral alprazolam 0.5 mg on the day before surgery.

After obtaining informed written consent, patients were randomly divided into 2 groups based on software generated random number table (www.random.org). The details of randomization and group allocation was with the principal investigator and not revealed to others till the completion of collection of data. The drug or placebo for infusion was prepared by a technician unaware of the study, as per the instructions of the principal investigator. The anesthesiologist who administered the drug or placebo solution and monitored the patient subsequently, and the patient were unaware of the content of the solution.

After shifting patient to the operating room, intravenous access was obtained and ringer lactate solution started. All patients were monitored with electrocardiography (ECG), pulse oximetry, non-invasive blood pressure (NIBP), end tidal carbon-dioxide (Et CO₂), and train of four (TOF) (hemodynamic and neuromuscular monitoring modules of Avance S5™ anesthesia workstation) and basal parameters were recorded.

Glycopyrrolate 5 µg/kg, midazolam 0.025 mg/kg and fentanyl 2 µg/kg were administered intravenously just before induction of anesthesia. Intravenous propofol 2 mg/kg was used for induction and intubation was facilitated with intravenous atracurium 0.5 mg/kg. Anesthesia was maintained with 66% nitrous oxide in oxygen and isoflurane 1%-2% titrated to maintain adequate depth of anesthesia, based on hemodynamic parameters. Muscle paralysis was maintained with a continuous infusion of atracurium. Atracurium infusion was started at a dose of 10 µg/kg/hr, 15 minutes after the administration of intubating dose, as guided by TOF count and titrated subsequently to maintain TOF count less than 2. Fentanyl 1 µg/kg was administered if there was an increase in heart rate and systolic blood pressures more than 20% baseline, despite of administration of 1.3 MAC of isoflurane.

At the beginning of the closure of skin incision, isoflurane was turned off and atracurium infusion stopped.
Group D (n=40) patients: received 0.5 µg/kg of dexmedetomidine diluted to 10 ml in normal saline. Group C (n=40) patients: received 10 ml of normal saline (placebo) prior to extubation. Both infusions were given over 10 minutes.

Nitrous oxide was stopped following end of infusion.

Residual neuromuscular blockade was reversed using neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg intravenously when TOF count was 4. Patients in both groups were extubated when all the following subjective and objective criteria were fulfilled:

1. Sustained head lift for 5 seconds.
2. Sustained hand grip for 5 seconds.
3. Obey commands.
4. Tidal volume >6 ml/kg.
5. TOF ratio 0.9.

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), percentage saturation of oxygen (SpO₂) and respiratory rate (RR) were recorded every 5 minutes intraoperatively; immediately prior to drug or placebo infusion; at 1, 2, 5, 7 and 10 minutes during infusion; following reversal administration; and then post extubation every 5 min for 15 min, and then every 15 min for next 2 hours thereafter.

Bradycardia was defined as HR <60 beats per minute (bpm), tachycardia being 20% increase from baseline, hypertension as either 20% increase from baseline or SBP >180 mm of Hg and hypotension as 20% decrease from baseline or SBP <80 mm of Hg.

Time to extubation and time to eye opening, i.e. interval between cut off of nitrous oxide to extubation and eye opening respectively were recorded.

Sedation was evaluated using Ramsay Sedation Scale\textsuperscript{12}. Complications such as coughing, laryngospasm, bronchospasm or desaturation were noted.

With the power of study being 80% and confidence limits at 95%, a minimum sample size required to detect 30% difference in heart rate between study and control groups, was 24 patients in each group. We conducted study with 40 patients in each group to make it more authentic. Descriptive and inferential statistical analysis was carried out. Results on continuous measurements are presented on Mean ± SD (standard deviation) and results on categorical measurements are presented in Number (%). Student test (two tailed, independent) was used to test the significance of study parameters on continuous scale for intergroup and intragroup analysis on metric parameters. Levene’s test for homogeneity of variance was performed to assess the homogeneity of variance. Chi-square/Fisher Exact test was used to test the significance of study parameters on categorical scale between two groups. Statistical software SPSS version 17.0 was used for the data analysis. P value <0.05 was considered statistically significant.

Results

Both the groups were comparable with respect to age, sex, body weight and duration of surgery (Table 1).

\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Parameter} & \textbf{GROUP C (n=40)} & \textbf{GROUP D (n=40)} & \textbf{P VALUE} \\
\hline
Age (yrs) & 33.7 ± 11.1 & 34.9 ± 10.7 & .582 \\
\hline
gender (M/F) & 20/20 & 18/22 & .398 \\
\hline
duration of surgery (min) & 65.7 ± 21.7 & 62.9 ± 22.2 & .522 \\
\hline
weight (kg) & 56.1 ± 9.8 & 56.8 ± 9.8 & .744 \\
\hline
ASA (I/II) & 34/6 & 35/5 & .774 \\
\hline
\end{tabular}
Basal heart rate (HR) was comparable in both the groups. In group D, HR was comparable to basal value from 5th minute of the start of drug infusion and at extubation, however it was lower than basal value post extubation till 30 minutes whereas HR in group C showed a steady rise compared to preoperative values which was significant (P < 0.001) at all these time intervals. Intergroup comparison of heart rate at various time intervals showed clinically and statistically significant reduction in group D compared to group C (Figure 1).

Both groups were comparable with respect to basal SBP, DBP and MAP values. SBP and DBP values were comparable to preoperative values in Group D from 7th minute of the start of dexmedetomidine infusion till post extubation for 30 min but the respective values were significantly higher in group C. Comparison of SBP and DBP values at these time intervals showed significant reduction in group D than group C. Beyond 30 minutes SBP and DBP values were comparable between the two groups (Figure 2).

SpO₂ (%) and RR (breaths per minute) in both the groups were comparable at all time intervals (P > 0.05).

The Ramsay sedation scale was significantly higher in patients of Group D compared to patients of Group C at the time of extubation and at 5, 10, 15 and 30 minutes post extubation (Figure 3). However the average Ramsay sedation score was <3 in patients of Group D and all patients were easily arousable. Time to extubation in group D was 18.70±3.36 minutes compared to 15.24±1.60 minutes in group C (P < 0.001), and time to eye opening was 17.04±3.19 minutes and 13.88±1.55 minutes in group D and C respectively (P < 0.001).

### Table 2

<table>
<thead>
<tr>
<th>Complications</th>
<th>Group C (n=40)</th>
<th>Group D (n=40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension, n(%)</td>
<td>0(0%)</td>
<td>9(22.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>28(70%)</td>
<td>0(0%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0(0%)</td>
<td>2(5%)</td>
<td>0.562</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>29 (72.5%)</td>
<td>2(5%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Agitation</td>
<td>9(22.5%)</td>
<td>0(0%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Coughing</td>
<td>12(30%)</td>
<td>2(5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Desaturation</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Incidence of hypotension was higher in Group D versus Group C. However, incidence of hypertension, tachycardia, agitation, and coughing were higher in Group C versus Group D (Table 2). Incidence of laryngospasm, bronchospasm, and oxygen desaturation were not different between the two groups.

**Discussion**

The present study shows that administration of...
0.5 µg/kg of dexmedetomidine as an infusion over 10 minutes at the time of skin closure will attenuate hemodynamic responses to extubation and provides smooth extubation.

Complications at extubation include hypertension, tachycardia, dysrhythmias, myocardial ischemia; coughing; laryngospasm and bronchospasm; impaired laryngeal competence and pulmonary aspiration and hypoventilation\(^\text{13,14}\). Untreated tachycardia or hypertension from the increased sympathoadrenal activity will result in increased myocardial oxygen consumption, resulting in myocardial ischemia in patients at risk (patients with diabetes mellitus, cardiac disease, pre-eclampsia and those undergoing intracranial, intraocular or vascular surgeries)\(^\text{13,15,16}\). Coughing at the time of extubation is mainly attributed to the presence of secretions in oral cavity and tracheobronchial tree\(^\text{17}\) and by itself can result in tachycardia, hypertension, myocardial ischemia, increased intracranial and intraocular pressures, bronchospasm and surgical bleeding and wound disruption\(^\text{18}\). So the technique or drug chosen at extubation should attenuate hemodynamic disturbance and provide smooth extubation with minimal or no side effects.

Extubation of trachea with patients in a deeper plane of anesthesia avoids cardiovascular stimulation. This can be achieved by inhalation or intravenous anaesthetic agents, opioids or both, however it carries the higher risk of hypoventilation and upper airway obstruction\(^\text{13}\). Coughing may be particularly troublesome during “light anesthesia” extubation and

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**Fig. 2**
Intergroup comparison of SBP and DBP (mm of Hg). Data expressed as mean ± SD

**Fig. 3**
Intergroup comparison of Ramsay Sedation Score (RSS). Data expressed as mean ± SD
cannot be entirely prevented\textsuperscript{14}.

Dexmedetomidine by its alpha\textsubscript{2} agonist action at multiple sites not only results in decrease in heart rate and blood pressure, by central sympatholysis but also in analgesia, sedation, and anxiolysis\textsuperscript{19}.

Dexmedetomidine has been found to be superior to fentanyl and lignocaine in blunting hemodynamic changes to extubation\textsuperscript{20,21}. In the current study, the heart rate and blood pressures remained below baseline in the post-extubation period and the incidence of tachycardia and hypertension were lower following administration of dexmedetomidine which is concurrent with the observation of earlier studies\textsuperscript{20-22}.

Incidence of bradycardia is higher when a higher dose of dexmedetomidine is used\textsuperscript{22}. Low incidence of bradycardia in the present study may be attributable to the lower dose of dexmedetomidine used. However incidence of hypotension was slightly higher compared to other studies\textsuperscript{23}. Bradycardia and hypotension were both transient and responded to atropine and intravenous fluids respectively in the present study.

Incidence of coughing was significantly lower in the group receiving dexmedetomidine which is in accordance with observations of Aksu R and colleagues\textsuperscript{20}. Guler G and colleagues also noted the effect of dexmedetomidine on children undergoing adenotonsillectomy wherein dexmedetomidine group had significantly decreased incidence and severity of agitation and a smooth extubation without any increase in incidence of side effects when dexmedetomidine was administered intraoperatively\textsuperscript{23}. Alpha\textsubscript{2} agonist activity of dexmedetomidine is known to reduce secretions of mucus glands, glands of oral and tracheobronchial tree in particular\textsuperscript{24}. Reduction in secretions may result in decreased incidence of coughing and other complications such as laryngospasm and bronchospasm. However none of the patients in the present study complained of dry mouth.

Fourty eight percent of patients receiving dexmedetomidine were drowsy (RSS=30) but responded to oral commands following extubation and is in concurrence with the observations of Kothari D et al\textsuperscript{21}. However after 30 min of extubation sedation scores were comparable in both groups. In a study by Bindu B et al, 84% of patients receiving dexmedetomidine had a sedation score (RSS) of 3 after extubation which was higher compared to the present study and is attributed to use of higher dose of dexmedetomidine\textsuperscript{22}.

Time to extubation and eye opening were significantly prolonged in the dexmedetomidine group. This observation is in agreement with study conducted by by Guler G and colleagues on emergence agitation wherein time to extubation and emergence were prolonged significantly\textsuperscript{23}. However Erdil F and colleagues observed a contradictory finding in pediatric patients receiving sevoflurane, where time to extubation and eye opening were similar to that of control group\textsuperscript{25}.

The major limitation of this study is that it is rather focused on general population and quality of extubation was not studied. Future studies may be done in specific patient populations such as geriatric, neurosurgical and ophthalmic patients where extubation responses are equally critical to that of intubation responses.

**Conclusion**

The present study demonstrates that dexmedetomidine 0.5 µg/kg given before extubation attenuates the airway and hemodynamic reflexes during emergence from anesthesia while providing smooth extubation without causing undue sedation.
References


Append

Ramsay Sedation Scale\textsuperscript{12}.
1. Anxious and agitated, restless.
2. Co-operative, oriented, tranquil.
3. Responsive to verbal commands, drowsy.
5. Asleep, slow response to stimulation.
6. No response to stimulation.
PERI-ANESTHESIA ANAPHYLAXIS (PAA): WE STILL HAVE NOT STARTED POST-PAA TESTING FOR INCITING ANESTHESIA-RELATED ALLERGENS

Taghreed Alshaeri*, Deepak Gupta** and Ananthamurthy Nagabhushana***

Anaphylaxis during anesthesia is uncommon. Diagnosis of peri-anesthesia anaphylaxis (PAA) requires anesthesia providers’ vigilance for prompt diagnosis and treatment. In this case report, we present a challenging case with suspected PAA including its perioperative management, intensive care unit (ICU) course, and post-discharge follow-up. A 44-year-old female (body mass index = 26) presented for elective abdominal panniculectomy. Post-intubation, severe bronchospasm occurred that was non-responsive to nebulized albuterol and intravenous epinephrine. Continuous infusion of epinephrine was initiated. After aborting surgical procedure, the patient was transferred to ICU on continuous intravenous infusion of epinephrine. Venous blood sampling showed elevated troponin level. Echocardiography revealed ejection fraction of 25% suspicious of Takotsubo cardiomyopathy (mid cavitary variant). Tracheal extubation was only possible after three days. Subsequently, patient was discharged home with a cardiology follow-up appointment and a referral to an allergy specialist. Unfortunately at our institution (an academic university hospital in United States) along with neighboring institutions in near-by areas, the only allergy skin tests available are for local anesthetics and antibiotics, while neuromuscular blocking agents (NMBAs) cannot be tested (the suspected anaphylactic agent in our case was presumably rocuronium). In summary, PAA requires and responds to emergent diagnosis and immediate treatment; however there is still a long way to go to ensure post-PAA testing for inciting anesthesia-related allergens.

Introduction

Anaphylaxis during anesthesia is uncommon with reported range of incidences from 1 in 6,000 anesthetics/procedures (Norwegian study) to 1 in 10,000 anesthetics/procedures (French study) and to 1 in 20,000 anesthetics/procedures (Australian study)1-4. Diagnosis of peri-anesthesia anaphylaxis (PAA) requires anesthesia providers’ vigilance for prompt diagnosis and treatment. In this case report, we present a challenging case with suspected PAA including its perioperative management, intensive care unit (ICU) course, and post-discharge follow-up.

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Case report

A 44-year-old female (body mass index = 26) presented for elective abdominal panniculectomy. Her past medical history was significant for gastro-esophageal reflux disease, penicillin allergy, laparoscopic banding for intentional weight loss, cigarette smoking and recreational alcohol use. Patient had history of phentermine use for weight loss which she had stopped a week earlier. She had been prescribed beta-blocker after her bariatric surgery for two weeks but she never followed up with her cardiologist. However she had very good exercise tolerance and could walk and run many miles. Additionally, patient had denied any psychosocial stressors. Pre-surgical evaluation revealed an asymptomatic non-distressed patient along with normal vital signs. Airway assessment was deemed easy with Mallampati score as grade II and intact dentition. Cardiovascular and respiratory examinations were within normal limits. Intra-operatively, standard monitors were applied. Anesthesia was induced with propofol, fentanyl and rocuronium after adequate pre-oxygenation. The airway was intubated with a 7.5 cuffed endotracheal tube under direct laryngoscopy with Cormack-Lehane grade I view. However, no breath sounds were detected on auscultation and no end tidal carbon dioxide was observed on the monitor. At this point, severe bronchospasm was diagnosed and immediate therapy was initiated with nebulized albuterol and intravenous epinephrine (50mcg one time dose). After one-minute, end tidal carbon dioxide became apparent along with peak airway pressures @ 48-50 cm of water. Oxygen saturation levels dropped to low 80s (82%-85%) that was accompanied with fall in systolic blood pressure into the range of 65-80mmHg. Examination of the patient revealed no skin rashes, and at this point a tentative diagnosis of anaphylaxis was made with treatment consisting of epinephrine as intermittent boluses of 50-100 mcg intravenously along with intravenous one time dose of hydrocortisone and diphenhydramine. Patient’s clinical status was not improving and continuous infusion of epinephrine was initiated along with arterial line and central venous line insertions. Arterial blood gas analysis revealed arterial hypoxemia, metabolic acidosis, and hypokalemia. Sodium bicarbonate and potassium chloride infusions were infused. An emergent bronchoscopy revealed normal tracheobronchial mucosa and small amount of clear secretions were suctioned out. Chest skiagram revealed bilateral lung field fluffy opacities and hence furosemide 20mg was given intravenously to counteract possible acute pulmonary congestion/edema. Due to patient’s critical condition, the surgical procedure was aborted after discussion with the surgeon. The patient was transferred to ICU on continuous intravenous infusion of epinephrine. On ICU arrival, respiratory therapists performed alveolar recruitment maneuvers repeatedly that improved patient’s oxygen saturation levels to the low 90s. Venous blood sampling showed elevated troponin level and white blood cell count whereas electrolytes panel and hemoglobin/hematocrit levels were normal. First lab sample for tryptase levels was sent within hours of suspected anaphylactic reaction; however there was a lab error and correct reactive tryptase levels could not be determined because a second sample was sent only after more than 24hrs of suspected anaphylactic reaction.

Due to elevated troponin levels, cardiology team initiated treatment for non-ST-elevation myocardial infarction. Echocardiography revealed an increase in left ventricular cavity size with normal left ventricular thickness, and there was a severely decreased left ventricular systolic function with ejection fraction of 25% suspicious of Takotsubo cardiomyopathy (mid cavity variant). Over the next 48-72 hrs, her poor cardiac function and limited/restricted cardio-pulmonary reserve secondary to pulmonary edema led to multiple failed weaning trials and potential airway edema led to failed cuff leak tests. Tracheal extubation was only possible after three days; however she was subsequently transferred to medical floor in stable condition soon after. Cardiac catheterization revealed global left ventricular function’s depression with ejection fraction 25 % but coronary arteries did not show any evidence of obstructive atherosclerosis/ arteriosclerosis. As clinically improved, patient was discharged home with a cardiology follow-up appointment and a referral to an allergy specialist. Unfortunately at our institution (an academic university hospital in United States) along with neighboring institutions in near-by areas, the only allergy skin tests available are for local anesthetics and antibiotics, while neuromuscular blocking agents (NMBAs) cannot be
tested (the suspected anaphylactic agent in our case was presumably rocuronium). Hereafter, patient was lost to follow-up and it could not be determined if her echocardiographic findings resolved that would have given affirmation that patient was suffering from Takotsubo (stress) cardiomyopathy secondary to acute stress of clinically suspected anaphylaxis although anaphylaxis was unconfirmed due to poorly timed tryptase levels that were drawn after 24hrs of event when post-anaphylaxis tryptase levels come down to normal baseline values unless patients are suffering from mastocytosis wherein even baseline tryptase levels are high. Additionally, as there was no pre-procedure echocardiogram available in our records for comparison with post-event echocardiogram so it could not be completely ruled out if she was just suffering from acute peri-operative worsening of chronically pre-existent non-ischemic cardiomyopathy.

Discussion

Allergic reactions include wide variety of symptoms from dermatological symptoms, airway reactivity events, hemodynamic compromise, deteriorating perfusion at tissue level, plethora of gastrointestinal symptomatology, to anaphylaxis-related fatality secondary to refractory cardiovascular collapse and cardiac arrest. Pathophysiology of anaphylaxis is mediated via IgE antibodies that develop due to patient’s prior exposure to an antigen (or a similar structure substance) and the second exposure to the antigenic substance triggers accentuated/accelerated mast cell degranulation and basophil breakdown leading to release of histamine, tryptase and chemotactic factors in massive amounts. Comparatively, anaphylactoid reactions do not need pre-sensitization/IgE antibodies but involve direct destabilization of mast cells and basophils by the inciting agents. Histamine can be measured in plasma within a few minutes of an anaphylactic reaction but has very short half life often precluding its appropriately timed laboratory evaluation in a highly dynamic emergent clinical management scenario of suspected anaphylaxis with potential of fatal/irreversible cardiorespiratory outcome wherein immediate management based on clinical suspicion overrides the laboratory confirmation of histamine levels. However, tryptase that is also released during anaphylaxis, has a half-life of 120 minutes which is much longer than histamine’s half-life allowing time for rapid response clinical team to timely send tryptase levels for confirmation of suspected anaphylaxis. Hence, it is recommended to sample within first 120 minutes of a suspected anaphylactic reaction. To obtain baseline levels of tryptase (so as to rule out abnormally high baseline values of tryptase in cases of pre-existent mastocytosis), another blood sample needs to be examined after at least 24 hours.

The suspected anaphylactic agent in our patient was rocuronium, because allergic reactions secondary to propofol and fentanyl are somewhat less common. Different European studies have revealed that NMBAs are most likely to cause PAA with one French study reporting up to 58% of all PAA events being related to NMBAs as causative agent with at least 4% mortality after post-NMBA PAA events despite prompt management per another study. Rocuronium is the most common NMBA that accounts for more than half of all post-NMBA PAA events; and cross reactivity between different NMBAs exists with cisatracurium having the lowest cross-reactivity in patients who had suffered post-rocuronium PAA events. A recent study from Mayo clinic, United States demonstrated antibiotics as the most common agent inciting severe PAA leading to abortions/cancellations of the surgical cases, myocardial ischemic events, and unplanned admissions to ICUs. Our patient had clinical manifestations that raised a high degree of clinical suspicion for the diagnosis of PAA; unfortunately tryptase levels were obtained more than 24hrs after resuscitation mitigating their value in the confirmation of our clinical diagnosis. Our patient was resuscitated successfully with fluids and continuous infusion of epinephrine that was weaned very slowly over the period of 48hrs. No other vasoactive agents were required. Although sugammadex (reversal antidote for rocuronium) is not available in the United States because it has not been approved by U.S. Food and Drug Administration (FDA), several case reports have observed an effective role of sugammadex in the management of refractory anaphylactic reactions after rocuronium, with complete resolution of anaphylactic symptoms within a few minutes.
During post-discharge outpatient follow-up, several tests can be utilized to confirm the diagnosis of anaphylaxis and delineate the plethora of agents inciting anaphylaxis/other allergies. These tests include skin prick test (SPT), intradermal test (IDT), and serum specific IgE antibodies. The anesthesiologist should be responsible for referring PAA patients for further investigations to allergy specialist. SPTs are highly sensitive for NMBAs and gelatins but have poor sensitivity for barbiturates, benzodiazepines, and opiates. IDTs are usually performed when SPTs are negative despite clinical suspicion for drug-related anaphylaxis being very high; however, the specificity of IDTs is still unknown. Skin testing is usually carried out 4–6 weeks after PAA event. Patients should be instructed to stop all antihistamines for five days prior to the scheduled skin testing17-18.

The processes to do when PAA is suspected is all well-known but we should also discuss what all it entails if as a healthcare institution, we are not able to do SPTs/IDTs for the patients after their PAA events. During peri-anesthesia period, the patients receive many medications almost simultaneously or in quick succession that makes it difficult to pinpoint which agent precipitated PAA. Now without outpatient SPTs/IDTs that could delineate the specific peri-anesthesia medications as the inciting agent for the PAA event, it becomes a dicey scenario for future anesthetic administrations because anesthesia practice is commonly based on limited plethora of medications and anesthetics as a whole class cannot be branded/avoided assuming “anesthesia” caused anaphylaxis. Therefore, it is general accepted that the drug responsible for PAA needs to be determined via investigation, collaborative outpatient clinics need to be established for efficient post-hoc investigations of PAA, with perioperative timely investigation of mast cell tryptase levels and appropriately timed outpatient SPTs/IDTs being the optimal methods for confirming clinical diagnosis of anaphylaxis18-19. In our case, we contacted our allergy and immunology department; however skin testing for anesthetic medications was not performed in our institution due to unavailability of tests with possible underlying reasons: (a) medically questionable non-definite sensitivity/specificity of SPTs/IDTs for anesthetic agents as anaphylactic agents limiting these post-PAA testing/investigations to only major tertiary healthcare institutions; (b) unclear standing of third-party payers (insurance coverage) in regards to these tests; and (c) lack of clear-cut mandated enforced institutional guidelines for appropriate work-up and follow-up of suspected PAA. Many (but not all) tertiary healthcare institutions (possibly with research aptitude and acumen) around the world including some in the United States have specialized clinics for allergy skin testing for anesthetic medications with appropriate follow-up mechanisms. It is our humble opinion that all tertiary hospital settings (with collective-cumulative peri-anesthesia patient catchment areas covering the whole population within the societies exposed to peri-anesthesia periods on regular basis) should have the facilities for allergy skin testing of anesthetic medications to definitely delineate the causative agents for PAA events.

Conclusion

Management of allergic reactions during anesthesia requires emergent diagnosis and immediate treatment. Post-event laboratory investigation and post-discharge outpatient follow-up are crucial for identifying causative anaphylactic peri-anesthesia agents. However there is still a long way to go to ensure that these suspected peri-anesthesia allergic reactions do get investigated and anaphylactic agent do get identified so that specific agents (and not the general class of “anesthetics” as such) can be avoided in future anesthetic administrations to prevent the expected PAA events.

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References


SEVOFLURANE AS A CAUSE OF TORSADE DE POINTES IN PATIENT WITH THE LONG QT SYNDROME

Case Report

DOMINIK W. CHOROMANSKI*, SAPAN AMIN** AND MARIA M ZESTOS***

Background: Long QT syndrome (LQTS) is a rare condition that in certain circumstances can lead to severe and potentially lethal cardiac arrhythmia known as Torsade de Pointes (TdP). Inhalational anesthetics are among many medications and conditions known to prolong QT and thus potentially predispose the patient to TdP. Although studies have shown that sevoflurane should be safe for the healthy patients, the situation is unclear in patients with LQTS. We present a case of 14-year-old Caucasian female with the diagnosis of LQTS who developed TdP during sevoflurane inhalational induction. At the end, an anesthetic plan for patients with LQTS will be suggested.

Introduction

The QT interval represents a period of ventricular depolarization and repolarization in the cardiac cycle, beginning with QRS complex and ending with T wave (Figure 1)

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Long QT syndrome (LQTS) is a rare medical condition affecting the heart that can lead to a potentially fatal heart dysrhythmia-Torsade de Pointes (TdP). Although 10-15% of population has a genetic variation in LQTS genes with 13 mutations identified, the majority of the patients affected remain asymptomatic. Fewer have non-specific symptoms such as palpitations, syncope, seizures or sudden cardiac arrest. QT prolongation can also be acquired by medication or electrolyte abnormalities.

QT is not a fixed interval but shortens or lengthens with the HR. Therefore, QT should be corrected for the HR. The Bazett’s formula is the most widely used for this purpose.

\[
QT_c = \frac{QT}{\sqrt{RR}}
\]

In men, QTc>460 ms is prolonged and 440-460 ms borderline prolonged. In women those values are QTc>470 ms and QTc of 450-470 ms respectively. Cardiac rhythm disturbances usually do not occur until QTc exceeds 500 ms.

We present a case of TdP that occurred on inhalational induction in a patient with LQTS. We also review existing data on safety of anesthetic agents in long QT patients.

This study was founded from departmental resources. The authors have no conflicts of interest to disclose.

Case report

A 14 year-old ASA II Caucasian female (43.5 kg, 159 cm) with LQTS and intermittent 2 degree AV block presented for pacemaker replacement and heart catheterization. Patient had no allergies and took her atenolol in the morning. Physical exam was unremarkable. ECG from 2 months before showed paced rhythm of 60 bpm, QTc of 540 ms.

Patient was extremely afraid of IV start. Therefore, inhalational induction was offered. Maintenance was planned with propofol TIVA. Premedication was omitted and patient was taken to the cardiac catheterization lab.

Standard ASA monitors were applied. Single breath inhalational induction with sevoflurane was performed. After successful induction, while IV was started, VT in form of TdP occurred (Figure 2).

Help was called, sevoflurane was stopped. Shortly after, spontaneous resolution of VT was observed. Since vital signs were stable and an IV had been started, propofol, fentanyl and vecuronium were given and the trachea successfully intubated. Case continued uneventfully under propofol TIVA. At the end of the case patient had TOF 4/4 -91%; no reversal was given. Recovery was uneventful and patient was discharged next day.

Discussion

TdP happens when early depolarization occurs during prolonged repolarization of the ventricle. There are numerous risk factors that predispose to QT prolongation: medications, female sex, elderly age, electrolyte deficiencies (low potassium, magnesium, calcium), slow heart rhythms, complete AV block, structural heart diseases.

Many drugs cause a QT interval prolongation, however there is no linear relationship between the length of QT and risk of arrhythmia. Recently, transmural dispersion of repolarization (TDR) has been
found to be a better predictor of which medication can cause TdP. (evaluation of difference between T-wave peak and end of action potential in endocardial, epicardial and mid-myocardial cells). Shortened TDR, despite prolonged QTc is protective against TdP.

Medications prolonging the phase 3 of cardiac cycle are proarrhythmic. Those affecting phase 2 will possess antiarrhythmic properties.

The list of medications known to be a risk factor for TdP is extensive (http://www.azcert.org/). Out of anesthetic gases and volatile anesthetics, only sevoflurane is listed. Medications such as thiopental, succinylcholine, some NDMR (atracurium, pancuronium) prolong QT, without predisposing patient to TdP. Some studies show no effect of volatile anesthetics on the length of QT at all6,7. Majority of studies, however, show that halothane, isoflurane, enflurane, sevoflurane and desflurane do prolong the QT interval8,9,10. Whether that makes them torsadogenic, remains questionable. In some studies, sevoflurane was found to decrease the TDR5,6,11. In some case reports sevoflurane induced TdP, however always in presence of other predisposing factors12,13. Propofol has been shown to prolong QT severely and cause TdP14. Other papers showed minimal change in QT interval15 or reversal of QT prolongation in healthy patients16. Not much can be stated about the benzodiazepines.

Conclusion

The review of data collected so far is inconclusive. Current opinion on taking patients with LQTS through the anesthetic safely includes17:

- Obtaining baseline ECG (assess QTc)
- Continuing beta-blockers
- Providing calm environment, premedication, measures to decrease sympathetic stimulation
- Availability of defibrillator
- Using general anesthesia, anesthetic of choice (propofol, fentanyl, vecuronium). The safest volatile anesthetic is isoflurane. Avoidance of muscle relaxation reversal.
- Intra-operative temperature monitoring and hypothermia prevention.
- Regional anesthesia with epinephrine free local anesthetics.
- Providing comfortable environment, adequate pain control, QTc monitoring and avoidance of medications known to prolong the QT interval in post-op period.

Should TdP occur, stop offending drugs and address risk factors. The cornerstone of TdP therapy includes IV magnesium. If that is not successful, appropriate steps from ACLS should be followed.

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A CASE OF GRANISETRON ASSOCIATED INTRAOPERATIVE CARDIAC ARREST

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We report a case of intraoperative severe bradycardia that resulted in asystole and cardiac arrest shortly after (<2 min) intravenous granisetron 1mg for postoperative nausea and vomiting prophylaxis, that occurred in a female patient who underwent an elective total thyroidectomy. After two cycles of cardiopulmonary resuscitation and defibrillation, spontaneous circulation and sinus rhythm returned successfully. Postoperatively, the patient was diagnosed with a drug-induced long QT syndrome. At the time of the event, granisetron was the only medication administered. Furthermore, there was no reason to suspect electrolyte abnormalities. We explore the association of the onset of severe sinus bradycardia with the intravenous administration of granisetron.

Keywords: Antiemetics, complications, cardiac arrest

Introduction

The 5 Hydroxytryptamine type 3 (5-HT3) serotonin receptor antagonists are widely used in the treatment of postoperative (PONV) and chemotherapy induced nausea and vomiting (CINV). Even though its clinical safety has been established in many trials, they have the ability to block human cardiac sodium and potassium channels which may cause adverse cardiac effects and may predispose to cardiac dysrhythmias. Labeling for some of the currently approved 5-HT3 antagonists indicates the potential for cardiac adverse events, primarily prolongation of the QT interval but also other changes of electrocardiogram (ECG) intervals.

Cardiac dysrhythmias have been reported with 5-HT3 antagonists during the perioperative period, especially with ondansetron and dolasetron including ventricular or supraventricular tachycardia, premature ventricular contractions, atrial fibrillation, coronary vasospasm with chest pain and intraoperative pulseless ventricular tachycardia. Furthermore, similar adverse events have been reported in cancer patients under chemotherapy.
In October 2009, labeling of granisetron (Kytril; Roche Laboratories, Basel, Switzerland) was changed to include a warning for precautionary use in patients potentially vulnerable to QT prolongation. In 2010 and 2011, the US Food and Drug Administration (FDA) required the withdrawal of intravenous (IV) dolasetron for the treatment of CINV due to cardiac safety concerns and expanded warnings in labeling regarding potential cardiac safety issues with ondansetron and granisetron.

Although small clinical trials with IV granisetron have not found any significant changes in QT intervals, individual reports of QT prolongation have been published. It is important to note that concerning granisetron, a thorough QT study has not yet conducted. However, no published case reports of severe cardiac events were reported with granisetron as the suspect agent. We report a case of intraoperative severe bradycardia that resulted in asystole and cardiac arrest after IV granisetron 1mg for PONV prophylaxis, occurred in a female patient who underwent an elective total thyroidectomy.

Consent for publication

Patient has given written consent for publication

Case Description

A 50 year old morbidly obese female (104kg, 150cm, BMI 46.2), ASA II, was admitted to our tertiary university hospital for an elective total thyroidectomy. Past medical history included seven pregnancies, hyperthyroidism and psychosis diagnosed one year ago. Upon admission to the hospital, the patient reported no known medication allergies. At the time of first diagnosis, cardiac echocardiography was normal and 12-lead electrocardiogram (ECG) showed mild left ventricular hypertrophy (LVH) and borderline QT prolongation (QTc 459ms). Initial daily drug therapy regimen included methimazole 30mg, propranolol 80mg and risperidone 4mg. Four months later the patient visited the pre-anesthesia clinic and was evaluated. Thyroid function and psychological status were normal. A 12-lead ECG showed similar borderline QT prolongation (QTc 452ms). Her daily therapy regimen included methimazole 15mg, propranolol 40mg and sulpiride 100mg.

On the day of surgery patient came to operating room without changes with preoperative evaluation. Induction in anesthesia included midazolam 1mg, fentanyl 100 mcg, propofol 200mg and rocuronium 60mg. During maintenance with oxygen, nitrous oxide and sevoflurane 2%, dexamethasone 8mg, morphine 5mg and paracetamol 1000mg were administered. Throughout surgery, the patient’s heart was in normal sinus rhythm. Towards the end of the procedure patient received IV granisetron 1mg for PONV prophylaxis. Then, in less than 2min patient developed severe sinus bradycardia (<30 beats/min). Atropine 0.6mg was given immediately and pushed with 20 ml of normal saline. Bradycardia resulted in asystole and cardiopulmonary resuscitation (CPR) was initiated immediately. After one cycle of CPR sinus rhythm presented for a few seconds and then converted to ventricular fibrillation (VF). One shock 200J delivered and a second cycle of CPR started and epinephrine 1mg was given. CPR resulted in return of spontaneous circulation and sinus rhythm. Total CPR duration was 6 minutes. Arterial blood gases showed: pH 7.221, PaCO2 61mmHg, PaO2 232 mmHg, Hb 13 g/dl, with normal blood sugar and electrolytes (Na+, K+, Ca++) within normal limits. A 12-lead ECG showed sinus rhythm and substantial QT prolongation (QTc 494ms). Patient was then extubated, recovered uneventfully and was transferred to cardiac ICU. Cardiac CT angiography showed mild non obstructive coronary artery disease and mild LVH. Cardiologists decided that the patient indicated a high likelihood of drug-induced long QT-syndrome (LQTS). One week later they proceeded with right ventricle intracardiac device implantation for secondary prevention for VF arrest and long QT. Transthoracic echocardiography with contrast showed only mild LVH and patient was discharged. About 3 months later 12-lead ECG showed sinus rhythm with 1st degree atrioventricular block and normal QT interval (QTc 381ms).

Discussion

It is clear that very shortly (<2min) after the IV administration of granisetron 1mg for PONV
prophylaxis, our patient developed severe sinus bradycardia which eventually resulted in asystole and cardiac arrest. To the best of our knowledge this is the first case with granisetron in a dose for PONV prophylaxis, to be associated with intraoperative cardiac arrest. However, we cannot conclusively establish granisetron as the cause. The patient was incidentally taking propranolol for her daily therapy regimen which probably contributed to cardiac conduction abnormalities and to sinus bradycardia. Additionally, the patient was in antipsychotic drug therapy with sulpiride, associated with QT prolongation\(^{17-19}\). This emphasizes the importance of drug-drug interactions in the perioperative setting\(^2\). However, at the time of the event, granisetron was the only medication administered. Furthermore, there was no reason to suspect electrolyte abnormalities in predisposing to this event. Nonetheless, it is logical in this case to explore the association of the onset of severe sinus bradycardia with the intravenous administration of granisetron. The non-significant past medical history, as well as the timing of administration of other medications, support our concern.

The QT interval is the ECG manifestation of ventricular depolarization and repolarization. The RR interval preceding the QT interval is measured for rate correction (QTc). Although there is no consensus about QTc normal values, most agree that QTc intervals <440 ms are clearly normal and intervals of 440-460 ms in men and 440-470 ms in women are considered borderline\(^{19,20}\). Preoperatively our patient presented a borderline QT prolongation (QTc 452ms), while in the immediate postoperative period experienced a substantial QT prolongation (QTc 494ms). However, recent study showed that postoperative QTc-interval prolongation is common\(^{21}\). Several perioperatively administered drugs were associated with a substantial QT-interval prolongation and drug-drug interactions appeared to be a major contributing factor to postoperative QTc-prolongation\(^{21}\). The authors emphasized that the exact cause of postoperative QTc-prolongation and its clinical relevance, remain unclear\(^{21}\).

Drug-induced long QT syndrome (LQTS) is characterized by acquired QT interval prolongation and increased risk of torsade de pointes (TdP)\(^{19,20}\). In our patient after the first cycle of CPR sinus rhythm appeared for a few seconds and then was converted to VF. However, there is no adequate evidence that TdP was an intermediate dysrhythmia. The fact that 3 months after the event our patient presented with normal QT interval (QTc 381ms) rather confirms a drug-induced LQTS. QT prolongation and TdP are the most common reasons pharmaceuticals are restricted from the US market\(^22\).

In our patient the exact cause of the onset of this severe intraoperative sinus bradycardia, which resulted in asystole is not clear. Multiple QT prolonging drugs (granisetron, propranolol and sulpiride) may be an evident explanation\(^{18}\). Granisetron has been shown to block human cardiac sodium channels, which may lead to clinically relevant sodium channel block. Sodium channel blockade is associated with QRS widening, which may predispose to cardiac dysrhythmias. Furthermore, granisetron possesses affinity for the potassium channels, which may prolong repolarization. The complexity of cardiovascular responses produced by 5-hydroxytryptamine, include heterogeneous, unpredictable and conflicting effects leading to bradycardia or tachycardia, hypotension or hypertension, and vasodilatation or vasoconstriction\(^{23}\). This has been explained by the capability of this monoamine to interact with different receptors in the central nervous system, the autonomic ganglia and postganglionic nerve endings, the vascular smooth muscle and endothelium, and the cardiac tissue\(^{23}\).

The prevailing point of view is that inhibition of 5-HT\(_3\) receptors in the heart could lead to unopposed action of other serotonin receptors leading to tachyarrhythmias as described in the literature\(^{2-8}\). Postulated mechanism in animal studies, included inhibition of Bezold-Jarisch like cardiac reflex and coronary vasoconstriction\(^{23}\). However, this has not been yet established in humans. Actually, our patient experienced severe sinus bradycardia which resulted to cardiac arrest, instead of tachyarrhythmia. Three other cases have been reported with severe sinus bradycardia (<30beats/min) after IV administration of ondansetron during induction in anesthesia, associated with respiratory arrest and loss of consciousness\(^{24-25}\). Theoretically, the inhibition of 5-HT\(_3\) receptors may also lead to bradycardia, mediated by unopposed
activation of 5-HT(1A) receptors on the ground of drug-induced long QTS. It seems that so far we miss the whole picture of drug interactions with the perioperative use of the 5-HT3 antagonists. This means that further in depth research is required. It is important that anesthesiologists should be vigilant of rare but potentially life-threatening cardiovascular compromise induced by these medications. As cardiac dysrhythmias have been reported with 5-HT3 antagonists, it is inevitable that as their utilization in the perioperative setting increases, the frequency of such reports will increase.

References

We report the case of a pediatric patient with tetralogy of Fallot (TOF) and cleft palate deformity with difficult intubation in which a laryngeal mask airway (LMA) was used and converted into an endotracheal tube through retrograde intubation. The patient with TOF was scheduled for repair of the congenital bilateral cleft lip and palate. Inhalational induction with 4% sevoflurane was started. Conventional tracheal intubation was impossible because the patient had a difficult airway, and the procedure could cause severe cyanosis and respiratory distress. An LMA was inserted to maintain ventilation and anesthesia and to facilitate intubation. Retrograde intubation and a catheter mount were used to convert the LMA into a conventional endotracheal tube without difficulty. Airway management for patients with TOF and cleft palate deformity is not clear. Retrograde intubation permits replacing an LMA with an endotracheal tube. This method enables maintaining the airway until the LMA is exchanged with an endotracheal tube. This technique seems useful to facilitate difficult airway intubation in pediatric patients with TOF and cleft palate deformity.

Introduction

Orofacial cleft deformities are among the most common birth anomalies. Congenital heart diseases (CHD) have been reported in 9.5% of patients with orofacial cleft deformities. In a study, tetralogy of Fallot (TOF) was detected in 0.9% of patients with orofacial cleft deformity. There is limited information regarding airway management in these patients.

Patients with TOF have severe cyanosis and frequently develop respiratory distress. They can become severely cyanotic, hyperpneic and lethargic. A hypercyanotic spell presents with rapidly falling oxygen saturation in response to surgical or other stimulation. Inherent anatomical characteristics of the pediatric airway include cleft alveolus, protruding premaxilla and a high vaulted arch, which make airway management difficult. The cleft lip and palate and related CHDs might increase difficulty in laryngoscopy and intubation. Depending on the skill and experience of the anesthesiologist and the availability of equipment, various airway management strategies have been used for similar pediatric patients.

We report the case of a pediatric patient with TOF and a cleft palate deformity with difficult intubation in which a laryngeal mask airway (LMA) was used and converted into an endotracheal tube through retrograde intubation.
Case report

A 7-month-old male infant weighing 6.1 kg with TOF was admitted for repair of congenital bilateral cleft lip and palate (Figure 1). However, the patient did not undergo yet the TOF surgery. The patient’s failure to thrive was attributed to feeding difficulties due to the cleft palate. He only rarely experienced cyanotic crises. Preoperative echocardiography showed anatomy consistent with Fallot-type ventricular septal defect. An echocardiogram showed a ventricular septal defect (the size of the VSD was 6 mm), supravalvar pulmonary stenosis with a gradient of 90 mmHg over the outflow tract, and overriding of the aorta (50%).

The main pulmonary artery was of adequate size.

The patient’s baseline blood pressure and heart rate were 81/57 mmHg and 127 bpm, respectively. Peripheral oxygen saturation before induction of anesthesia was 86% on room air. The patient was induced with sevoflurane in oxygen. The inspired concentrations delivered via a mask were increased from 2% to 8% gradually. Anesthesia was induced with 8% sevoflurane in oxygen and a # 2 LMA was inserted successfully. Subsequently the lungs were ventilated without difficulty. Rocuronium 0.6 mg/kg was given as a slow intravenous bolus to facilitate tracheal intubation, followed by 2 mcg/kg fentanyl. The end tidal concentration of sevoflurane was maintained at approximately 3%.

Local infiltration of lignocaine (2%) was administered over the subcricoid region in the midline, and a puncture needle was introduced into the trachea by piercing the cricotraheal ligament in the cephalic plane at a 45° angle. After aspiration of free flow air, a 0.035 inch guidewire was introduced through the puncture needle and passed rostrally to emerge through the LMA. Then a 3.5-mm ID tracheal tube was introduced via the LMA over the retrograde guidewire (Figure 2). Tracheal intubation was confirmed by detecting exhaled CO₂. The connector of the introducing tube was removed, and the LMA was withdrawn, leaving the 3.5-mm tracheal tube in situ with the help of another intubation tube. When breathing sounds and CO₂ exhalation were reaffirmed, the guidewire was removed. Oxygen saturation remained satisfactory throughout intubation, ranging from 90% to 96%. Reconstructive surgery was performed without incident, and at the end of the procedure, the trachea was extubated following reversal of neuromuscular relaxation. The trachea was extubated when the patient was fully awake. The patient was then taken to the recovery room.

Discussion

Unsuccessful or difficult tracheal intubation remains an important cause of mortality and morbidity during anesthesia. Difficulties are more frequent in pediatric patients because of their anatomical variations. Anesthesiologists treating a patient with a difficult airway can use the following techniques: 1) awake fibreoptic intubation; 2) LMA; and 3) placing...
an alternative airway, such as an endotracheal tube\textsuperscript{11}. Appropriate airway management in patients with TOF and cleft palate deformity is not clear. Awake fibreoptic intubation might be unpleasant due to severe cyanosis and the development of respiratory distress in such pediatric patients. Using a LMA to repair congenital bilateral cleft lip and palate is difficult due to the risk of aspiration and blockage of the surgical site. Direct laryngoscopy has been avoided in such cases to prevent severe cyanosis and respiratory distress during airway management. Most anesthetic morbidity related to cleft lip repair procedures is due to difficult laryngoscopy and intubation or postoperative airway obstruction.

LMA is indicated for airway establishment in patients whose tracheas are difficult to intubate or whose lungs cannot be ventilated or oxygenated before progressing to cricothyroidotomy. The LMA creates a conduit that can provide better conditions for intubation\textsuperscript{14}.

Intubation via LMA using the fibreoptic bronchoscope to convert the LMA into an endotracheal tube has been described\textsuperscript{11}. In this technique, a 3.0-mm ID PVC tracheal tube is connected to the tip of another 2.5-mm tube to extend its length. The tracheal tube is introduced blindly via the bronchoscope adapter concave anteriorly. A major hazard of this technique is that, during advancement, the endotracheal tube can telescope blindly through the LMA, causing the tube to go into the esophagus\textsuperscript{15}. The retrograde guidewire allows placing the tracheal tube in the trachea. Another study indicated that a similar technique is possible in adult patients using retrograde intubation and a pediatric bronchoscope under direct visualisation\textsuperscript{12}. However, to the best of our knowledge, intubation via LMA using retrograde intubation in pediatric patients with TOF and cleft palate deformity has not been described.

In this case, a standard catheter mount was placed between the LMA connector and the anesthesia circuit. The retrograde wire was then advanced up to the tubular portion of the LMA while ventilating the lungs using the reservoir bag of the anesthesia machine.

A disadvantage of our case is the lack of the inclusion of a pediatric bronchoscope. The retrograde wire was advanced blindly through the LMA. However, in this case, desaturation did not occur during intubation because the laryngeal mask created a conduit that provided good conditions for intubation.

The LMA ventilates the lungs using the reservoir bag of the anesthesia machine, which can provide sufficient oxygen saturation during retrograde intubation. The LMA provides a conduit to relieve soft tissue obstruction, allow instrumentation of the airway and maintain oxygenation, ventilation and delivery of anesthetic gases. Retrograde intubation provides an improved guidewire method to convert an LMA into an endotracheal tube.

In conclusion, intubation via LMA using retrograde intubation was performed successfully for intubation of difficult airways in a pediatric patient with TOF and cleft palate deformity. This technique might be recommended to perform difficult airway intubation in pediatric patients with TOF and cleft palate deformity.
References


ANESTHETIC MANAGEMENT OF FEMORAL FRACTURE REPAIR IN A PATIENT WITH CERVICAL MYELOPATHY, AUTONOMIC DYSFUNCTION, AND DIFFICULT AIRWAY

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Spinal stenosis is a potentially serious condition that can lead to myelopathies and autonomic instability, both of which, as a result, may complicate anesthetic management. Additionally, neuraxial anesthesia appears to increase the risk of worsened neurological outcomes in this population. A 56-year-old female with spinal stenosis, autonomic dysfunction, and known difficult airway who required anesthesia for repair of a femur fracture is presented. After pre-operative arterial line and femoral block placement, an ultrasound guided subarachnoid block was safely placed. This supports the notion that in the appropriate setting, a safe, successful neuraxial blockade can be performed when a general anesthetic may be fraught with more risk.

Introduction

Spinal stenosis is a known cause of myelopathy, the symptoms of which are variable and depend on the degree of stenosis as well as spinal level(s) affected. Existing spinal stenosis with autonomic instability can complicate the anesthetic management of patients who require general anesthesia or neuraxial blockade1. These patients are thought to be at higher risk for exacerbation of symptoms with neuraxial anesthesia, thus often precluding it in many cases2.

We present a case of a 56-year-old female with cervical spinal stenosis, autonomic dysfunction, and known difficult airway previously necessitating emergent tracheostomy, now requiring anesthesia for an open reduction and internal fixation of a femur fracture.

Case Report

A 56-year-old Caucasian female with a history of rheumatoid arthritis on long-term steroid therapy, severe contractures, severe C5-C6 cervical stenosis with autonomic dysfunction, and profound neck stiffness with known difficult airway presented with right supracondylar femur fracture, necessitating repair in the operating room.

Pre-operative evaluation of the patient revealed a recent MRI (Figure 1) demonstrating significant cervical stenosis at the C5-C6 level with cord compression and worsening symptoms. She also had significant kyphosis, and had previously been told that she was a “difficult intubation,” requiring previous emergent tracheostomy at an outside institution during elective circumstances.

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Given this clinical picture, a spinal anesthetic was performed, in conjunction with pre-operative femoral nerve block. A radial arterial catheter was also placed, prior to placement of the spinal.

Intraoperatively, the patient experienced a transient 20 mmHg drop in mean arterial blood pressure after the spinal, for which a phenylephrine drip was initiated and titrated. A low dose propofol infusion was also infused for sedation, with high vigilance given to prevent potential apnea, while a difficult airway cart was also readily available. The procedure was completed successfully without complications.

Discussion

Given the patient’s complex history, a neuraxial anesthetic was chosen to minimize potential airway compromise. However, this was also complicated by her autonomic instability and spinal cord pathology. Because her cord compression was in the cervical area with no apparent thoracic or lumbar involvement, we proceeded with an isobaric bupivacaine spinal for primary surgical anesthesia, a technique often overlooked in cases of autonomic instability. Vaspressors and resuscitative drugs were readily available.

Our case report demonstrates that despite cervical spinal cord pathology and autonomic instability, regional anesthesia can be safely implemented with proper preparation and monitoring, even in cases where general anesthesia is almost always precluded.

References

ANESTHETIC MANAGEMENT IN UNEXPECTED EXTRA-ADRENAL PHEOCROMOCYTOMA PRESENTING WITH THORACIC SPINAL CORD COMPRESSION.

A case report

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A 52 year-old female presented with a thoracic paravertebral tumour causing spinal nerve root compression and lower limbs neurologic symptoms. The patient was scheduled to undergo thoracic decompression laminectomy and instrumentation. Markedly severe hemodynamic fluctuations happened during the manipulation of the tumor and continued after the tumor was removed. After multimodal antihypertensive therapy the vital signs were adequately managed and the surgery was successfully performed without complications. The patient was discharged without any sequelae ten days later. The pathology report indicated the diagnosis of extra-adrenal pheochromocytoma. Unexpected pheochromocytoma may lead to a fatal hypertensive crisis during surgery. For anesthesiologists and surgeons who encounter an unexpected hypertensive crisis during surgery, undiagnosed pheochromocytoma should always be considered.

Introduction

Extra-adrenal pheochromocytomas (PHEOs) of the neural crest-derived sympathetic ganglia are known as paragangliomas (PGLs) and account for 15% of all PHEOs1,2. PGLs are more likely to be malignant (29-40%) than adrenal PHEOs (10-15%)1,2. Extra adrenal PHEOs or catecholamine-secreting PGLs develop in the paraganglion chromaffin cells of the sympathetic nervous system. Subsequently, they are widely distributed near or within the autonomic nervous system and therefore they can be found anywhere in the sympathetic ganglia along the sympathetic chain from the base of the skull and neck to the pelvis, prostate gland and bladder3-5.

Most extra-adrenal PGLs are histologically benign but some can synthesize, store, and secrete catecholamines from the tumor. The presence of synchronous metastases is rare at initial diagnosis (approximately 10% for PHEOs and 34% for PGLs), but can occur even 20 years after diagnosis with the most common metastatic sites being the local lymph nodes, bone (50%), liver (50%) and lung (30%)6. Recently, specific genes related to PHEOs/PGLs pathogenesis were found to confer
an increased malignancy risk. Sometimes, extra-adrenal PHEO’s can be discovered during procedures or interventions that provoke release of catecholamines from the tumor. In such situations, endocrine emergency can occur with an unpredictable course and hemodynamic instability during surgery, especially in patients who have not been appropriately prepared for surgery.

PHEOs/PGLs of the spine will seldom be considered in a presurgical differential diagnosis due to its rarity (17%) and nonspecific imaging features. Only 14 thoracic spinal PGLs have been reported, and spinal cord compression was the presenting feature in every case. Three of those cases involved metastases and two were functional.

We report a case of a patient with a past surgical history of laparoscopic excision of PHEO ten years ago, who presented with a thoracic paravertebral tumor causing spinal nerve root compression and lower limbs neurologic symptoms.

**Case report**

A 52-year old female (77kg, 164cm), ASA II, presented to the hospital with thoracic back pain and lower limb weakness. She had a history of type 2 diabetes mellitus treated with oral hypoglycemic agents, and a past surgical history of laparoscopic excision of pheochromocytoma ten years ago. However, after the adrenalectomy procedure the patient was normotensive. At admission the blood pressure (BP) was 132/78 mmHg and the pulse rate 76 beats/min.

MRI confirmed the presence of a large, not well-demarcated tumour in the left paraspinal region of the T1–T4 vertebrae (Fig.1). Findings were suggestive of a narrow infiltrative process with an extraosseous soft tissue component extending through the neural foramina and epidural space compressing the spinal cord at T1 and T3 levels, causing cord compression at T3 level. The patient was initially diagnosed to have thoracic paravertebral tumor (neuroendocrine carcinoid tumour) with spinal nerve root compression and was scheduled for thoracic decompression laminectomy and instrumentation.

On the morning of surgery the patient was premedicated with diazepam 5 mg orally. In the operating room standard monitoring was applied, with electrocardiogram (ECG), pulse oximetry, and noninvasive blood pressure (BP) before the induction of anesthesia. Anesthesia was induced intravenously with propofol 160 mg, fentanyl...
100 mcg, and rocuronium 60mg. After tracheal intubation, additional monitoring included central venous pressure and continuous arterial pressure measurement. Electrodes for neurophysiologic monitoring of somatosensory evoked potential and motor evoked potentials were applied and the patient was positioned in prone position with pressure points secured. The patient remained hemodynamically stable during induction, intubation, and surgical incision. Sevoflurane was discontinued for better neurophysiology monitoring, but sometimes it was used, after informing the neurophysiologist. Propofol infusion 100 mcg/kg/min and remifentanil infusion 0.06 μg/kg/min on 50% air-oxygen mixture were used for maintenance of anesthesia.

During intra operative manipulation of the tumor, there was a sudden surge of blood pressure to 250/125 mmHg with tachycardia 140 beats/minute. The ECG showed supraventricular arrhythmia and T wave inversion. Therefore an extra-adrenal pheochromocytoma was suspected. Initially this was managed by stepping up the dose of propofol and remifentanil infusions, increasing the depth of anesthesia. The surgeon was asked to stop immediately the tumor manipulation in order to prepare additional medication. During surgical manipulations anesthesia was further deepened by increasing propofol from 100 to 250mcg/kg/min and remifentanil from 0.6 to 3.0 mcg/kg/min, respectively. The value of BIS decreased from 40-50 to 25. However, the BP continued to be high (190/110 mmHg). Nitroglycerine infusion was started at 5mcq/min and titrated up to 20 mcq/min, and labetalol intravenous boluses (a combined α-and β-adrenergic blockade) were administered (20 mg of labetalol in four doses of 5 mg each) to control the heart rate. Additionally, hydralazine intravenous boluses were administered (50 mg in ten doses of 5 mg each). Due to surgical technical reasons the tumor was not totally removed since it was attached to the spinal cord. After surgery the patient was taken intubated and ventilated to the intensive care unit with low dose nitroglycerine infusion. The patient was discharged home 10 days later. The pathology report confirmed the diagnosis of metastatic pheochromocytoma.

Discussion

The perioperative course and anesthetic management of patients with undiagnosed catecholamine-secreting PHEOs or PGLs has typically been reported only in small case series. The true incidence of unsuspected intraoperative catecholamine producing neuroendocrine tumors remains unknown. Although considered rare tumors with a prevalence of 0.1-0.5% in the general population, they are diagnosed in only half of the patients on whom a pheochromocytoma is found on autopsy.

Extra-adrenal PHEOs exhibit a highly variable clinical presentation depending on their secretory profile with 88% of cases presenting with headaches, sweating, palpitations, and paroxysmal or sustained hypertension. Hypertension is constant in 50% of patients, paroxysmal in 30% and absent in 20% of patients. However, in the absence of typical hypertension or for its rarity and nonspecific signs and symptoms, and diagnosis may be delayed or overlooked. Instead, most patients presented with mass effect related symptoms or incidentally from imaging studies such as a CT or MRI for other clinical conditions. Only 20% of extra-adrenal paragangliomas have been discovered due to hyper-functioning tumors.

Interestingly, in our case the patient was normotensive, after the past surgical laparoscopic excision of PHEO ten years ago, and presented with a thoracic paravertebral tumour causing spinal nerve root compression and lower limbs neurologic symptoms. Additionally, the patient remained hemodynamically stable during induction, laryngoscopy and surgical incision. An undiagnosed extraadrenal PHEO was highly suspected based on the hypertensive crisis caused by tumor manipulation during the surgery. This is only the 4th documented case and only the third to present functional adrenergic symptoms.

Intraoperative manipulation of such tumors likely causes increased levels of catecholamine release and dramatic or even catastrophic hemodynamic changes. Historically they have been associated with a mortality rate of up to 40%, while others increase the mortality rate close to 80%. However, recent literature using the collective experience extracted from case reports and case series of...
incidental catecholamine producing neuroendocrine tumors, suggests a lower than historically reported perioperative mortality to 8%\(^9\). Improved monitoring, better availability of intravenous antihypertensives, and advances in anesthesiology may partially explain this finding\(^9\). The diagnosis of pheochromocytoma was suspected intraoperatively only in 26% of patients\(^9\).

A higher index of suspicion intraoperatively may improve outcomes for patients with such tumors by promoting earlier and more aggressive hemodynamic management. Cooperation with the surgical team is important. Like in our case the surgeon should be asked to stop immediately the tumor manipulation in order to stop the trigger of catecholamine release and give time to anesthetist to prepare additional medication. Multimodal antihypertensive therapy including the use of an alpha adrenergic blocker or a combination antihypertensive medication containing an alpha receptor blocking component should be given early for the treatment of unexplained perioperative hypertensive crisis. The majority of the cases report nitrates as the intraoperative antihypertensives used, followed by beta-blockers and limited use of some form of alpha receptor blockage (33%)\(^9,10\).

We controlled hypertensive responses with deepening of anesthesia and analgesia levels like in other cases\(^19,20\). Especially, the use of high dose remifentanil infusion (>2mcg/kg/min) has been proved a safe and effective temporary treatment and may give the necessary time for preparing advanced antihypertensive medications\(^20\). The use of long-acting vasoactive medications compared to short-acting may exacerbate the hemodynamic instability\(^8,10\). When wide and perceptuous swing in the BP and heart rate, more short-acting vasoactive drugs rather than long-acting drugs are preferred and recommended\(^8,10\).

Based on the current evidence, it is very common for the patient to present persistent hypotension after tumor removal\(^13,5,8,12,19,20\). This may be ascribed to abrupt fall in catecholamine which leaded to a sudden dilation of the vasculature, leading in profound hypotension. However, in our case this did not occur and instead the patient needed low dose nitroglycerine infusion (1-5 mcg/min). This may attributed to the fact that the functional tumor was not totally removed. Therefore, there was a small part of the tumor still secreting catecholamines at a lower concentrations.

Although malignancy rate of these tumors are approximately 10%, their overall 5-year survival rate is less than 60%\(^6,21\). Malignant PHEO usually has poor prognosis. Malignant PGLs can also be treated surgically, but the prognosis depends primarily on whether the tumour metastasises. Spinal metastatic PHEOs/PGLs have led to pathologic fractures and spinal cord compression. The best combination of therapy for metastatic spinal PHEOs/PGLs appears to be surgical decompression followed by chemotherapy, molecular targeted therapy and radionuclide therapy with either 131I-MIBG or radiolabelled somatostatin analogues\(^22\).

In conclusion, unexpected pheochromocytoma causes increased levels of catecholamine release and may lead to dramatic or even catastrophic hemodynamic changes during surgery. A higher index of suspicion intraoperatively may improve outcomes for patients with such tumors by promoting earlier and more aggressive hemodynamic management. For anesthesiologists and surgeons who encounter an unexpected severe hypertensive crisis during surgery, undiagnosed pheochromocytoma should always be considered.
UN EXPECTED EXTRA-ABDOMINAL PHEOCROMOCYTOMA

References

A 66 year old man diagnosed with myasthenia gravis (Type IIa) three months prior to hospital admission maintained on pyridostigmine 180mg and prednisone 40 mg orally daily, presented with dyspnea and chest pain. Severe aortic stenosis (surface valve area: 0.96 cm²) was found on echocardiography and he was scheduled for aortic valve replacement.

Balanced technique of general anesthesia was performed using thiopental, sufentanil and rocuronium for anesthesia induction. A Datex Ohmeda M-NMT Module was attached and we aimed to produce deep neuromuscular blockade with rocuronium. Patient required 0.3mg/kg bolus and 0.1mg/kg/hr for maintenance for 4 hours. At the end of the procedure sugammadex 4mg/kg was given. Complete recovery of neuromuscular blockade was observed as evidenced by full recovery of the twitch response and the TOF (T4/T1 > 90%) following 210 seconds from the sugammadex dose. After fulfillment of the criteria of extubation (maximal inspiratory pressure of -20 cmH2O and tidal volume of more than 10mL/kg), the trachea was extubated at one hour after the end of surgery in the surgical cardiac intensive care unit.

Postoperative course was uneventful. Patient was discharged home on day four postoperatively.

In conclusion, this case report shows that the combination of rocuronium and sugammadex for neuromuscular blockade and its reversal, in a myasthenic patient on pyridostigmine, undergoing open heart surgery under cardiopulmonary bypass, is safe and efficient without untoward effects.

Introduction

Myasthenia Gravis (MG) is an autoimmune disease characterized by the release of antibodies against acetylcholine receptors at the neuromuscular junction. Therefore, careful perioperative management is required because of the unpredictable susceptibility to analgesia and muscle relaxants. To date, however, there have been very few reports which describe perioperative management in patients with myasthenia gravis undergoing cardiac surgery. In this report, we describe the successful perioperative management of a patient with myasthenia gravis who underwent aortic valve replacement under cardiopulmonary bypass.

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Case Report

A 66 year old man with severe ocular and limb muscle weakness along with mild oropharyngeal muscle weakness of three months duration. Edrophonium test was performed that showed an improvement in strength consistent with MG. Repetitive nerve stimulation was also done that showed evidence of muscle fatigue consistent with MG. A positive blood test for elevated concentration the acetylcholine receptor antibody test was strongly indicative of MG. Patient was diagnosed to have MG (ClassIIA) and was maintained on pyridostigmine 60mg orally three times daily and prednisone 40 mg once daily. He was also suffering from shortness of breath with ordinary physical activity that improved with rest (New York Heart Association class 2). Electrocardiogram revealed sinus rhythm. A chest x-ray showed a cardiothoracic ratio of 50% with no abnormal shadow. Cardiac echocardiography demonstrated normal left ventricular function with an ejection fraction of 65% and a cardiac index of 3.56 L/min/m2. Left atrium was severely dilated with severe aortic stenosis (The aortic valve surface area equal 0.96 cm2) so he was referred to our hospital for aortic valve replacement surgery.

On the day of surgery, blood pressure was 110/60 mmHg and heart rate was 63 beats per minute. The patient was premedicated with 5 mg diazepam orally 1 hour before operation after taking his morning dose of pyridostigmine 60mg and prednisone 40mg. Upon arrival to the operating room, patient was attached to standard monitors (5 leads electrocardiography, noninvasive blood pressure, pulse oximeter and, a neuromuscular stimulator (NMS) (Datex Ohmeda M-NMT module as part of Datex Ohmeda Aisys ventilator, Helsinki, Finland) with output 40 mA, impulse duration 200 ms, and an interval of 1 min was applied at the right ulnar nerve near the wrist and measured isotonic contractions of the adductor pollicis muscle. An intravenous and radial artery catheters were inserted. General anesthesia was induced with thiopental (1mg/kg), sufentanil (0.5 micg/kg, intravenously), lidocaine (1 mg/kg) and rocuronium (0.3 mg/kg). The trachea was then intubated without difficulty. Anesthesia was maintained with sevoflurane (1.0-1.5%), intermittent administration of sufentanil (1 mcg/kg), intravenously and a continuous infusion of rocuronium (0.1 mg/kg/hr intravenously) with no twitch on the train of four and a single stimulus following tetanic stimulation (deep neuromuscular blockade)8. During cardiopulmonary bypass(CPB) the nonpulsatile perfusion flow was kept at 2.5 L/min/m2, and mean arterial pressure was maintained between 60 and 70 mmHg. The myocardium was protected with intermittent antegrade cold blood cardioplegia. Aortic valve replacement was done, CPB was terminated at a rectal temperature of 36.5° uneventfully. There was no patient movement throughout the procedure. A total of 0.75 mg/kg (60 mg) rocuronium was administered during surgery. At the end of surgery and after sevoflurane was washed out, end expiratory concentration of 0.15% of its minimum alveolar concentration, sugammadex (4mg/kg) was given to reverse the deep neuromuscular blockade8. Complete recovery of neuromuscular blockade was observed as evidenced by full recovery of the twitch response and the TOF (T4/T1 > 90%) following 210 seconds from the sugammadex dose. After fulfillment of the criteria of extubation (maximal inspiratory pressure of -20 cmH2O and tidal volume of more than 10mL/kg), the trachea was extubated at one hour after the end of surgery in the cardiac surgical unit. Arterial blood gas on 5L O2 by face mask revealed PO2 = 167 mmHg, PCO2 = 36 mmHg, and pH = 7.47, oxygen saturation of 98%. Postoperative course was uneventful and the patient was discharged home on day 4 postoperatively.

Discussion

Any myasthenia gravis patient undergoing cardiac surgery requires proper preoperative preparation, appropriate selection and administration of anesthesia, with close monitoring because of the risk of respiratory failure in the postoperative period3-7.

There are different anesthetic techniques reported for myasthenia gravis patients undergoing cardiac surgery under general anesthesia that range from no use of any muscle relaxants3,4 with total intravenous anesthesia, restriction of opioids and the use of propofol1; however the presence of unwanted patient movement, diaphragmatic contractions, and difficult surgical conditions were observed4; to continuous monitoring of neuromuscular junction...
function with the use of muscle relaxants and high dose analgesia\(^6\), in order to provide the deep general anesthesia sufficient to prevent movement required to produce a quiescent operative field and postoperative sedation during and after cardiac surgery\(^5\). However, inadequate restoration of muscle function, especially of respiratory and swallowing muscles, causing prolonged mechanical ventilation, gastroesophageal reflux and pulmonary infection were observed\(^5\). Also, although currently used neuromuscular transmission blockers are considered safe, with the recovery of normal muscle function occurring after a period specific to each drug but the recovery of muscle relaxation may take more than 12 hours when vecuronium is used\(^7\). Acetylcholine esterase inhibitors use to reverse neuromuscular blockers presents a special problem in myasthenia gravis patients\(^9\) especially for patients maintained on cholinergic drugs till the day of surgery, cholinergic crisis may occur with muscular weakness that complicates postoperative course\(^9\).

The availability of sugammadex allowed different authors to be more courageous in the use of rocuronium and vecuronium in myasthenia gravis patients\(^10\). Sugammadex has a unique cyclodextrin for steroid nucleus neuromuscular blockers (NMB) reversal. Predictable, complete, and rapid reversal at any depth of neuromuscular block induced by rocuronium in adults, allows more use of deep neuromuscular blockade, with encapsulation of rocuronium and vecuronium\(^14,15\). It is associated with both a statistically and clinically significant shorter period of potentially unsafe recovery\(^16\). The Length of stay in the operating room (OR) and OR discharge-ready time were decreased with sugammadex reversal of deep NMB compared with placebo\(^17\).

Although, persistence of fade on the TOF was reported despite reversal of rocuronium by 12 mg/kg of sugammadex in a myasthenic patient undergoing thymectomy\(^18\). Rocuronium used in our case, with the dosage titrated and minimized using a neuromuscular transmission monitor intraoperatively maintaining a deep neuromuscular blockade that was reversed with sugammadex (4 mg/kg) at the end of the surgery, as was proposed by Duvaldestin et al\(^8\). Postoperative course was uneventful. Sugammadex made it possible to perform a safe general anesthesia procedure with skeletal muscle relaxants without prolonging mechanical ventilation. Reversal of rocuronium induced neuromuscular block by sugammadex in our patient with myasthenia gravis was rapid, efficient, and without signs of postoperative residual neuromuscular block. In conclusion, this case report shows that the combination of rocuronium and sugammadex for neuromuscular block and its reversal, in a myasthenic patient on pyridostigmine, undergoing open heart surgery under cardiopulmonary bypass, is safe and efficient without untoward effects.
References

PATIENT-VENTILATION ASYNCHRONY CAUSING NEGATIVE PRESSURE PULMONARY EDEMA IN AN INTUBATED OBESE PATIENT

Sahar M. Siddik-Sayyid*, Waseem AlFahel**
and Mohamad F. El-Khatib*

Negative pressure pulmonary edema is a potentially life-threatening condition that may occur when a large negative intrathoracic pressure is generated against a ‘physically’ obstructed upper airway during emergence from anesthesia. We report a 35 year old male patient who is morbidly obese and undergoing laparoscopic gastric bypass who developed negative pressure pulmonary edema without any evidence of a ‘physical’ upper airway obstruction. In our patient, the negative pressure pulmonary edema occurred after complete reversal of neuromuscular blockade and during manual positive pressure ventilation with the endotracheal tube still in place and in the presence of an oral airway. Since the patient was still intubated and had an airway in place with no possibility for physical obstruction, we speculate that the occurrence of the negative pressure pulmonary edema was mainly due to a ‘functional’ obstruction secondary to the severe patient-ventilation asynchrony that ensued upon reversal of the neuromuscular blockade.

Keywords: Negative pressure pulmonary edema; endotracheal tube; Asynchronized ventilation

Negative pressure pulmonary edema (NPPE) is a serious complication that may develop in the event of upper airway obstruction (UAO) during the emergence from anesthesia following extubation. Normally the airway obstruction is physical and is manifested as a laryngospasm or other causes of physical upper airway obstructions. Patients with difficult airways due to anatomic variations (i.e. short neck, nasopharyngeal soft tissue disorders), history of obstructive sleep apnea (OSA), obesity, and acromegaly are considered to be at higher risk for developing UAO and NPPE while emerging from anesthesia. We report an unusual case of NPPE in an obese patient upon emergence from general anesthesia for bariatric surgery, while the patient was still intubated and having an oral airway in situ with no chance for biting on the tube and no possibility of an obstruction. We postulate that NPPE in our patient was secondary to a ‘functional’ rather than ‘physical’ upper airway obstruction. Written informed consent was obtained from the patient.

Case Presentation

A 35 year old male patient presented for an elective laparoscopic gastric bypass under general anesthesia. The patient had a past medical history of hypertension (controlled by amlodipine) and OSA. His body mass index (BMI) was 42 kg/m². The preoperative assessment revealed Mallampati class II, adequate mouth opening, thyromental distance of 5 cm, and a large neck circumference. His laboratory investigations were all within normal limits. Echocardiography was normal with an
ejection fraction of 60-64%.

In the operating room, general anesthesia was induced with midazolam, xylocaine, fentanyl, and propofol. The patient was given succinylcholine and was smoothly and successfully intubated by direct laryngoscopy with the aid of a bougie. Anesthesia was maintained with sevoflurane and remifentanil. Intermittent boluses of rocuronium were supplemented to maintain adequate level of neuromuscular blockade (NMB). The patient received a total of 2 liters of crystalloids given that the blood loss was minimal, and his hemodynamics variables were all well maintained. At the end of the surgery which lasted for 2 hours, sevoflurane and remifentanil were stopped, and morphine 5 mg IV was given to control postoperative pain. Furthermore, sugammadex (400 mg IV) was administered to ensure complete reversal of NMB. The patient began spontaneous breathing and started regaining his consciousness while receiving gentle manual ventilation with an oxygen saturation of 98-99%. However, prior to extubation and removal of the oral airway and upon performing gentle suctioning of the oropharynx, the patient became severely agitated. Only forceful manual ventilation could be applied to overcome the patient’s agitation and ensure adequate ventilation. This was very difficult to impossible as the patient was extremely agitated and fighting against the manual breaths; then oxygen saturation started to decrease and reached 70-75%. Propofol (50 mg IV) was given immediately to sedate the patient and enable synchronized and efficient ventilation. Endotracheal tube (ETT) suctioning showed large amount of pink frothy secretions. Chest auscultation revealed bilateral inspiratory crepitus. The patient was kept intubated and manually ventilated. Chest x-ray (CXR) showed bilateral infiltrates with congestion consistent with the diagnosis of pulmonary edema. Manual positive pressure ventilation was continued and resulted in improvement in oxygen saturation to the range of 85% to 90%, and lasix (20 mg IV) was given. Thirty minutes later, the patient started to wake up and became fully conscious, more cooperative, and able to maintain his oxygenation (85%-90%) by spontaneous breathing without manual ventilation. Arterial blood gases revealed pH=7.31, PO$_2$=59mmHg, PCO$_2$=47mmHg, HCO$_3$=23mEq/L, SaO$_2$=88%, BD=-2.7mEq/L. The patient was extubated to noninvasive ventilatory support in the form of bilevel positive airway pressure (BiPAP) and was transferred to the recovery room where he received an additional dose of lasix (40 mg IV), and was kept on BiPAP. His oxygen saturation improved to 95-96%. The next day, arterial blood gas showed significant improvement in arterial blood gases (pH=7.41, PaO$_2$=102mmHg, PaCO$_2$=43mmHg, HCO$_3$=27mEq/L, Spo2=98%, BD=2.7mEq/L). Consequently, the patient was deescalated to oxygen facemask, and was transferred to a regular floor. He was discharged home two days later after showing normal clinical and radiological findings.

Discussion

The pathophysiology of the NPPE is multifactorial, and is thought to be a result of a gradient between the negative intrathoracic pressure generated by vigorous inspiratory efforts against an obstructed airway and the positive hydrostatic pressure of the pulmonary capillaries (created mainly by the increased venous return to the right heart accompanied by the hypoxic-induced systemic and pulmonary vasoconstriction). This gradient favors a transudation of fluid from capillaries into alveoli, and the resulting edema is referred to as type I NPPE.

In our case, the clinical findings (rapid desaturation, pink frothy secretion and inspiratory crepitus on chest auscultation) as well as the radiological findings (bilateral infiltrates with congestion) were strongly suggestive of pulmonary edema. The negative cardiac history of the patient speaks against a cardiac source for the observed lung edema. The presence of an ETT although decreases but does not eliminate the possibility for an obstruction and subsequently the development of NPPE. Sow Nam et al. reported a case of significant negative pressure pulmonary edema in an intubated patient who was biting on the ETT and causing airway obstruction. However in our intubated patient, an oral airway was inserted throughout the whole procedure which excludes the possibility of external airway obstruction by biting on the endotracheal tube.

At the time our patient developed pulmonary edema, he was still intubated but had already regained full muscle power following administration of
sugammadex. Forceful breathing against a physical obstruction could not be the underlying cause of NPPE in our patient since he was still intubated and could not bite on the ET tube secondary to the presence of the mouth piece. We speculate that the main cause for the NPPE in our patient is the severe and repetitive asynchronization between the patient’s vigorous breathing efforts and the aggressive prolonged and deep manual ventilation that was provided by the anesthesia team while the patient was agitated and exhibiting oxygen desaturation in an attempt to provide ventilation to the patient’s lungs and reverse the oxygen desaturation. Bhaskar and Fraser described a type II NPPE that is related to forceful exhalation against an obstruction which creates intrinsic positive end expiratory pressure in the alveoli. This mimics the valsalva maneuver which increases the alveolar pressure and decreases the venous return to the pulmonary vasculature, thus decreasing the pulmonary capillary pressure. Sudden relief of the obstruction causes abrupt decrease in alveolar pressure as well as increase in the venous return to the pulmonary capillaries, which in turn increases the hydrostatic pulmonary capillary pressure. Consequently, the pressure gradient will increase leading to pulmonary edema. Due to the severe agitation, it is highly probable that our patient was forcefully exhaling while positive pressure was being applied through aggressive manual ventilation. This could have created an obstruction against the patient exhaled breath. Releasing the bag and pausing manual ventilation would result in abrupt resolution of the obstruction which may contribute to the development of pulmonary edema type II by the above-mentioned mechanism.

Our unusual case illustrates the possibility of severe patient-manual ventilation asynchrony in the development of NPPE. This highlights the importance of smooth resumption of spontaneous breathing prior to extubation especially in such scenarios where the patient is obese, young, with a history of OSA and with full recovery of neuromuscular power. In such scenarios, we recommend the use of pressure support ventilation that can provide adequate ventilatory assistance while maintaining superior synchrony with the patients’ spontaneous breaths.
References

LETTER TO THE EDITOR

EFFECT OF YOKUKANsan, JAPANESE HERBAL MEDicINE, ON PHANTOM-LIMB PAIN

YUSuKE SUGASAWA∗

To the Editor:

Phantom-limb pain is highly prevalent after limb amputation but remains an extremely challenging pain condition to treat1,2. The treatment must be multimodal and mechanism-based because the underlying pathological changes occur in both the peripheral and the central nervous system after amputation1,2. We report a patient who had suffered from intractable phantom-limb pain for years, successfully treated with Japanese herbal medicine yokukansan.

A 30-year-old woman, who had undergone amputation of the left lower extremity under the knee consequence of trauma three years ago, was referred to our institution for the treatment of intractable chronic phantom-limb pain. Although the patient had been treated by medications with pregabalin (300 mg/day), and mixture of acetaminophen (1500 mg/day) and tramadol (150 mg/day), the numerical rating scale (NRS) at the first visit was 7/10. The NRS showed that the pain was not alleviated enough. Antidepressants and epidural block according to the recommendation on phantom-limb pain1,2 were ineffective in this case.

Keywords: Phantom-limb pain, Yokukansan, Japanese herbal medicine, Kampo.

The symptom in Kampo theory including anger, anxiety, and increased tonus of rectus abdominis indicated yokukansan should be suitable for the patient. Therefore, we intended to treat the patient with yokukansan (7.5 g/day) as a complemental treatment in combination with pregabalin, acetaminophen, and tramadol. Yokukansan successfully treated the phantom-limb pain and ameliorated NRS to 2/10 after 28 days. Recent researches suggest that yokukansan can inhibit opioid tolerance3, and attenuate neuropathic pain4,5.

Kampo, a traditional Japanese herbal medicine, is an alternative medical approach to intractable chronic pain. Yokukansan may be effective on patients suffering from phantom-limb pain without serious adverse reaction.

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Conflicts of interest: None.
References


SIMULATION LAB: “A CONTEMPORARY MEDICAL ESSENTIAL”

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Introduction

Simulation-Based Medical Education (SBME) has become a standard in medical schools and residency training programs. Although it can be difficult to show direct improvements in patient outcomes from the use of SBME, many areas of medical education are improved such as medical knowledge, comfort in procedural skills, and quality education improvement in simulation proficiency and team communications and teamwork. SBME has gradually filtered down to the undergraduate level and is being used increasingly by nursing and allied health programs. Utilization of simulation at all levels is sometimes referred to as, “simulation-based mastery learning” (SBML). Results from the incorporation of SBML are founded upon evidenced-based medicine and are translational to educational laboratories, improved patient care practices, improved patient outcomes and positive collateral effects downstream the can be difficult to quantify. Progressive results from the use of SBML are obtained through “thematic, sustained and cumulative” use in their local programs.

Why Simulation Labs?

The primary interest of most SBME users is in determining the effectiveness of simulation in improving the clinical reasoning skills of students. Manuals containing scenarios that are either purchased from proprietary sources and/or written in-house are typically developed. Simulation lab sites can develop workshops for use by nursing and allied health students to enhance theory-based lectures and to practice/apply skill sets in the team-based patient care atmosphere. Full use of any simulation lab includes utilization by students, local medical affiliates, community groups, disaster preparedness organizations and licensed training professionals such as BLS/ACLS/PALS & NRP providers. Suggested uses for any proposed simulation lab include partnerships with the local community to improve the health and education awareness of citizens. Simulation labs also have the potential to become involved in research projects linked to their college/university, local hospitals and investigations connected to local, regional and national research studies. Depending

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on local laws, rules and requirements, simulation labs may have the potential to be financially independent, based upon how they are managed and utilized. Of course, accreditation of simulation labs is available through the Society for Simulation in Healthcare (SSH) though currently this is optional for operation.

Teaching Strategy

Use of high-fidelity simulation as a teaching strategy with medical residents, nursing students and other allied health related programs is becoming a standard. Programs that have established simulation labs and SBME must work with faculty and staff to properly train all personnel involved to integrate the high-fidelity simulation into the curriculum. In addition, simulation labs can reach out to existing healthcare professionals, allowing them the opportunity to use simulation to refresh and develop patient care and procedural skills as a means of maximizing the use of the facility.

Simulation labs are encouraged to conduct and support research into the use of high-fidelity simulation as a teaching strategy to promote student success and enhanced development of critical-thinking (CT) skills. In one study, the link between CT and decision-making (DM) skills showed a positive correlation in respiratory therapists that were trained using simulation-based scenarios. In another study, the performance of respiratory therapists was evaluated using simulation-based training versus traditional methods for mini Bronchoalveolar lavage (mini-BAL) and showed an enhanced outcome through the use of comprehensive simulation training. The use of high-fidelity simulation in the training of respiratory therapists caring for patients on mechanical ventilators brings together critical care technology and the simulation environment in perfect synergy.

Low-Fidelity Options

The cost of building and outfitting a full hi-fidelity simulation lab can be prohibitive for many budgets. A recommended option available to programs everywhere is the employment of low-fidelity simulation medical education. Low-fidelity simulation can range from the use of low-fidelity manikins to standardized patients who either role-play or who actually manifest the disease(s) under study. The cost of purchasing low-fidelity manikins and hosting standardized patients within regular classrooms and labs is much less than their hi-fidelity counterparts and far more likely to fall within the budgets of education programs. Low-fidelity simulators can be used by respiratory care education programs and hospitals to certify skills competencies and for updating procedural and skills renewal. An important point, regardless of the level of simulation used, is that it is based on establishing and refreshing skills and progressing to, not replacing, the live clinical experience.

Hidden Benefits

Additional hidden benefits of utilizing SBME include significant areas of consideration in the changing world of patient care and the complexity of diseases in this century and beyond. Simulation can teach cultural sensitivity in healthcare for diverse populations in a wide variety of settings. In addition to using SBME to achieve the highest standard of training, the stewardship of human and material resources can also be taught. Simulation can assist with student critiques and expedite the use of research findings application to clinical practice. Simulation, fully utilized, needs to be incorporated throughout the curriculum in order to expose students to a wide variety of disease processes, competencies, scenarios and patient acuities.

SBME, for all levels, can be used to facilitate interdisciplinary communication and collaboration that has become part of contemporary best practice. Simulation labs are typically designed as replicas of patient care areas such as the intensive care unit, emergency department, surgical suites or a standard hospital room. The labs can be arranged fully equipped with storage areas, electronic pharmacy access, telephone communication and a private debriefing room. A contemporary trend in simulation lab utilization is scenario participation by interdisciplinary team members, including physicians, nurses, respiratory therapists, pharmacists, family members and other care-givers, in addition to a hi-fidelity
simulation manikin. We strongly recommend that hi-fidelity simulation labs be added to all undergraduate and graduate medical, nursing and allied healthcare training programs as a requirement for program accreditation and, additionally, that simulation be integrated into the curriculum for safe patient outcomes and best practices.

**Challenges**

Building and maintaining a simulation lab is not without unique challenges. One essential piece for the operation of a simulation lab is properly trained personnel to staff and run the scenarios, community outreach and to supervise all uses of the facility. Faculty members need to embrace the concept of simulation along with the hi-fidelity technical training. Simulation labs require the support of information technology (IT) staff as technology issues are expected with normal use of these tools. The greatest hurdle facing any group planning for a simulation laboratory is finding the funding and political support to move forward with construction, purchases and training. One pillar in the camp for any such group is the body of evidenced-based literature which has expanded during the last couple of decades in the area of simulation use in medical education.

**Summary**

Simulation-based medical education (SBME) and simulation-based mastery learning (SBML) has become well-established in undergraduate and graduate medical, nursing and allied healthcare training programs. Although still in its relative infancy, the use of hi-fidelity simulation to train students in a variety of health-related professions is becoming a foundational cornerstone in program curriculum in the United States and, increasingly, in the international circle. The entire investment return resulting from the inclusion of simulation training labs in healthcare programs has just begun to be realized. The future is bright for this approach to education and healthcare to become an essential tool in the resource education box for colleges, universities, hospitals and research facilities as they serve the mission of training healthcare professionals to meet the growing needs of aging populations.
References


ERRATUM

The correct spelling name of the Last author of the article entitled "Submucosal dissection of the retropharyngeal space during nasal intubation" and published in the October 2015 issue of the Middle East Journal of Anesthesiology (pp. 309--314) is "JOSEPH D. TOBIAS" and not "qoseph D. Tobias".

ERRATUM

The affiliation of the author: "Jayeeta Verma" in the following article: "Malpositioned LMA confused as foreign body in nasal cavity", published in Vol. 23, No. 3 October 2015 of the Middle East Journal of Anesthesiology (pp. 351--354), should appear as:

"Dr. Jayeeta Verma, Lecturer, MGMDCH, Sector 1, Kamothe, Navi Mumbai. Pin 410 209. (India)" instead of : “Emergency Medicine and Intensive Care Department, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia: SolamyS@sng. med. sa” 6, October 2012

ERRATUM

The affiliation of the authors: "Adesanmi Akinsulore*a, Afolabi M. Owojuyigbe **b, Aramide F. Faponle**c, Femi O. Fatoye*d" in the following article: "Assessment of preoperative and postoperative anxiety among elective major surgery patients in a tertiary hospital in Nigeria", published in Vol. 23, No. 2, June 2015 of the Middle East Journal of Anesthesiology (pp. 235-240) should appear as :

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