VOLUME 22 No. 1 FEBRUARY 2013
ISSN 0544-0440

MIDDLE EAST JOURNAL OF ANESTHESIOLOGY

"For some must watch, while some must sleep"

HAMLET - Act. III, Sc.ii

Publication of the Department of Anesthesiology of the American University of Beirut Medical Center
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MIDDLE EAST JOURNAL OF ANESTHESIOLOGY
Department of Anesthesiology
American University of Beirut Medical Center
P.O. Box 11-0236. Beirut 1107-2020, Lebanon

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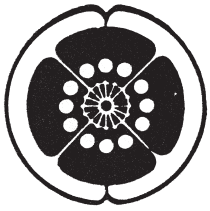

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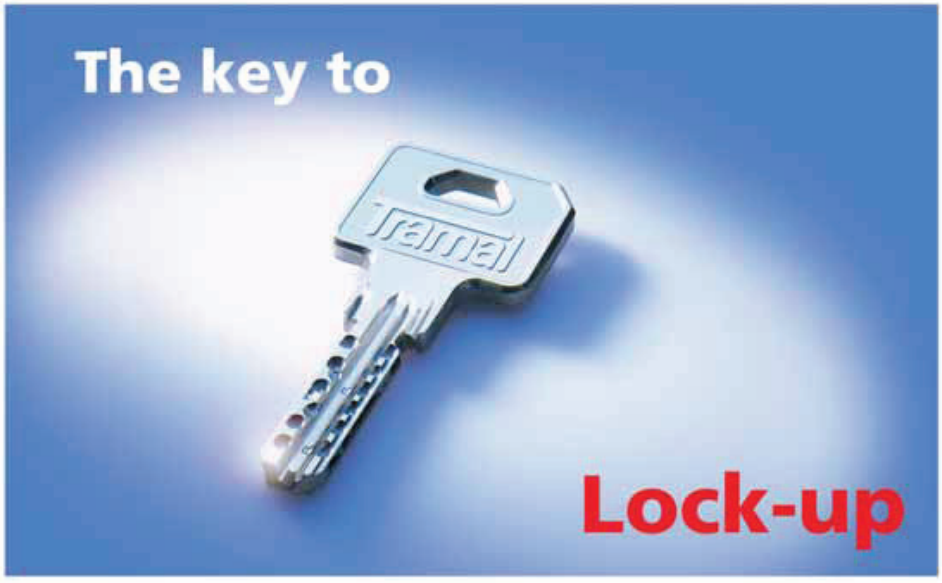

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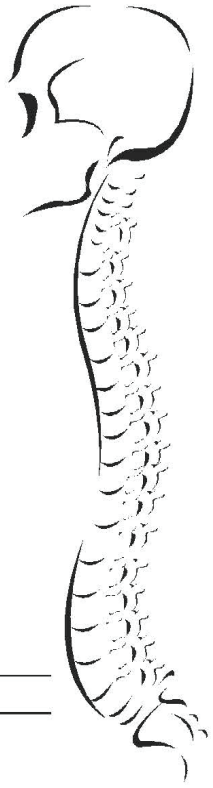

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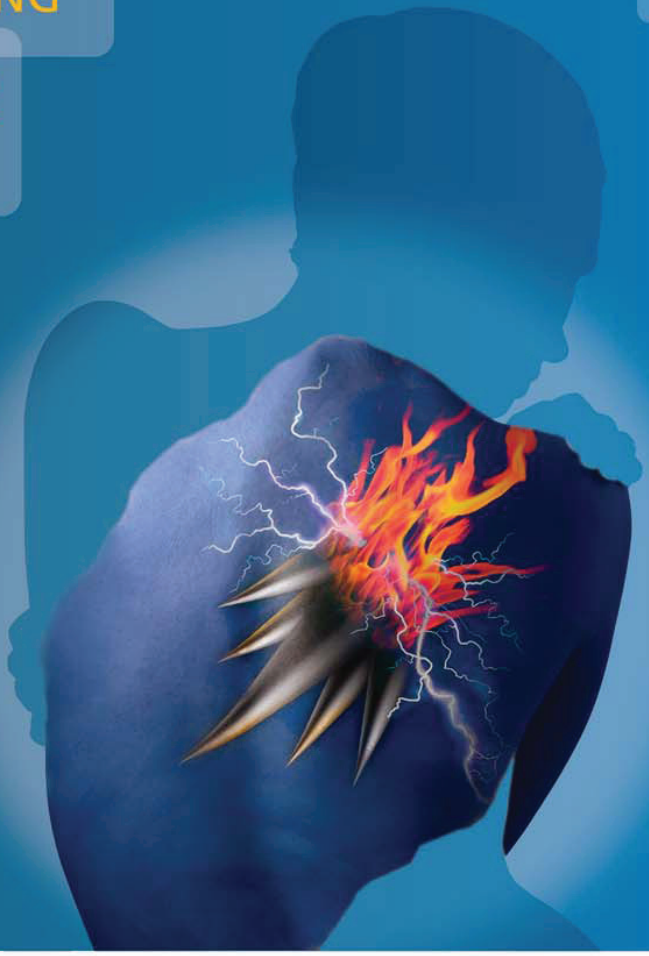

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* Train-of-four
† Post-tetanic counts
‡ Second twitch

REFERENCES: 1. BRIDION Summary of Product Characteristics (SPC) **2.** Blobner M, Eriksson LI, Scholz J, Motsch J, Della Rocca G, Prins ME. Reversal of rocuronium-induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. [published online ahead of print July 30, 2010]. Eur J Anaesthesiol. doi:10.1097/EJA.0b013e32833d56b7.
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Middle East Journal of Anesthesiology
Vol. 22, No. 1, February 2013

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EDUCATIONAL REPORT

In Loving Memory Of

Dr. Michel Slim

"a student of life"

Dr. Michel Slim

On January 12, 2013, Dr. Michel Slim of Rye, NY passed away surrounded with love by his family. Dr. Slim was the father of Pediatric Surgery in Lebanon and the Middle East. Dr. Slim completed his General Surgical Residency at AUB in 1958, followed by additional surgical residency training at Case Western Reserve University in Cleveland. He obtained his Pediatric Surgery Fellowship followed by a Pediatric Cardiac Surgery Fellowship at The University of Pittsburgh. Dr. Slim returned to AUB in 1962 and stayed on faculty till 1986. During that period he was instrumental in developing Pediatric Surgery in Lebanon and the Middle East. He played a major role in initiating Pediatric Cardiac Surgery teams at AUBMC and the region. In 1986, Dr Slim joined New York Medical College and became Chief of Pediatric Surgery and Director of Pediatric Trauma. He was one of the founders of Maria Fareri children's hospital and performed the first surgical procedure after its opening. He continued to support AUB and AUB graduates in every possible way. Upon retirement in 2006, Dr. Slim was honored as an Emeritus Professor of Pediatric Surgery at New York Medical College. He continued to be active in teaching medical students and residents until he suffered a stroke two years ago. Dr. Slim authored and co-authored a large number of papers and book chapters and was a pioneer in Pediatric Surgery. He was a member of most prestigious surgical societies and served as the president of the AUB Surgical Alumni Society of North America.

Dr. Slim was a great teacher and a talented surgeon. He had a big smile and a big heart. He was passionately devoted to each and every patient in his care. He mentored and supported many students, residents and physicians and was very committed to AUB. He is survived by his wife Norma and his three daughters: Julie, Lina, and Nayla and his five grandchildren. He will be dearly missed.

EDITORIAL

SUCCINYLCHOLINE-TRIGGERRED "MASSETER SPASM"

- MAY BE A VARIANT NORMAL RESPONSE -

Succinylcholine-triggered "masseter spasm"[1] is a marked increase in tension of the jaw muscles after administration of succinylcholine (Sch). Muscle testing reveals 50% incidence of malignant hyperthermia (MH) in patients who have an episode of succinylcholine-triggered "masseter spasm"[2]. However, succinylcholine-triggered "masseter spasm" may be the normal pharmacologic response of the masseter muscle to succinylcholine [3-5].

A tremendous breakthrough in the understanding of "masseter spasm" is the recent finding that the increased tone in the masseter muscle seen after succinylcholine may be a normal response[3-5]. Correlative study of the physiologic and morphologic characteristics of the masseter muscle of the rat has shown that the masseter muscle does not easily fatigue by tetanic stimulation, and is rich with oxidoreductive enzymatic activity[6]. Such characteristics may explain, in part, the continued contracture of the masseter muscle without fatigue in response to succinylcholine. A study of structure, pattern of innervations, and mechanical properties of vertebrate muscles has shown that succinylcholine-induced contracture may occur in "tonic" muscle fibers of mammals[7]. Thus, succinylcholine-induced contracture may be the normal pharmacologic response of the masseter muscle, similar to the succinylcholine-induced contracture of the extraocular muscles[8].

The masseter muscles contain slow "tonic" fibers that can respond to depolarizing neuromuscular blockers with a contracture. There is a spectrum of responses: a tight jaw that becomes a rigid jaw and then a very rigid (locked) jaw. In more than 80% of patients with isolated succinylcholine-induced trismus but not associated with rigidity of other muscles, or signs of hypermetabolism, it is a variant normal response, similar to the succinylcholine-induced contracture of the extraocular muscles.

The extraocular muscles are "tonic" muscles, and unlike other mammalian striated muscles, they are multiply innervated, and have several neuromuscular junctions along the surface of each muscle cell[9]. Also, in contrast with other muscles, the extraocular muscles contain both mature and immature fetal receptors. That is why succinylcholine, instead of causing a brief contraction followed by paralysis, the drug causes a long-lasting contracture response, associated with an increase of the intra-ocular pressure. The incidence of succinylcholine-induced "masseter spasm" may be as high as 2.6% in children with strabismus[10].

Muscle testing (in-vitro contracture test) in patients who had an episode of "masseter spasm" revealed a 50% incidence of MH susceptibility, and yet very few patients who have MH susceptibility even had an episode of MH.

Succinylcholine-triggered "masseter spasm" should always be presumptive of MH susceptibility until proven otherwise. However, before condemning a patient as MH susceptible, we must exclude other causes of "masseter spasm" such as a variant normal response, a contracture response of a denervated masseter muscle, or the presence of myotonia[11].

Previous reports have shown that succinylcholine-induced muscle contracture can occur in

denervated limb muscles[12]. This has been attributed to denervation supersensitivity to succinylcholine secondary to extrajunctional spread of the endplate receptors over the entire muscle membrane, and to change of the mature receptors into the immature fetal type(up-regulation). A similar response can occur at the denervated masseter and temporalis muscles which are innervated by the mandibular division of the trigeminal nerve. Similar to the denervated limb muscles, Sch-induced contracture of the denervated jaw muscles can be relaxed by a high dose of nondepolarising neuromuscular blocking drug[12-14].

Succinylcholine can also trigger generalized tonic contracture of skeletal muscles including "masseter spasm" in myotonic patients. Myotonia is characterized by hperexitability of skeletal muscles, which respond by repetitive firing of action potentials to either direct or indirect muscle stimulation. The disease is observed in patients with three hereditary muscle disorders that compromise the myotonic syndrome: myoyonia congenita, myotonia dystrophica, and paramyotonia; the three disorders are probably manifestations of a single disease. Also, hypothyroidism can result in a myotonia-like syndrome11. Abnormal response to succinylcholine has been observed in myotonic animals and in man. Sch depolarizes the endplate, producing a long-lasting endplate potential which is capable of firing repetitive action potentials associated with tonic contracture of the myotonic skeletal muscles allover the body. Sch-induced myotonic contractures can be prevented and/or controlled by nondepolarising muscle relaxants. Thus, nondepolarising relaxants have been successfully used to control Sch-induced myotonic contractures[11].

Muscle testing (in-vitro contracture test) in patients who had an episode of "masseter spasm" revealed a 50% incidence of MH susceptibility, and yet very few patients who have MH susceptibility have ever had an episode of MH[15-17].

The pathology of skeletal muscles in MH is restricted to the excitation-contraction coupling and the sarcoplasmic reticulum, while the neuromuscular junction and the contraction elements are normal[18]. Thus, MH contracture is not inhibited by neuromuscular blockers, but by dantrolene which inhibits the action potential-contraction coupling. It may be reasonable to suggest that the "masseter spasm" does not mark MH susceptibility, if it is isolated, not associated with hypermetabolism, as evidenced by increased body temperature, and elevated end-tidal CO_2 associated with decreased SVO_2. Also, if the "masseter spasm" is readily relieved by nondepolarising muscle relaxant. In contrast, succinylcholine-induced "masseter spasm" secondary to other causes such as a normal variant response, myotonia 11 or denervation[12-14] is usually isolated except when associated with myotonia, is not associated with hypermetabolism, and is readily relieved by nondepolarising muscle relaxant.

In conclusion, it can be suggested that an isolated succinylcholine-induced 'masseter spasm", which is not associated with hypermetabolic signs, and is readily relieved by nondepolarising muscle relaxant may not indicate malignant hyperthermia susceptibility.

Anis Baraka, MD, FRCA (Hon)

Emeritus Professor, American University of Beirut

Emeritus Editor-in-Chief, Middle East Journal of Anesthesiology

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REVIEW ARTICLE

ANALGESIC EFFICACY OF CONTINUOUS INTRAVENOUS MAGNESIUM INFUSION AS AN ADJUVANT TO MORPHINE FOR POSTOPERATIVE ANALGESIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Jamie D. Murphy*, Janaki Paskaradevan**, Lisa L. Eisler***, Jean-Pierre P. Ouanes****, Vicente A. Garcia tomas*****, Elizabeth A. Freck* and Christopher L. Wu******

Abstract

Background: The efficacy of perioperative intravenous magnesium administration on postoperative opioid use, opioid-related side effects (e.g., nausea and vomiting) and pain are uncertain, as randomized controlled trials on this topic have reported disparate results. The objective of this systematic review is to determine if perioperative magnesium reduces opioid use, opioid-related side effects, and postoperative pain.

Methods: An electronic search was conducted using the Library of Medicine's PubMed and EMBASE databases. Included studies consisted of randomized controlled trials in an adult population with a clearly defined comparison of perioperative intravenous magnesium administration to a control with a documented assessment of opioid usage and postoperative pain. Relevant data was abstracted from included studies. Pooled estimates for weighted mean difference (WMD) with 95% confidence intervals (CI) were obtained for our primary outcome (opioid usage) using the Cochrane Collaboration's RevMan version 4.2.7 (Cochrane Collaboration; Oxford, United Kingdom). WMD and odds ratios (OR) were calculated using a random effects model.

Results: The literature search ultimately yielded 22 trials, enrolling 1177 (599 magnesium, 578 control) patients, who were included in the analysis. A significant decrease in morphine usage by those patients who received magnesium was noted (WMD = -7.40; 95% CI: -9.40 to -5.41, $p < 0.00001$). Perioperative magnesium administration was not associated with a difference in postoperative nausea or vomiting (RR = 0.76; 95% CI: 0.52 to 1.09, $p = 0.14$). The pooled visual analog scores for pain at 4-6 hours after surgery were significantly less in those patients who received magnesium surgery (WMD = -0.67; 95% CI: -1.12 to -0.23, $p = 0.003$); however, there was no difference in pain scores at 20-24 hours after surgery (WMD = -0.25; 95% CI: -0.62 to 0.71, $p = 0.17$).

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Conclusion: Based on the results of this systematic review, perioperative intravenous magnesium may be a useful adjuvant for the management of postoperative pain providing analgesia through a different mechanism of action than that of opioids and would make a potential addition to a multimodal analgesic treatment plan; however, the decrease in opioid use with perioperative magnesium infusion does not appear to be associated with a decrease in opioid-related side effects.

Financial support: This study was supported by the Department of Anesthesiology and Critical Care Medicine at the Johns Hopkins University.

Introduction

Opioid-based analgesia plays a significant role in the control of postsurgical pain; however, use of opioid may lead to significant side effects (e.g., nausea and vomiting) and adverse events (e.g., respiratory depression), which may be associated with significantly longer hospital stays and higher hospital costs in the postsurgical setting[1,2]. Since these adverse events occur more often in patients receiving higher doses of opioids[1], it is important to find ways to reduce opioid use in the postoperative period. Multimodal analgesia, using a non-opioid analgesic in addition to an opioid analgesic, has been suggested as a way to improve postoperative pain control and reduce opioid use[2].

Magnesium is a non-opioid analgesic that has been studied as an adjuvant to opioid analgesics[3]. Magnesium sulfate has been found to have anesthetic, analgesic, and muscle relaxation effects and it has been suggested that magnesium may play a role in reducing analgesic requirements during the postoperative period[4]. However, conflicting results have been found regarding the degree to which magnesium can reduce postoperative pain, postoperative analgesic requirements and postoperative side effects due to opioid use. As such, we have undertaken a systematic review and meta-analysis of published randomized control trials (RCTs) investigating perioperative intravenous magnesium infusion and postoperative outcomes to further examine these issues.

Methods

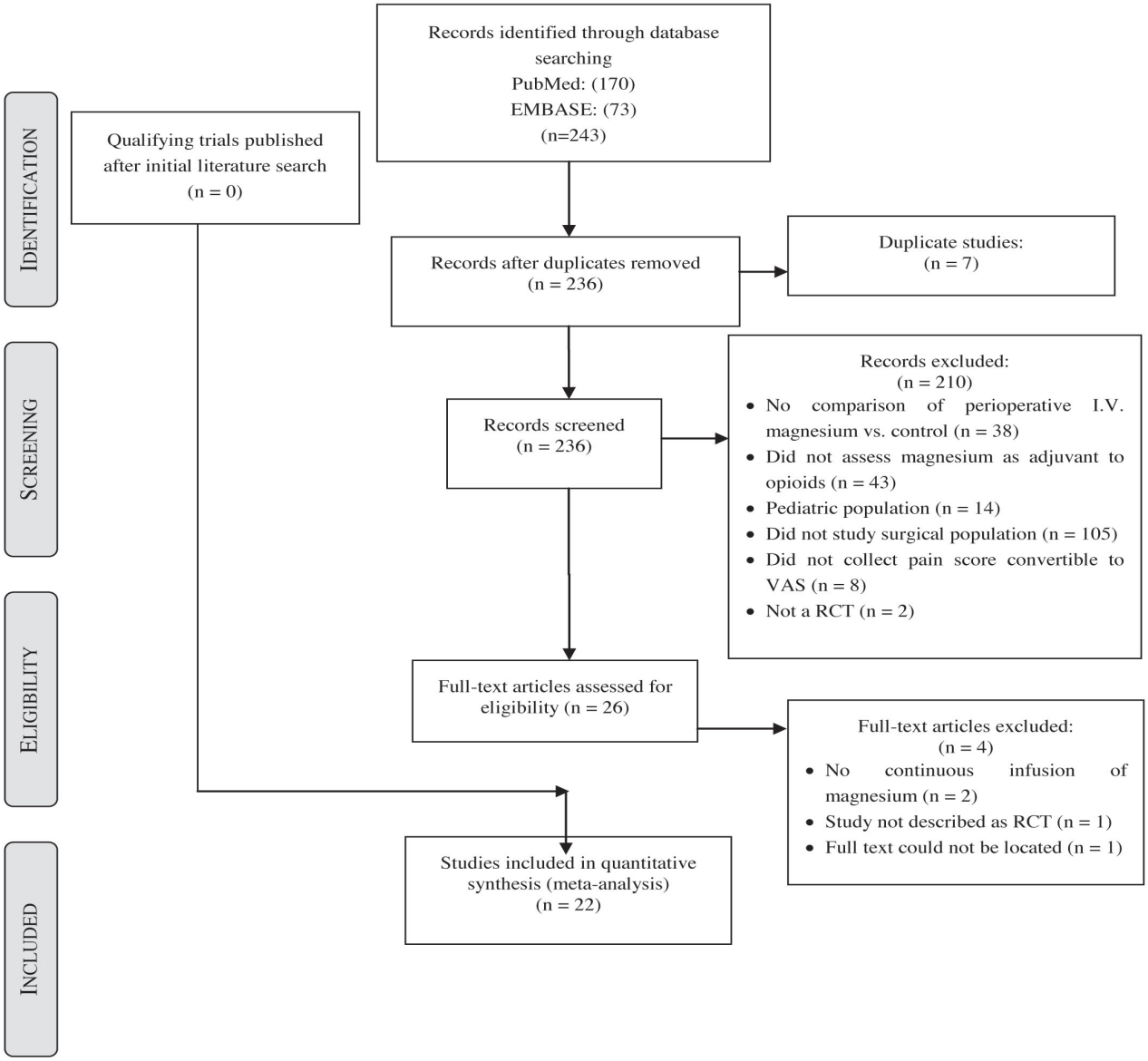
This study was exempt from the Johns Hopkins Institutional Review Board. The aim of this study was to review all relevant randomized controlled trials (RCTs) assessing the role of magnesium as an adjuvant to opioid based postoperative analgesia. In conducting this study, we followed the recommended checklist provided by the PRISMA statement[5]. An electronic literature search of the Library of Medicine's PubMed and EMBASE databases was conducted in July, 2011. Searches were limited to RCTs and the search terms used were "magnesium" and "pain". Abstracts were screened based on the following criteria for inclusion: 1) adult study population; 2) surgical population; 3) clear comparison of perioperative (with or without bolus) intravenous magnesium infusion ($\geq$ 15 min) vs. control; 4) assessment of magnesium as an analgesic adjuvant to opioids; 5) measurement of pain score that could be converted to visual analogue scale (VAS) pain score. Studies that did not meet these criteria were excluded. There were no language restrictions for study inclusion.

Data extraction was completed by two independent reviewers who were given full text versions of each article. Data were extracted from all trials that met inclusion criteria including first author, publication year, study location, patient demographics, study size, exclusion criteria, region of surgery, postoperative opioid analgesic used, perioperative magnesium technique used, control, postoperative opioid consumption, postoperative pain scores (visual analogue or numerical rating scale), and minor complications and side effects. Study quality was assessed for all articles by scoring each trial for both a Cochrane Collaboration for assessing risk of bias and Jadad score[6,7]. The primary outcome variable was postoperative opioid consumption in the 24 hours after surgery and opioid related postoperative side effects. Secondary outcomes were VAS or numerical rating scale (NRS) pain scores 4 to 6 and 20 to 24 hours after surgery. A random effects model was used. The level of significance for all tests was set at an alpha level of 0.05. All statistical analyses were performed with RevMan 4.2.7 (The Cochrane Collaboration, 2004; Oxford, United Kingdom).

Results

The search resulted in 243 abstracts (Figure 1). After duplicates were removed, 236 abstracts remained from which the original articles were obtained. A total of 22 studies (Table 1[8-29]) met all inclusion criteria. A total of 210 articles were rejected upon abstract screening for the following reasons: 38 did not compare perioperative intravenous magnesium versus control, 43 did not assess magnesium as an adjuvant to opioids, 14 did not study an adult population, 105 did not study a surgical population, 8 did not have a pain score that could be converted to VAS, and 2 were not RCTs. An additional 4 articles were excluded after full text screening for the following reasons: 2 did not use a continuous infusion of magnesium, 1 was not described as a RCT and 1 where the full text could not be located. A summary of the 22 articles used for the meta-analysis is shown in Table 1. There were 599 subjects who received perioperative intravenous magnesium and 578 subjects who received a control.

Fig. 1
PRISMA Flow Diagram: Literature Search Results



This figure shows the PRISMA flow diagram showing literature search results. A total of 23 randomized controlled trials were ultimately used for the analysis.

Table 1
Characteristics of Studies Included in Meta-analysis

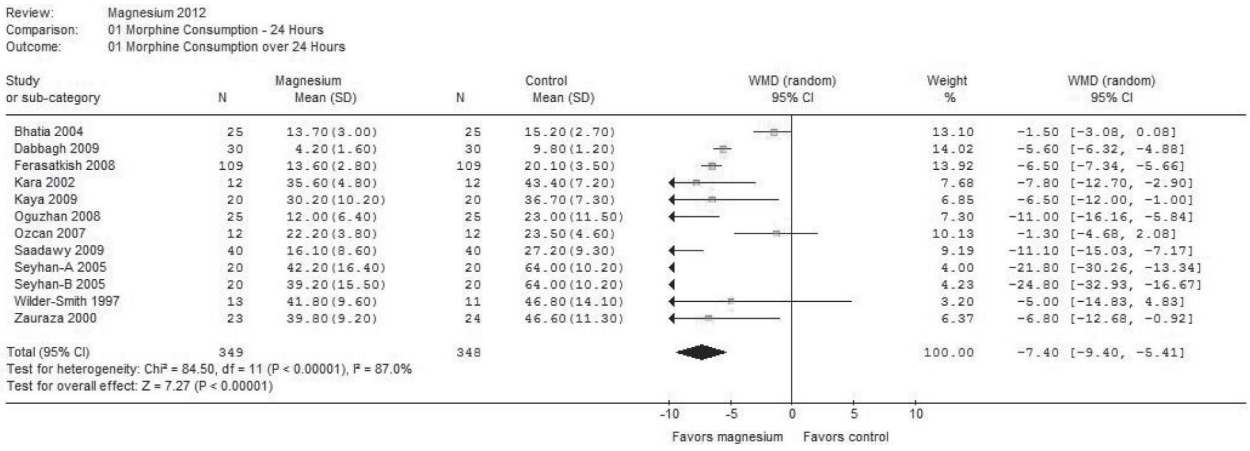
Author (Year)	Study Location	Sex	Region of Surgery	Subjects (n, Mg/C)	Method of magnesium administration	Rate of Magnesium Infusion	Control	Cochrane Quality Score	Jadad Score
Tramer[8] (1996)	Europe	F	Abdominal	21 Mg/21 C	Bolus + continuous infusion	500 mg/h (I,P)	Saline	4	4
Wilder-Smith[9] (1997)	Europe	F	Abdominal	13 Mg/11 C	Bolus + continuous infusion	200 mg/h (I,P)	Placebo	4	4
Zauraza[10] (2000)	Europe	M/F	Multiple	23 Mg/24 C	Bolus + continuous infusion	10 mg/kg/h (I,P)	Placebo pill and saline	5	4
Ko[11] (2001)	Asia	F	Abdominal	29 Mg/29 C	Bolus + continuous infusion	15 mg/kg/h (I, P)	Saline	3	3
Kara[12] (2002)	Europe	F	Abdominal	12 Mg/12 C	Bolus + continuous infusion	500 mg/h (I, P)	Saline	1	1
Levaux[13] (2002)	Europe	M/F	Lumbar	12 Mg/12 C	Continuous infusion only	25 mg/kg/h (I)	Saline	5	2
Unlugenc[14] (2002)	Europe	M/F	Abdominal	23 Mg/21 C	Bolus + continuous infusion	Used in patient-controlled analgesia	No Mg	2	2
Apan[15] (2004)	Europe	M/F	Multiple	25 Mg/ 25 C	Bolus + continuous infusion	500 mg/h (I, P)	Saline	4	3
Bhatia[16] (2004)	Asia	M/F	Abdominal	25 Mg/25 C	Bolus + continuous infusion	15 mg/kg/h (I)	Saline	4	3
Ayoglu[17] (2005)	Europe	M/F	Abdominal	20 Mg/20 C	Bolus + continuous infusion	8 mg/kg/h (I, P)	Saline	5	4
Seyhan[18] (2005)	USA	F	Abdominal	40 Mg/20 C	Bolus + continuous infusion	10-20 mg/ kg/h (I, P)	Saline	6	4
Steinlechner[19] (2006)	Europe	M/F	Thoracic	19 Mg/20 C	Bolus + continuous infusion	13.8 mg/kg/h (I, P)	Saline	4	3
Tauzin-Fin[20] (2006)	Europe	M	Pelvic	15 Mg/15 C	Continuous infusion only	16.7 mg/kg/h (I)	Saline	6	4
Ozcan[21] (2007)	Europe	M/F	Thoracic	12 Mg/12 C	Bolus + continuous infusion	10 mg/kg/h (P)	Saline	4	3
Ryu[22] (2008)	Asia	F	Abdominal	25 Mg/25 C	Bolus + continuous infusion	15 mg/kg/h (I)	Saline	6	4
Ferasatkish[23] (2008)	Asia	M/F	Thoracic	109 Mg/109 C	Continuous infusion only	32 nmol/kg/h	Saline	6	4
Mentes[24] (2008)	Europe	M/F	Abdominal	41 Mg/42 C	Continuous infusion only	n/a (I)	Saline	3	3
Oguzhan[25] (2008)	Europe	M/F	Lumbar	25 Mg/25 C	Continuous infusion only	10 mg/kg/h (I)	Saline	7	5
Dabbagh[26] (2009)	Asia	M/F	Lower Extremity	30 Mg/30 C	Continuous infusion only	8 mg/kg/h (I)	Saline	6	4
Hwang[27] (2009)	Asia	M/F	Lower Extremity	20 Mg/20 C	Bolus + continuous infusion	15 mg/kg/h (I)	Saline	6	4
Kaya[28] (2009)	Europe	F	Abdominal	20 Mg/20 C	Bolus + continuous infusion	500 mg/h (I)	Saline	6	4
Saadawy[29] (2009)	Africa	M/F	Abdominal	40 Mg/40 C	Bolus + continuous infusion	25 mg/kg/h (I)	Saline	7	5

Abbreviations: C: control, F: female, I: intraoperative; M: male, Mg: magnesium; n/a: not available; P: postoperative; USA: United States of America.

Perioperative administration of magnesium was associated with a significant decrease in postoperative morphine usage postoperatively (weighted mean difference [WMD] = -7.40 mg; 95% CI: -9.40 to -5.41, $p < 0.00001$) (Figure 2); however, there were no differences in the incidence of nausea and vomiting in the postoperative period (relative risk [RR] = 0.76; 95% CI: 0.52 to 1.09, $p = 0.14$) (Figure 3). Figures 4 and 5 show the effect of perioperative intravenous magnesium on pain scores 4-6 and 20-24 hours after surgery, respectively. Perioperative administration of magnesium was associated with a decrease in postoperative pain at 4-6 hours (WMD = -0.67; 95% CI: -1.12 to -0.23, $p = 0.003$); however, there was no difference in pain scores at 20-24 hours after surgery (WMD = -0.25; 95% CI: -0.62 to 0.71, $p = 0.17$).

Fig. 2

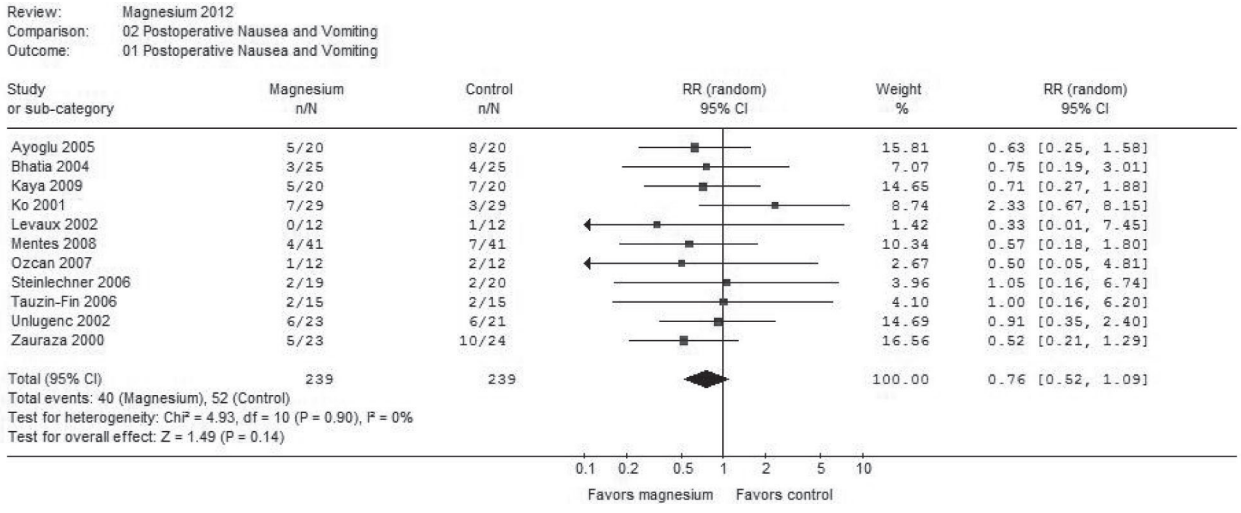
Pooled estimates for opioid consumption in postoperative period: magnesium vs. control



The weighted (pooled) estimate for the effect of perioperative intravenous magnesium on opioid consumption as measured by parenteral morphine equivalents (in milligrams). "N" represents the number of subjects in each experimental group. The entire diamond (pooled estimate) lies to the left of the WMD = 0 (which represents "no difference"), suggesting that magnesium administration is associated with lower postoperative opioid consumption (WMD = -7.40 mg; 95% CI: -9.40 to -5.41, p < 0.00001).

Fig. 3

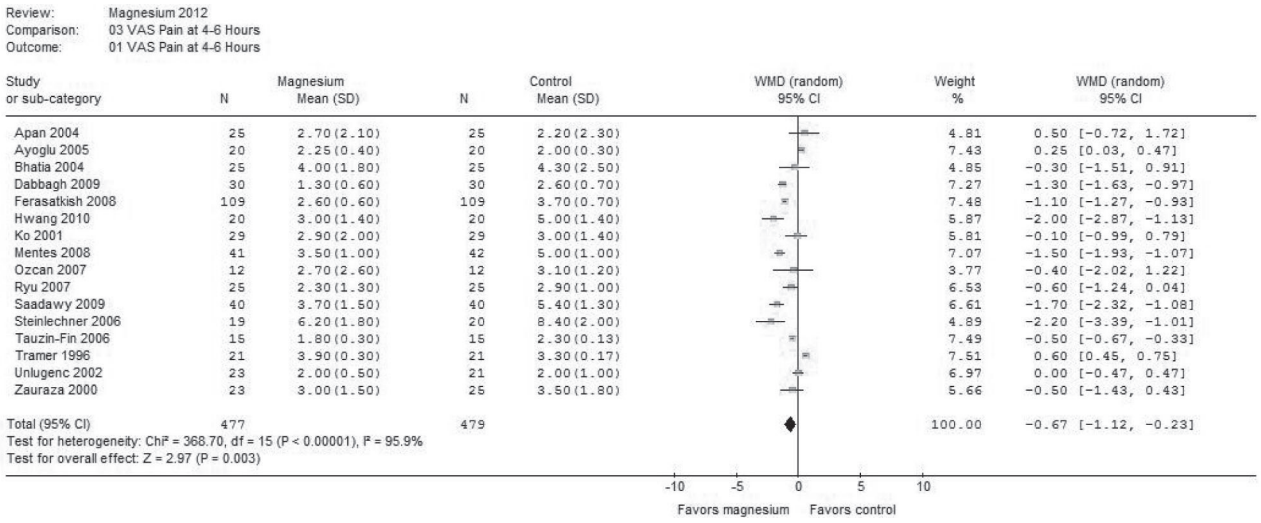
Pooled estimates for incidence of nausea and vomiting: magnesium vs. control



The weighted (pooled) estimate for the effect of perioperative intravenous magnesium on the incidence of nausea and vomiting. "n" represents the number of subjects within an experimental group who reported nausea or vomiting. "N" represents the number of subjects in each experimental group. The entire diamond (pooled estimate) overlies the RR = 1 (which represents "no difference"), suggesting that magnesium administration is not associated with the incidence of nausea or vomiting (RR = 0.76; 95% CI: 0.52 to 1.09, p = 0.14).

Fig. 4

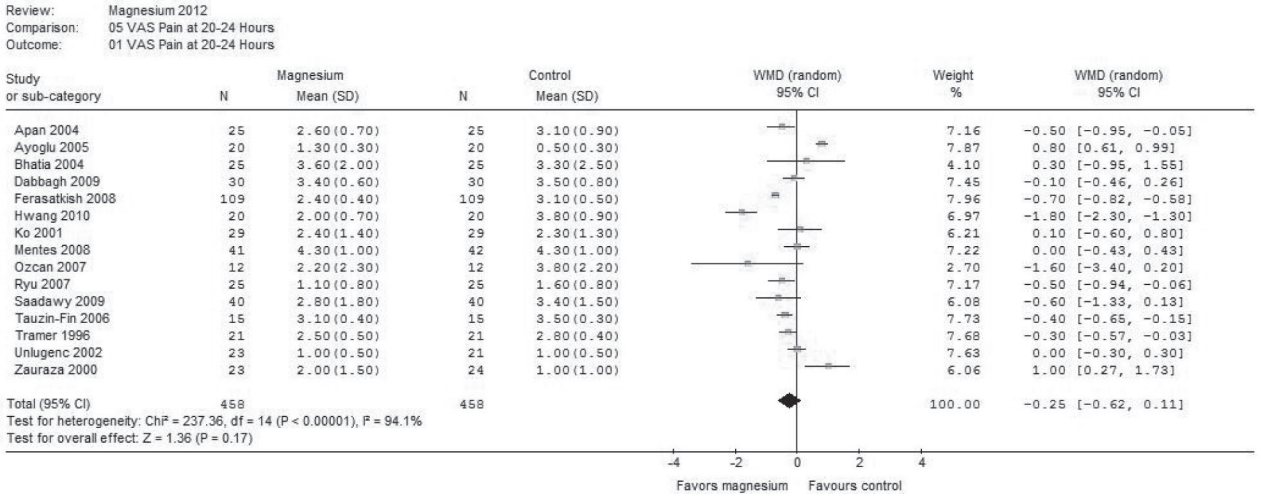
Pooled estimates for pain at 4 to 6 hours after surgery: magnesium vs. control



The weighted (pooled) estimate for the effect of perioperative intravenous magnesium on pain as measured by VAS 4-6 hours after surgery. "N" represents the number of subjects in each experimental group. The entire diamond (pooled estimate) lies to the left of the WMD = 0 (which represents "no difference"), suggesting that magnesium administration is associated with lower pain scores (WMD = -0.67; 95% CI: -1.12 to -0.23, p = 0.003) at 4-6 hours after surgery.

Fig. 5

Pooled estimates for pain at 20 to 24 hours after surgery: magnesium vs. control



The weighted (pooled) estimate for the effect of perioperative intravenous magnesium on pain as measured by VAS 20-24 hours after surgery. "N" represents the number of subjects in each experimental group. The entire diamond (pooled estimate) crosses WMD = 0 (which represents "no difference"), suggesting that magnesium administration is not associated with lower pain scores (WMD = -0.25; 95% CI: -0.62 to 0.71, p = 0.17) at 20-24 hours after surgery.

Discussion

We found that perioperative infusion of magnesium was associated with a decrease in postoperative opioid consumption; however, the decrease in opioid consumption was not associated with a decrease in opioid-related side effects such as postoperative nausea and vomiting. In addition, we also found that perioperative magnesium infusion was associated with a decrease in VAS pain scores up to 4-6 hours after surgery but there was no benefit from magnesium infusion at 20-24 hours after surgery. Our results are similar to those from a previous systematic review[31] although our analysis included more studies (22 versus 14), many of which were published after the previous systematic review.

In comparing our results to the previous published systematic review[30], both studies demonstrated a decrease in opioid consumption with the perioperative use of magnesium. We noted a weighted mean difference of approximately 7.4 mg of morphine at 24 hours after surgery while the prior systematic review found that cumulative morphine consumption was decreased by a median of 28% (range of 12-47%)[30]. This decrease in morphine consumption in patients receiving perioperative magnesium infusion did not result in an apparent decrease in the presumed opioid-related side effect, postoperative nausea and vomiting. The lack of decreased in the incidence of opioid-related side effects despite the presence of an opioid sparing effect may not be surprising as use of other adjuvants (e.g., acetaminophen) may also not be associated with a decrease in opioid-related side effects[31].

Our study also noted a relatively brief period of analgesic benefit (<20-24 hours after surgery) for perioperative magnesium infusion. This finding may not be surprising as the previous systematic review[30] concluded that the randomized studies investigating perioperative magnesium as an adjuvant did not provide convincing evidence for analgesic efficacy. Our findings suggest that if there is an analgesic benefit for perioperative magnesium infusion, it would be limited to the immediate postoperative period. Furthermore, it is uncertain whether the decreases in VAS pain scores for the time period where there was a benefit for magnesium (i.e., 4-6 after surgery) would actually be clinically meaningful[32]. The mechanism of analgesia for magnesium is unclear; however, possible mechanisms include inhibition of calcium influx, antagonism of N-methyl-D-aspartate receptors, and attenuation of central sensitization[33].

Several points need to be made in interpreting our results. Not all studies used morphine for postoperative analgesia and not all assessed cumulative opioid consumption at 24 hours. Although equianalgesic tables are available for conversion of some of these opioids, we elected to exclude these studies from the 24 hour cumulative morphine analysis in an attempt to make this analysis more uniform. In addition, there was limited available data on opioid-related side effects other than postoperative nausea and vomiting. There was no or limited data on pruritus, sedation, urinary retention, and respiratory depression. Nevertheless, it is unlikely that perioperative magnesium infusion would have a significant effect on major adverse events such as respiratory depression, as prior studies indicate that perioperative administration of other adjuvants (e.g., acetaminophen, nonsteroidal anti-inflammatory agents, ketamine) do not significantly decrease opioid-related adverse events despite the presence of an opioid-sparing effect[31,34].

There are several limitations to our study. The sample size of the included studies was relatively small (typically < 50 subjects/study) and as a result, there may have been little data on less frequent outcomes of interest (such as respiratory depression). We included only studies that utilized infusions with or without a bolus (i.e., did not include those that used only a bolus dose) as we presumed that an infusion would have a prolonged effect on postoperative analgesia, our primary interest. There was heterogeneity present in several of the analyses; however, we attempted to minimize this effect by using a more conservative random effect model for our meta-analysis. We attempted to minimize publication bias by searching several databases and including non-English language papers. Finally, there are general limitations to the meta-analytic technique which have been discussed elsewhere[35].

In summary, we found a decrease in postoperative opioid consumption which was not associated with a decrease in opioid-related side effects such as

postoperative nausea and vomiting with the use of perioperative infusion of magnesium. Although perioperative magnesium infusion was associated with a decrease in VAS pain scores up to 4-6 hours after surgery, there was no benefit from magnesium infusion at 20-24 hours after surgery. The overall analgesic benefit of perioperative magnesium is uncertain; however, larger scale trials are probably needed to address some of the limitations of currently available randomized trials.

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A COMPARATIVE STUDY OF POST OPERATIVE ANALGESIA, SIDE EFFECTS PROFILE AND PATIENT SATISFACTION USING INTRATHECAL FENTANYL WITH AND WITHOUT MORPHINE 0.1 MG IN CAESAREAN SECTION

Wirzafeldi Sawi* and Choy YC**

Abstract

Background: This was a double-blinded, prospective randomized controlled trial to compare the postoperative analgesia, side effects profile and overall satisfaction in patients who received intrathecal fentanyl with or without morphine for elective Caesarean.

Methods: Sixty ASA I and II parturients were randomized into two groups. Group I received intrathecal fentanyl with 0.1 mg morphine and Group II received intrathecal fentanyl only. Post-operatively, all patients were provided with oral analgesics. The degree of post-operative pain score was assessed by verbal pain score. The incidence of side effects was assessed every 4 hours for 24 hours, which included incidence of nausea, vomiting, pruritus, sedation and evidence of respiratory depression. Patient's overall satisfaction was also recorded.

Results: The verbal pain score was significantly lower in morphine group up to 20 hours postoperative period. The incidence of pruritus, nausea and vomiting were statistically significant up to 12 hours postoperative. There was no incidence of severe side effects in all the patients. There was significant difference between the morphine and no morphine group in terms of overall patient satisfaction.

Conclusion: There was significant difference in terms of lower pain score, higher incidence of side effects with better patients' overall satisfaction in morphine group.

Conflict of interest: No financial relationships between authors and commercial interests with a vested interest in the outcome of the study.

Sources of financial support: Hospital Universiti Kebangsaan Malaysia.

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Introduction

Caesarean deliveries can result in moderate to severe post operative pain. Adequate pain relief will certainly improve maternal satisfaction, speed up maternal recovery and allow the parturient to adequately nurse her newborn baby. This can be eventually translated into a reduction in the cost of treatment as a result of shorter hospital stay without compromising the quality of medical care given towards patient. Spinal anaesthesia is commonly used for Caesarean section. While intrathecal fentanyl improves intraoperative analgesia, intrathecal morphine on the other hand has become widely accepted to enhance postoperative analgesia. However, there is a general concern about the side effects of intrathecal morphine, particularly pruritus, nausea, vomiting and sedation. It has also been associated with delayed respiratory depression which is the most feared complication of intrathecal morphine[1]. These may affect overall patient satisfaction and have raised doubts about their advantages.

Intrathecal morphine in Caesarean section has been used for more than 20 years following the discovery of dorsal horn opioid receptors[2]. Palmer *et al* (1999) published a report on the dose-response relationship between 0 and 0.5 mg of intrathecal morphine for post Caesarean section analgesia involving 108 healthy parturients. The authors concluded that a dose of 0.1 mg intrathecal morphine provides optimal analgesia[3]. A study conducted by Milner *et al* (1996) also revealed the same result[4]. However, none of the patients was completely pain free and all patients requested additional intravenous analgesia[3].

Pruritus is the most frequent undesirable side effects associated with intrathecal morphine[5]. The incidence is reported to be between 43-94%[5,6]. Meanwhile, incidence of nausea and vomiting were demonstrated to be 10% and 12% respectively following intrathecal morphine 0.1 mg[6]. By using higher doses, the incidence of nausea and vomiting increased[3]. Delayed respiratory depression on the other hand occurs between 3.5 and 12 hours after injection with a peak at 6 hours[2]. The true incidence of respiratory depression following intrathecal morphine is unknown. Two large studies quote the incidence in obstetric population between 0.003-0.01%[1,7]. The main objective of the study was to compare postoperative analgesia, side effects profile and overall satisfaction in patients scheduled for elective Caesarean section who received intrathecal fentanyl with and without morphine 0.1 mg.

Methods

This was a double blinded, prospective randomized controlled trial involving patients undergoing elective Caesarean section in maternity operation theatre, PPUKM. Approval was obtained from Dissertation Committee, Department of Anaesthesiology and Intensive Care, PPUKM and Ethics Committee, PPUKM. Following written informed consent, 60 patients were randomized into 2 groups which are morphine group and no morphine group. Random allocation was performed by shuffling sealed envelopes. Inclusion criteria were ASA physical status I and II and age between 18-45 years old. Exclusion criteria were patient refusal to participate in this study, contraindication to spinal anaesthesia and history of allergic reaction towards opioids.

Patients scheduled for elective surgery were fasted overnight and received ranitidine 150 mg orally the night before and on the morning of the operation. 30 mls of sodium citrate 0.3M was served once they were called to operation theatre. With the patient in sitting position, the subarachnoid space was identified using a 27G pencil-point spinal needle via the L3-4 or L2-3 interspace after infiltration with lignocaine 2%. On aspiration of clear cerebrospinal fluid, 1.8-2 mls of hyperbaric bupivacaine 0.5% plus 25 mcg of fentanyl were injected (no morphine group). The morphine group had morphine 0.1 mg added into spinal solution. This preparation was made by anaesthestist performing the spinal anaesthesia who took no further part in this study.

Following intrathecal injection, the patient was placed in a modified supine position with 15^{o} of left lateral tilt. After adequate spinal anaesthesia was established, Caesarean section was allowed to proceed. Those with inadequate spinal anaesthesia requiring conversion to general anaesthesia were excluded. Hartmann's solution was given accordingly to replace fluid deficit and for maintenance during the

case. Boluses of phenylephrine intravenously were given in order to maintain normal blood pressure at the discretion of anaesthetist.

Following surgical delivery of neonate, 5 units of slow bolus intravenous oxytocin was given upon clamping of the umbilical cord. For the supplemental analgesia, all patients received regular dose of oral NSAIDs based on obstetrician's desire post operatively. In the events that rescue analgesia was required for breakthrough pain, co-administration of opioids were allowed with strict monitoring in acute cubicle. The observers and the patients were not aware of intrathecal drugs used.

The incidence of side effects was assessed every 4 hours for 24 hours. Patients were advised to immediately alert ward staff if any adverse event occurred and not just their present state at the particular time they were seen. Pruritus was assessed using a 4 point score: 0=no pruritus, 1=mild pruritus, 2=moderate pruritus and 3=severe pruritus. Nausea was assessed using a 4 point score: 0=no nausea, 1=mild nausea, 2=moderate nausea and 3=severe nausea. Vomiting was assessed as yes/no and number of episodes within 24 hours will be recorded. Sedation was assessed using a 4 point score: 0=alert, 1=occasionally drowsy, 2=frequently drowsy but easy to arouse and 3=drowsy and difficult to arouse.

The patient was cared for in a post natal ward following their operation. As usual, vital signs which include blood pressure, heart rate and respiratory rate were recorded every 4 hours. Respiratory depression was assessed by monitoring respiratory rate. At the same time, degree of post-operative pain score was evaluated based on verbal pain score, VPS: 0=no pain and 10=worst imaginable pain. Subsequently, the pain scores were categorized into mild (VPS $\leq$3), moderate (VPS 4-7) and severe pain (VPS $\geq$8). Overall satisfaction was assessed at 24 hours as 0=very unsatisfied, 1=unsatisfied, 2=satisfied and 3=very satisfied.

With α value determined at 0.05 and power of study at 80%, this study required 50 patients. Allowing for dropout rate of 20%, 60 patients were recruited as sample. Statistical data analysis was done using Predictive Analytics Software (PASW) Statistics. Data were analyzed using Mann-Whitney U test or Chi-square test where appropriate. A p-value of <0.05 was considered statistically significant.

Results

Sixty patients were enrolled in this study. None of the patients experienced intraoperative adverse surgical or anaesthesia related complications which required conversion to general anaesthesia. There were an equal number of patients in each studied group, morphine and no morphine. Table I summarised the details of socio-demographic data of the study population. There were no significant differences between the two groups with respect to age, weight, ASA grouping and gravidity.

Over the 24-hour study period, statistical analysis showed that there were significantly ($p<0.05$) lower VPS at 4, 8, 12, 16 and 20 hours in morphine group in

Table 1
Socio-Demographic Data

	Morphine group N=30	Non- morphine group N=30	P value
Age (years)*	31.2 ± 4.5	30.17 ± 5.7	0.209
Weight (kg)*	70.383 ± 12.6	68.917 ± 12.6	1.000
Height (cm)*	156.5 ± 6.2	157.0 ± 7.2	0.426
ASA 1:2	22:8	26:4	0.333
Gravidity (primigravida: multigravida)	11:19	17:13	0.195

* Results are expressed as mean ± SD

comparison to no morphine group as shown in Figure 1. At least 86% of the patients in morphine group reported mild pain (VPS ≤3) compared to only 63% in no morphine group between 4 to 16 hours. Meanwhile at 20 and 24 hours postoperative, about 90% of the patients in morphine group and 77% of the patients in no morphine group experienced mild pain. About 40% of the patients in no morphine group experienced breakthrough pain and requested for rescue analgesia at some point of time within 24 hours postoperative period. They were served with intramuscular pethidine 75 mg stat. None of the patients in morphine group however had similar problem within the same period of time.

Fig. 1
mean verbal pain score

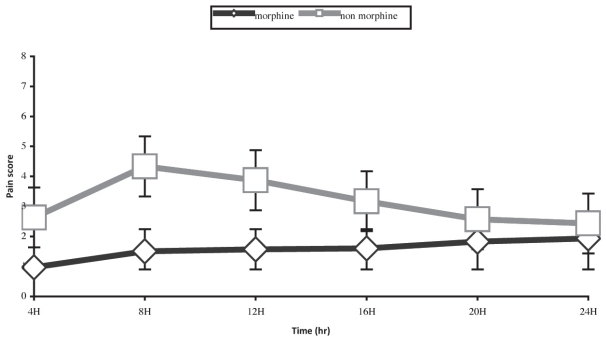
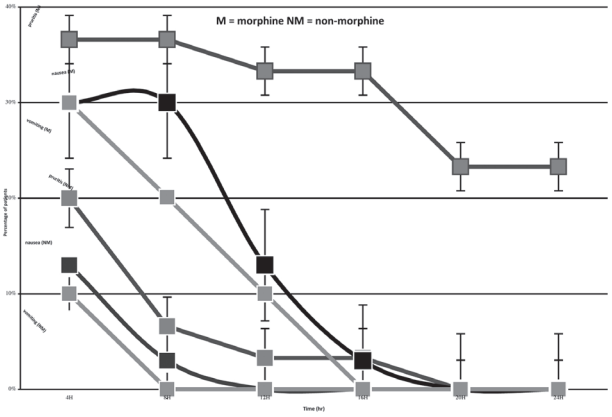


Figure 2 showed the incidence of side effects in both groups. There was no incidence of severe pruritus, nausea or vomiting in the studied populations. However, statistical analysis showed that there was a significant difference ($p<0.05$) between the two groups

Fig. 2
incidence of side effects in 24 hour



in the incidence of pruritus at every assessment period except at 4 hours postoperative period. There was a statistically significant difference ($p=0.044$) between the two groups in the incidence of nausea at 8 hours postoperative. None of the patients in both groups reported nausea after 16 hours postoperative period. Patients who received morphine experienced higher incidence of vomiting and there was a statistically significant difference between the two groups at 8 hours ($p=0.013$) and 12 hours ($p=0.011$). However, none of the patients reported any vomiting after 12 hours postoperative period.

Overall patient satisfaction is good as only 13% from the morphine group and 20% from the non-morphine group were unsatisfied. It seems to be relatively clear that overall satisfaction in this study is higher in morphine group. None of the patients developed sedation or respiratory depression. In this study, both groups received multimodal analgesia in the form of oral etoricoxib 120 mg twice or naproxen 250 mg three times per day postoperatively.

Discussion

Neuraxial opioids have contributed to improved analgesia during intraoperative as well as postoperative Caesarean delivery. Two routes of administration are possible for neuraxial opioids, either intrathecal or epidural injection. There is no clear evidence to recommend one technique over the other[8]. It is worth to note that the most important clinical question that emerges from the present reviews is whether the analgesic benefits worth the side effects induced by neuraxial opioids.

We found that in this study, the quality of postoperative analgesia with intrathecal fentanyl 25 mcg alone was inferior to that with addition of intrathecal morphine 0.1 mg. It is consistent with the study conducted by Chung et al (1997) where they added meperidine (pethidine) to intrathecal morphine and compared the quality of pain relief with either morphine or meperidine alone. The mixture was superior to either agent alone, showing the lowest pain scores, the lowest need for intravenous supplementation and higher degree of satisfaction[9].

Palmer et al (1999) reported that intrathecal

morphine for control of post Caesarean delivery pain is usually quite effective for the first 24 hours. However, none of the patients was completely pain free and all patients requested additional intravenous analgesia[1]. In our study, lower VPS was demonstrated up to 24 hours in morphine group compared to no morphine group. Siti Salmah and Choy (2009) meanwhile compared the quality of postoperative analgesia between intrathecal fentanyl 25 mcg and intrathecal morphine 0.1 mg in patients undergoing Caesarean section. They found that postoperative analgesia of intrathecal fentanyl was inferior to that of intrathecal morphine[10].

Single epidural administration of morphine has also been used to control postoperative pain. Shymala and Choy (2008) studied the effectiveness and duration of analgesia of epidural morphine 4 mg and 5 mg for postoperative analgesia following Caesarean section. They found that epidural morphine 5 mg provided adequate and longer duration of analgesia but resulted in higher incidence of pruritus and vomiting[10]. Sarvela et al (2002) compared intrathecal morphine 0.1 mg and 0.2 mg with epidural morphine 3 mg. They found that pain control were equally good for elective Caesarean delivery[12].

Pruritus is the most frequent undesirable side effects associated with neuraxial opioids. In this study, the incidence of pruritus following intrathecal morphine in patient underwent Caesarean delivery was 37%. This result was consistent to that reported by Jorgen et al (1999)[3]. Most of the patients in morphine group who experienced pruritus claimed it lasted up to 24 hours. On the other hand, the incidence of pruritus in no morphine group was 20% and mostly resolved within 8 hours. The sites of pruritus in both groups were predominantly at facial area, neck, trunk and back.

This study demonstrated that the incidence of nausea and vomiting in the morphine group was 30%. It turned out to be higher than that reported by Jorgen et al (1999) which was 10% and 12% repectively[3]. This can be attributed to an inclusion of fentanyl 25 mcg as a standard spinal solution in this study which significantly contributed to the increased incidence of nausea and vomiting in the morphine group. Majority of the patient recovered within 12 hours post-spinal administration. On the other hand, the incidence of nausea and vomiting in the no morphine group was 13% and 10% respectively, mostly resolved within 8 hours.

The aetiology of nausea and vomiting in parturients undergoing spinal anaesthesia for Caesarean delivery is complex and dependent on various factors. Maternal hypotension after induction of spinal anaesthesia is associated with increased incidence of intraoperative as well as postoperative nausea and vomiting. Hypotension leads to brainstem hypoxia, thus stimulates the vomiting centre to induce emesis[6]. In this study, fluid infusion to replace deficit, left uterine displacement or administration of phenylephrine were performed accordingly for the prevention and early treatment of hypotension. This ensured that the incidence of nausea and vomiting can be attributed to the study drugs.

Delayed respiratory depression is the most feared side effect of intrathecal morphine. Unfortunately, there is a lack of proper definition of the term ‘respiratory depression’ in the literature. Rie Kato et al (2008) reported 6 out of 1915 patients exhibited bradypnoea as defined by respiratory rate of less than 10 breaths per minute within 24 hours following intrathecal morphine 0.15 mg[7]. In our study, we used a combination of respiratory rate and level of sedation to monitor respiratory depression postoperatively. However, none of our patients experienced bradypnoea or had difficulty to arouse from sleep. As delayed respiratory depression is a rare event, we concluded that larger samples are required to determine its incidence.

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ESMOLOL VERSUS DEXMEDETOMIDINE IN SCOLIOSIS SURGERY: STUDY ON INTRAOPERATIVE BLOOD LOSS AND HEMODYNAMIC CHANGES

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Abstract

Background: Surgical correction of scoliosis carries significant blood loss and needs for blood transfusion with its inherent risks and cost. The aim of this double-blind, randomized, controlled study was to compare the effects of esmolol or dexmedetomidine on intraoperative blood loss, anesthetics consumption, intra operative hemodynamic and effects on spinal cord monitoring in patients undergoing scoliosis surgery.

Methods: After obtaining institute review board approval and written informed consent, 60 adolescents (ASA physical status I–II), 14–18-year of age scheduled for posterior spinal fusion scoliosis surgery were enrolled in the study. Using computer generator software patients were randomly allocated to receive either saline as a control (group C), esmolol (Group E) or dexmedetomidine (Group D).

Results: There was a significant reduction in blood loss in patients who received esmolol and dexmeditomidine compared to control it was as follow; in control group 782±86.4ml ($P \leq 0.001$), esmolol group 667±145.2 ml ($P \leq 0.001$) and dexmeditomidine group 465±115.3ml ($P \leq 0.001$). Mean intraoperative total fentanyl and propofol consumption in the esmolol group was significantly higher than in the dexmedetomidine group, this was especially dramatic for the dexmedetomidine group where the propofol consumption was twice less $P \leq 0.001$. There was no significant effect seen in SSEPs (amplitude or latency) but there was isolated decrease in motor evoked potential (MEP) amplitude which was within acceptable range that was seen in 6 patients receiving dexmeditomidine at a dose of 0. 7 μg/Kg/H.

Conclusion: Both esmolol and dexmedetomidine, added to anesthetic regimen, provided an effective and well-tolerated method to reduce the amount of blood loss in patients undergoing scoliosis surgery. dexmedetomidine, was associated with plonoged extubation and recovery times.

Key words: Esmolol, Dexmedetomidine, Scoliosis, Blood loss.

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Introduction

Scoliosis surgery carries significant morbidity associated with intraoperative blood loss and the resultant transfusion therapy. Surgical stress plays an important role on the perioperative blood loss. We think that manipulating adrenergic receptors could attenuate this response and may thereby reduce intra operative blood loss. It has been suggested that esmolol and dexmedetomidine influence core components of an anesthetic regimen, such as analgesia, hypnosis, and memory function and have the ability to reduce both the anesthetic and opioid analgesic requirements during the perioperative period[1-2]. This study designed to compare the effects of esmolol versus dexmedetomidine on intraoperative blood loss, anesthetics consumption, intra operative hemodynamic changes and effects on spinal cord monitoring in patients undergoing scoliosis surgery.

Methods

After obtaining institute review board approval and written informed consent, 60 patients (ASA physical status I–II), 14–18-year of age, scheduled for posterior spinal fusion for scoliosis surgery were studied according to a randomized, double blind, placebo-controlled protocol. A block randomization software was used in order to keep equal the sizes of treatment while blindness of the studied drugs was achieved with the help of the hospital central pharmacy which provided coded identical intravenous bags containing either the dexmedetomidine, esmolol or saline as a control. The surgical and anesthesiologist team were blinded as to the type of solution. The author collecting the data was as well blinded to the type of studied drug delivered.Exclusion criteria included; patients with motor or sensory deficits in lower limbs, patients with neuromuscular scoliosis, allergy to or contraindication to drugs used in the study, severe cardiopulmonary disease, morbid obesity (BMI more than 40%) and underlying coagulation abnormalities.

Anesthesia Technique

On arrival to operating room patients were monitored with an electrocardiograph, pulse oximeter, and an automatic noninvasive arterial pressure monitor before induction of anesthesia.

Induction of anesthesia: Fentanyl 1µg/ kg, Propofol (2 -2.5 mg/kg), and a single dose of Rocuronium (0.6 mg/kg) to facilitate endotracheal intubation. Then arterial line and a urinary catheter were placed for invasive continuous measurement of arterial blood pressure and urine output. No additional muscle relaxants were given during the procedure. Temperature probe and bispectral index monitor (BIS) were used during the procedure to monitor temperature and maintain depth of anesthesia (BIS between 40 to 70). Mechanical ventilation was adjusted to maintain normocapnia (end-tidal CO2 35–40 mm Hg).

After patients were turned to prone position, anesthesia was maintained with total intravenous anesthesia (TIVA) using propofol infusion at a rate of a rate of 80 –100 µg / kg/min, and fentanyl at rate of 1 to 3µg/kg/h in all patients. All patients received 10 ml/kg pentastarch (Pentaspan, Bristol-Myers Squibb, Montreal, Canada) plus intravenous fluid requirements were replaced with balanced crystalloid solutions Hemodynamic monitoring and total blood loss were estimated during whole procedure and after serial blood gas analysis patients received blood transfusion if a hemoglobin concentration of less than 8 gm/dl.

The administered drugs were prepared by the co investigator with the help of clinical pharmacist in identical intravenous bags each 100 ml saline contained either 400 µg (4 µg/ml) dexmedetomidine or 250 mg (2.5 mg/ml) esmolol, and normal saline bags as a control. Boluses and infusion rates were adjusted in a rate of 5 ml to 10 ml by co-investigator. Both the surgical and primary anesthetic investigator teams were blinded to the choice of the drug. Using computer generator software patients were randomly allocated to receive either saline as a control (group C), esmolol (Group E) or dexmedetomidine (Group D).

After obtaining baseline measurement of heart rate (HR) and mean arterial blood pressure (MAP), BIS and stabilization of the patients in prone position, patients were received fixed bolus dose of 10 ml and infusion of the 3 studied drugs in a dose as follow: 0.5 mg/kg esmolol was infused over 10 minutes, followed by maintenance rate of 0.25-0.50 mg/kg/h. In

dexmedetomidine group (D) loading dose was infused intravenously over 10 minutes at a rate of 0.5 to 1 µg/kg followed by a maintenance rate of 0.4-0.7 µg/kg/h, and normal saline as a control. All infusions were adjusted according to hemodynamic in a range of 5-10 ml/h.

Neurophysiologic monitoring of spinal cord integrity using somatosensory-evoked potentials and transcranial motor-evoked potentials were used. Patients were then monitored in the post operative care unit (PACU) and then transferred to a regular ward, where preordered morphine Patient control analgesia was started with the first report of pain.

Statistics

All continuous data were tested for normality using the Kolgomorov-Smirnov method. For data sets that followed a normal distribution, parametric tests were used. For all other data sets, the appropriate nonparametric tests were applied. Data were analyzed using SPSS V12.0.1 (SPSS Inc., Chicago, IL) and MedCalc - V 9.3.1 (MedCalc Software, Mariakerke, Belgium). A *P* value smaller than 0.05 was considered statistically significant. The size of our treatment groups was determined by a power calculation within statistical packages and software on internet sites.

Results

Patients in all groups did not vary significantly in age, weight, preoperative hemoglobin, duration of surgery or number of vertebrae fused (Table 1).

Effect on anesthetic consumption and recovery

Mean intraoperative total fentanyl and propofol consumption in the esmolol group was significantly higher than in the dexmedetomidine group this was especially dramatic for the dexmedetomidine group where the propofol consumption was twice less. In the control and esmolol group, the mean times to extubation and to recovery from anesthesia were significantly shorter than those of the dexmedetomidine group (17.0 ± 9.4, 19.1 ±11.7 versus 27.2± 13.4 minutes, respectively; (P = 0.001) (Table 1).

Table 1

Demographic data and operative parameters expressed as Mean ± SD

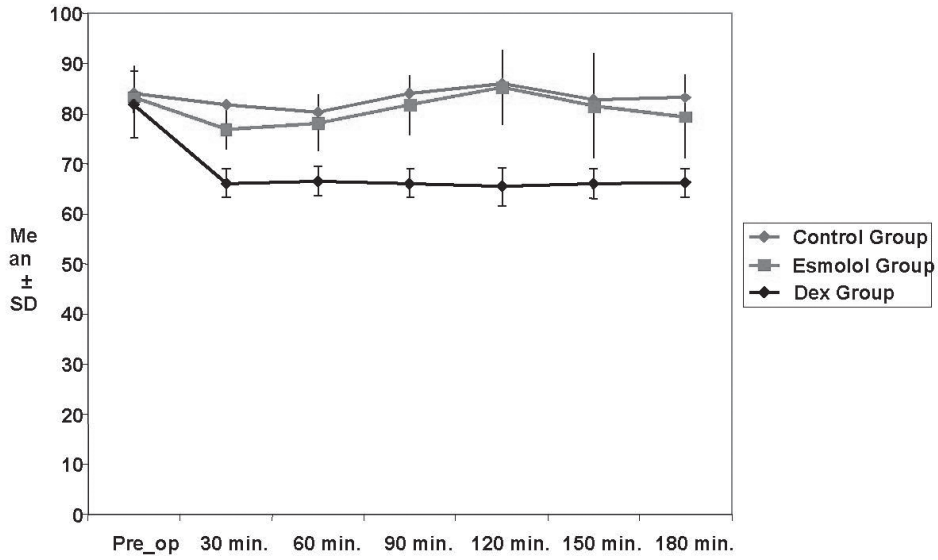
Group	Control group (C)	Esmolol group (E)	Dex group (D)
Number	20	20	20
Gender f/m	13/7	18/2	16/4
Age (yr)	13.63±1.64	14.4±1.64	14.85±3.065
Weight (kg)	41.15±4.717	41.10±5.919	42.15±4.89
Duration of surgery (hr)	4.72±46.3min	4.91±50.19min	4.966±36.31min
Numbers of vertebrae being fused	10.65±1.72	9.20±1.93	9.9±1.158
Intraoperative blood loss (ml)	782±86.4	667±145.2	465±115.3**
Preoperative Hb	13.03±1.009	13.35±.898	13.115±1.18
Post-operative Hb	8.8100±1.08	8.78±.637	9.945±.6533*
No. of patients received Blood	16	11**	5***
Total fentanyl consumption (mic)	511±90.43	441.5±65.79	384.5±50.62***
Total propofol consumption (mg)	1339.5±201.74	918.5±178.83	635.5±161.064***
Time to eye opening (min)	17.0 ± 9.4,	19.1 ±11.7	27.2± 13.4***

* Significance P less than 0.05.

** Moderate Significance P less than 0.01.

*** High Significance P less than 0.001.

Fig. 1
Mean Arterial Blood Pressure (Mean ± SD) in different times



Effects on Hemodynamic parameters and blood requirement

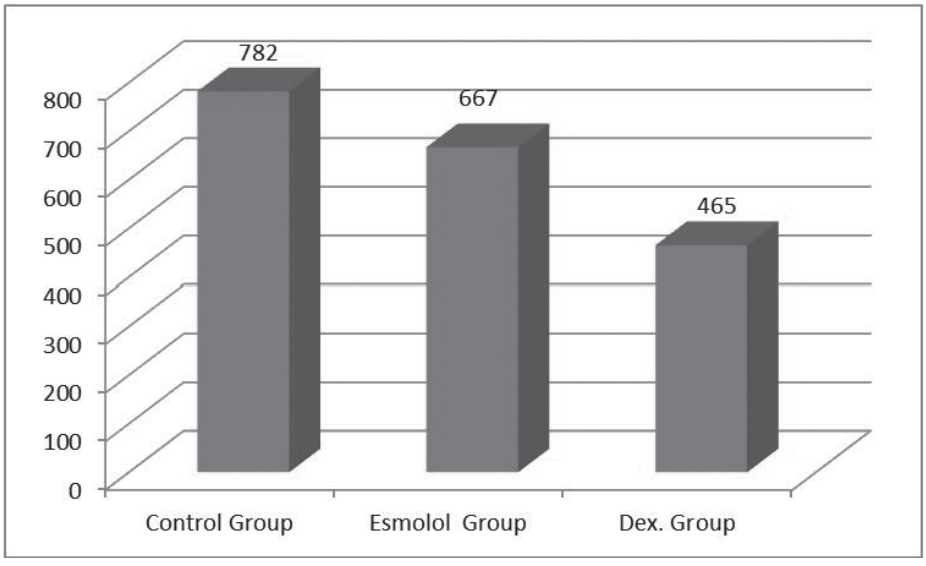
Blood loss was significantly reduced in patients who received esmolol and dexmeditomidine compared to control: as follow; in control group 782±86.4ml ($P \leq 0.001$), esmolol group 667±145.2 ml ($P \leq 0.001$) and dexmeditomidine group 465±115.3ml ($P \leq 0.001$).

The mean arterial blood pressure and heart rate were significantly low in the Dexmedetomidine group compared to control and esmolol groups; results were 86.05 ± 6.89 in control group, 85.3 ± 7.47 in esmolol group and 65.5 ± 3.79 mmHg in dexmedetomidine group. The mean arterial blood pressure was on average 20 mm of mercury less at 66 mmHg in the dexmedetomidine group constantly throughout the case once the induction period was passed (Figure 1).

Only five patients in the dexmedetomidine group were transfused with homologous blood. The mean total number of units of blood required in Group C and E was 1.9 compared with 1.2 in Group D.

A comparable drop in haemoglobin concentration was observed in both groups after operation despite clinically adequate blood replacement (Figure 2).

Fig. 2
Mean Intraoperative blood loss (ml) expressed as Mean ± SD



Effects on Spinal cord monitoring

There was no significant effect seen in SSEPs (amplitude or latency) but there was isolated decrease in motor evoked potential (MEP) amplitude which was within acceptable range that was seen in 6 patients receiving dexmeditomidine at a dose of 0. 7 µg/Kg/H. We think this due to a synergistic effect of propofol and dexmedetomidine without downward adjustment of propofol produced a dose-dependent depression of MEPs. The MEP amplitude depression observed was overcome immediatly by multipulse and increase level of stimulation. There was no neurological deficits observed in all patients, we rely depression in MEP due to drug effects.

Discussion

The present study compared the effects of esmolol versus dexmedetomidine as an adjuvant to the total intravenous anesthesia using propofol and fentanyl in providing controlled hypotension and reducing need for transfusion during scoliosis surgery. Many techniques have been used to maintain dry surgical field, limit intraoperative blood loss and need for transfusion during spinal surgery 3,4**.** This study showed a significant and clinically relevant reduction in blood loss in patients who received esmolol or dexmedetomidine compared to control group. However, our results demonstrated that dexmedetomidine has more advantages, and its usage was associated with more stable haemodynamics and less fluctuation in MAP and HR than esmolol and control groups.

The anesthetic depth during the surgery was to maintain the values of bispectral index BIS between 50-70, that was used in previous studies during scoliosis surgery[5]. In the present study, the majority of patients in both groups esmolol and dexmedetomidine had a good depth of anesthesia condition and the surgical team did not complain of major issues during the surgical procedure such as bleeding or major neurological deficits as detected by neurophysiologic monitoring. In this study total blood loss was significantly reduced in the dexmedetomidine group as well as transfusion requirement was reduced by more than 40% compared to esmolol and control groups.

One of the consequences of surgical stress is the intense activation of the sympathetic nervous system that leads to cardiovascular fluctuations meanwhile, use of adrenergic antagonists can minimize this unwanted response and maintain hemodynamic stability during surgery[6].

Selection of used drugs in our study based on reports that, Esmolol is a moderate lipophilic drug with *B* receptor activity and could be involved in the modulation of central adrenergic activity[7], although some repots seem to argue whether it crosses the blood–brain barrier. Alpha 2 receptors are found in the peripheral and central nervous systems, the analgesic effects of dexmedetomidine are mediated through the activation of a2-adrenergic receptors in the dorsal horn of the spinal cord and inhibition of substance P release[8].

Based on assumption that esmolol has an opioid sparing effect, Collard and his colleges in 2007 enrolled Ninety (90) patients scheduled for laparoscopic cholecystectomy in a prospective randomized study to compare continuous infusion of esmolol versus intermittent fentanyl on postoperative oppioid sparing effect. The authors found that esmolol infusion significantly reduce opioid administration and allow early postoperative discharge[9].

Coloma et al have used esmolol as an alternative to ramifentanyl during desflurane anesthesia in patients undergoing outpatient gynecologic laparoscopic suergery[10]. The authers found that esmolol can be used instead of ramifentanyl to maintain hemodynamic stability. In our study, fentanyl and propofol consumption were significantly lower in the dexmedetomidine group compared with the esmolol and control groups. Bulow et al found that dexmedetomidine can also be used as an alternative to ramifentanyl in maintaining hemodynamic stability and reducing the stress response to surgery[11].

The same conclusion was reported by Unlugenc, who found that dexmedetomidine reduced postoperative morphine consumption with no effect on postoperative recovery time[12]. In the postoperative ICU setting, narcotic requirements were reduced by 50% when patients were receiving a dexmedetomidine drip compared with placebo[13].

We found that dexmedetomidine promoted

controlled hypotension and reduced blood loss more than esmolol through its effects on cardiovascular system that include; decreased heart rate; decreased systemic vascular resistance; and indirectly decreased myocardial contractility, cardiac output, and systemic blood pressure. Tanskanen et al demonstrated that dexmedetomidine plasma target doses of 0.2 and 0.4 μg/mL decreased the haemodynamic responses caused by stimuli during anaesthesia[14]. Others noted that hypotension and bradycardia are the main side effects associated with dexmedetomidine, in our study lowest level of mean arterial pressure was 66 mmHg which was maintained by reducing and manipulating the infusion doses of propofol and fentanyl[15,16].

On the other hand Richa et al reported that dexmedetomidine, at the doses of 0.4-0.8 μg kg/h, was less effective than remifentanil in producing controlled hypotension, and good surgical field exposure during tympanoplasty[17].

Many studies have shown that concomitant administration of dexmedetomidine and prpofol has been found to reduce the anesthetic requirements for propofol as well as the inhalational anesthetic agents[18-19,20].

In the current study, patients received dexmedetomidine were associated with significantly longer recovery times, this effect was reported in previous studies[21-22] when they added dexmedetomidine to anesthetic regimen. Concerns regarding delayed recovery may related to development of significant hypothermia in spite of all warming measures. This may be explained by dexmedetomidine effect on the α2C-adrenoceptors subtype that has been shown to modulate dopaminergic neurotransmission, thermoregulation, hypothermia and a variety of behavioral responses[23-24].

We noted that six patients developed isolated decrease in motor evoked potential (MEP) amplitude when dexmedetomidine was administered without adjusting dose of propofol infusion rate. In that patient, there was a decrease in the BIS from 58 to 30. In the remaining patients, when the propofol infusion was decreased accordingly during the dexmedetomidine loading dose and maintenance, no interference with either SSEP or MEP monitoring noted.

It is likely that, if the anesthetic depth is not adjusted, adding dexmedetomidine may adversely affect MEPs due to either a drug effect of dexmedetomidine or related to the increased depth of anesthesia. Recently, Tobias et al reported that a dexmedetomidine infusion at a rate of 0.5 ug/kg/h) does not interfere with electrophysiologic monitoring or adversely affect SSEP or MEP monitoring[25]. Other studies reported that both SSEPs and MEPs were maintained within a clinically acceptable range during the scoliosis surgical procedure and concluded that dexmedetomidine did not interfere with intraoperative neurophysiologic monitoring the monitoring of either SSEPs or MEPs[26-27].

Conclusion

Both esmolol and dexmedetomidine, added to anesthetic regimen, provided an effective and well- tolerated method to reduce the amount of blood loss in patients undergoing scoliosis surgery. Dexmedetomidine, was associated with plonoged extubation and recovery times.

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THE EFFECTS OF MIDAZOLAM AND DEXMEDETOMIDINE INFUSION ON PERI-OPERATIVE ANXIETY IN REGIONAL ANESTHESIA

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Abstract

Background: This study aimed to compare the influences of midazolam and dexmedetomidine infusion on anxiety scores in patients undergoing surgery with regional anesthesia.

Methods: Eighty ASA I or II class patient undergoing elective surgery with regional anesthesia were included in the study. Permanent anxiety scores were determined using the State-Trait Anxiety Inventory (STAI)-1 and 2 one day before the surgery. In Group I patients, dexmedetomidine 0.5 μg/kg basal infusion for 10 min and 0.5 μg/kg/h for maintenance was administered. In Group II patients, midazolam infusion at a rate of 0.05 mg/kg for 10 min and 0.05 mg/kg/h for maintenance was administered. The sedation scores were determined every 5 min. The steady state anxiety scores of the patients were determined one day before, 30 min after operation, at the end of the operation, and at 30 min and day 7 postoperatively using STAI-1 score. Side effects were determined and recorded.

Results: Sedation scores were comparable in both of two treatment groups. Anxiety scores were maintained with drug infusions. The incidences of side effects were significantly decreased in midazolam group compared to the dexmedetomidine group.

Conclusion: Midazolam infusion was found to be more appropriate and efficient than dexmedetomidine during regional anesthesia practice. Dexmedetomidine infusion should be cautiously used in regional anesthetic techniques performing symphathetic blockade.

Key words: Anxiety, dexmedetomidine, midazolam, regional anesthesia, sedation.

Conflict of interest: Authors declare that there is no conflict of interest.

Disclose source: The study was performed without requiring external source.

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Introduction

Surgical operation is one of the most serious stresses experienced by humans and fear and anxiety may influence the mortality by increasing neuroendocrine stress response[1].

Regional anesthesia used commonly in day-case surgery offers advantages such as, being vigilant during surgery, continuing spontaneous breathing, and preservation of protective reflexes such as swallowing and coughing. In addition, early mobilization in the postoperative period, minimizing pulmonary complications, persisting analgesia, and shortening of the duration of hospitalization are other benefits. On the other hand, vigilance during surgery may increase concerns including being aware of surgical intervention and pain. Pain at the puncture site, needle fear, and recalling the procedures are the other undesired concerns regarding regional anesthesia. Patients may hence experience intense stress and anxiety, which is unfavorable for patient, anesthesia and surgical team. These points may be alleviated by sedating the patient during surgery.

Dexmedetomidine activates central nervous system and decreases plasma cathecholamine level with stimulation of α-2 adrenoreceptors in postsynaptic site, resulting in decrease of heart rate and blood pressure and is used for sedation and anxiolysis. It was demonstrated to decrease pain and cathecholamine response to cold pressure in healthy volunteers[2]. In a study comparing dexmedetomidine with propofol infusion, only propofol was found to be efficient on anxiety in healthy volunteers[3].

Midazolam which is a short acting, water soluble form of benzodiazepine is commonly used for premedication in order to perform amnesia, sedation and to reduce peri-operative anxiety. This effect depends on to binding to the gamma amino butyrate receptors at benzodiazepine site[4]. It is also shown in a placebo controlled study that, premedication with midazolam was decreased nausea and vomiting in patients undergoing day-case surgery[5]. Although it was shown a decrease in psychomotor performance with midazolam, there was no change on attention span[6].

The aim of the present study was to compare dexmedetomidine and midazolam for the quality of sedation, hemodynamic changes, influence on perioperative anxiety and side effect profiles.

Methods

The uni-centric study was conducted at Departments of Anesthesiology and Psychiatry in Kırıkkale University Süleyman Demirel Training and Investigation Hospital after obtaining approval from Local Ethics Committee (2009/038). Eighty American Society of Anesthesiology (ASA) class I-II patients scheduled for elective extremity surgery under regional anesthesia, aged between 18-70 years were randomly recruited. Randomization was performed using sealed opaque envelopes chosen from the patients before the operation. Drug dilutions were prepared and labeled in a separate room from an investigator (AA) who was not participated to the further evaluation.

Patients including ASA class III or more, aged under 18 years or more than 70 years, with morbid obesity (patients exceeds 50% of their ideal body weight), with asthma and other pulmonary disorders, with uncontrolled systemic pathology (such as diabetes mellitus), with unknown central nervous system disease, with debility or disorders influencing cooperation, with known psychiatric disorders, with history of sleep apnea, patients with obvious arrhythmia or conduction defects, with analgesic use within 3 days, receiving monoamineoxydase type of antihypertensive drug, alcohol, drugs including carbamazepine, agonist antagonist type of opioids, allergy to the any type of anesthetics used including midazolam and dexmedetomidine were excluded from the study. All patients were informed about the procedure and written consents were obtained a day before surgery. Steady state (State Trait Anxiety Inventory: STAI-2) and anxiety levels (STAI-1) were determined using anxiety scores[7] and values before sedative infusions was accepted as baseline. Patients were randomly allocated into two equal groups (40 in each) namely dexmedetomidine (Group D) and midazolam (Group M). Venous access was found at non dominant site of dorsum of hand in the holding area using 20 G cannula, lactate ringer infusion was started initially at a rate of 7-8 $mL.kg^{-1}.h^{-1}$ within 15-20 min as pre-hydration and decreased to 5 $mL.kg^{-}$

$^{1}.h^{-1}$. Premedication was not performed. A nasal cannula was applied and oxygen was supplemented at a rate of 2 $L.min^{-1}$. As a standard anesthetic care, vital parameters including ECG at V5 derivation and oxygen saturation were monitored continuously; arterial blood pressure was determined and recorded every 5 min (Datex-Ohmeda Cardiocap 5, Helsinki, Finland). Regional anesthesia was performed after obtaining appropriate position and cleansing. Anesthetic distribution was determined using pin pricks.

Sedative drugs (Midazolam 20 mg or dexmedetomidine 200 μg) were diluted in 50 mL saline and started via stopcock. Midazolam initial bolus dose 0.05 $mg.kg^{-1}$ infused within 10 min and followed at a dose of 0.05 $mg.kg^{-1}.h^{-1}$ in Group M, or dexmedetomidine 0.5 $\mu g.kg^{-1}$.was given within 10 min and infusion was made with 0.5 $\mu g.kg^{-1}.h^{-1}$ in Group D according to calculated volumes (Body weight / 8 = mL for initial bolus and maintenance infusion). Sedation was monitored by determining Observer's Assessment of Alertness Scale (OAAS) determined before and every 5 min during infusion[8]. Infusion was adjusted according to the target OAAS around 4. Infusion was stopped in lower and increased in higher values. OAA/S was rated as follows 5: response to the question asked with the normal voice, 4: lethargic response to the normal voice (sleepy), 3: response to only repeated or loud voice, 2: response to the gentle shaking or pushing, 1: no response to the gentle shaking or pushing. Patient's anxiety was also assessed using STAI-1 at 30 min after starting the operation, at the end of the operation, 30 min after operation and 1 week after operation with a telephone interview. Sedative infusion was followed until skin closure. Recovery time was accepted as time to reach OAA/S 5.

Perioperative side effects including hypotension (MAP<70 mmHg or decrease more than 20% from initial value), bradycardia (HR<45 beats. min), desaturation (SpO2<90 for more than 5 sec), headache, nausea and vomiting were noted. Infusion of crystalloid fluid was increased for hypotension and ephedrine at a dose of 5 mg iv was given and repeated when indicated, and atropine sulphate 0.5 mg iv was administered for bradycardia. Metoclopramide 10 mg iv was performed slowly in the case of moderate and severe nausea and/or vomiting. Patients were evaluated for an hour at recovery area. Supplemental O_2 2 $L.min^{-1}$ was given through nasal cannula, vital signs were also determined during this period.

Statistical analysis

Statistical analysis was performed using package program (SPSS15.0, Chicago, USA). Our preliminary data indicates that 28 patients in each group was required to find any difference between side effect profiles with a power of 80%. We therefore included 40 patents in each group in order to increase power and to account for possible dropouts. Demographic variables were compared using chi-square, continuous variables were evaluated with t test, and non parametric data with using Kruskal-Wallis analysis. A p value under 0.05 was considered for statistical significance.

Results

All patients in either group completed the study. Demographic variable, duration of surgery and anesthesia are shown in Table 1. There were no differences between study groups with respect to these parameters. Table 2 indicates the distribution of regional techniques performed in study groups.

Table 1
Patient characteristics, duration of surgery and anesthesia, ASA: American society of Anesthesiology

	Group D	**Group M**
	n= 40	n= 40
Age (year)	39.7 ± 14.9	39.2± 12.6
Height (cm)	167.9 ± 10.3	169.5 ± 9.8
Weight (kg)	74.6 ± 13.9	80.2 ± 9.9
Gender (F/M)	18/22	13/27
ASA physical status (I/II)	28/12	26/14
Duration of operation (min)	73.6 ± 17.9	82.8 ± 24.0
Duration of anesthesia (min)	85.1 ± 18.2	93.7 ± 24.2

Table 2

Distribution of regional anesthetic techniques, BPB: brachial plexus block, SNB: sciatic nerve block, N (%)

	Group D	Group M
	n= 40	n= 40
Spinal	21 (52.5%)	17 (42.5%)
Spinal and epidural	1 (2.5%)	3 (7.5%)
Axillary BPB	11 (27.5%)	17 (42.5%)
Supraclavicular BPB	6 (15%)	3 (7.5%)
Popliteal SNB	1 (2.5%)	0 (0%)

Hemodynamic variables including HR and MAP pressure in the perioperative and early postoperative period are shown in Figure 1 and 2. There was no significant difference between groups during the observation period.

Fig. 1

Heart rate (HR) variables

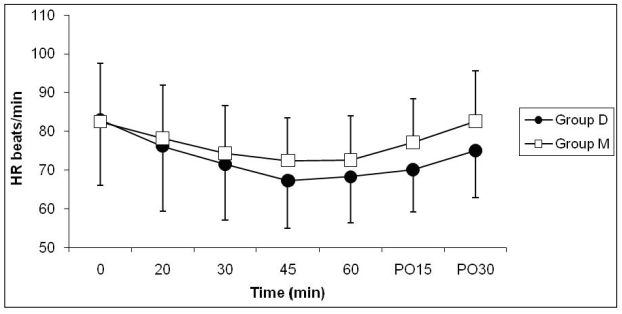
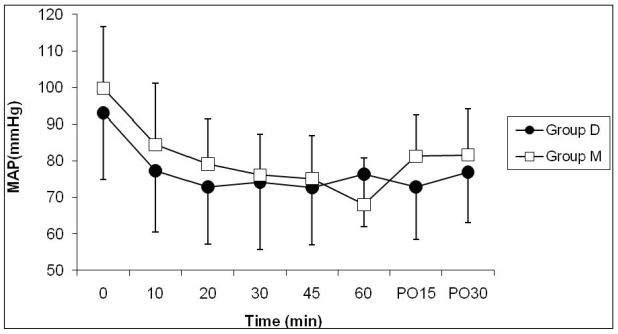


Fig. 2

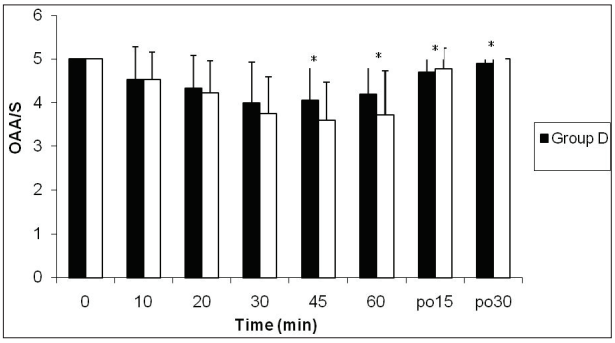
Mean arterial blood pressure (MAP) changes



Sedation scores are shown in Figure 3. While, patients in the Group D were significantly more sedated at 45 and 60 min during perioperative period, sedation was more pronounced in Group M at postoperative 15 and 30 min periods ($p<0.05$).

Fig. 3

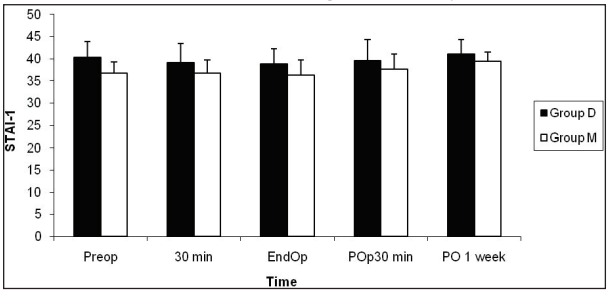
*Sedation determined with observer's assessment of alertness (OAA/S) scale, *: $p<0.05$*



Anxiety scores of study groups (STAI-1) are shown in Figure 4. Although there were significant differences between groups in each time period, no significant change was found compared to the baseline value. Steady state anxiety levels (STAI-2) were similar between treatments (Group D; 42.0 ± 4.6, Group M: 42.9 ± 5.1, p=0.411).

Fig. 4

Time-related changes on anxiety



Side effect profiles of the study groups in perioperative and early postoperative periods are summarized in Table 3. Bradycardia was significantly increased in Group D (25% versus 2.5%, p= 0.004). Nausea was increased in Group M (10% versus 2.5%, p= 0.041).

Table 3

Side effects during perioperative and early postoperative period, N(%)

	Group D	Group M
	n= 40	n= 40
Hypotension	4 (10%)	1 (2.5%)
Bradycardia	10 (25%)	1 (2.5%)
Nausea	1 (%2.5)	4 (10%)
Vomiting	-	1 (2.5%)
Dizziness	-	-
Headache	2 (5%)	-

Discussion

The results of the present study showed that, in equal sedative doses dexmedetomidine and midazolam demonstrated the same level of anxiolysis, but side effect profiles were increased with dexmedetomidine infusion during regional anesthetic practice.

When compared with the preoperative values, heart rates decreased in both study groups. While there was only one patient in midazolam group that required treatment for bradycardia, there were eight patients with bradycardia and two patients with hypotension along with bradycardia in dexmedetomidine infusion group that necessitated treatment. Spinal anesthesia was performed in 10 patients in whom bradycardia and hypotension developed. It was concluded that decrease in HR and MAP occurred at the same period due to sympathetic block established during spinal anesthesia and pharmacologic effects of dexmedetomidine, and therefore side effects were increased.

Dexmedetomidine dose dependently decreases heart rate and arterial blood pressure by decreasing plasma cathecholamine levels[9]. Mean arterial blood pressure and heart rate was significantly decreased by 22% and 27% respectively in ten healthy volunteers after infusion in a rate of $2\mu.kg^{-1}/h^{-1}$[(10)]. A transient increase in blood pressure may occur due to peripheral α-2 adrenoceptor activation induced vasoconstriction[11]. In our study, compared to the intraoperative measurements, the baseline MAP values were higher in both of two groups, with more significant increase in dexmetedetomidine. In contrast, the changes in HR were more pronounced and the decrease in dexmedetomidine was greater than in midazolam. However, changes were not able to reach significance level at any observation period.

There are few studies performing intraoperative sedation during regional anesthesia with dexmedetomidine. Kuzucuoglu et al.[12] compared dexmedetomidine and midazolam infusion when epidural anesthesia reached the predetermined level and similar decrease in HR with dexmedetomidine and relatively stable MAP changes were observed in our study. They concluded that both drugs may be used for sedation but choosing midazolam should be more appropriate. Comparing propofol with dexmedetomidine sedation during postoperative period of cervical spine surgery in adult patients, Terao et al.[13] indicated that hemodynamic variations were more prominent with dexmedetomidine.

Alhashemi[14] compared midazolam and dexmedetomidine during cataract surgery according to the Ramsay sedation scale (RSS) and they concluded although dexmedetomidine caused more prominent decreasing on MAP and HR, it had no significant superiority to midazolam. In a similar study with omitting initial bolus dose, we revealed no significant difference between two drugs[15].

Anxiety scores determined with visual analogue scale were similarly decreased with dexmedetomidine or midazolam infusion during gastroscopy in adult patients[16]. We used STAI1-2 for determining anxiety scores and there was no significant difference between study groups with respect to the anxiety. Both drugs were found to be effective in decreasing perioperative anxiety during regional anesthesia.

In conclusion, dexmedetomidine and midazolam infusion preserved anxiety levels and caused no obvious variations in vital signs but midazolam might be preferred due to the side effect profile. Anesthetists should beware of dexmedetomidine infusion especially in patients performing central neuroaxial blockade.

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A COMPARISON OF RECTAL MISOPROSTOL AND INTRAVENOUS OXYTOCIN ON HEMORRHAGE AND HOMEOSTATIC CHANGES DURING CESAREAN SECTION

Mohammad Reza Fazel[*], Mansoure-Samimi[**], and Esmaeil-Fakharian[***]

Abstract

Background: Post partum bleeding is a major cause of mortality and morbidity in pregnant women. In this study the effects of rectal misoprostol and oxytocin on post-cesarean bleeding are compared.

Methods: In this clinical trial 100 pregnant women candidate of elective cesarean section (CS) were randomly allocated in one of two groups of patients receiving either 400 µg of misoprostol, rectally, after spinal anesthesia, or intravenous oxytocin, after delivery of the baby. Intra-operative bleeding, hemoglobin level before and 24 hour after operation, mean arterial blood pressure, heart rate before and after the administration of the drugs, and adverse drug effects.

Results: There was no difference between the groups in age, duration and number of pregnancy, and surgery. The amount of the blood lost in misoprostol group was 578±185 cc, and in oxytocin group 620±213 cc (p=0.39). Decrease in hemoglobin level in the two groups was not statistically significant (p=0.55). Changes in mean arterial pressure and heart rate were only significant in oxytocin group. Shivering was significantly more common in the misoprostol group and respiratory distress in the oxytocin group. Other adverse effects were equally seen in both groups.

Conclusion: Misoprostol is an appropriate alternative for intravenous oxytocin in patients undergoing cesarean section, with lesser side effects and longer duration of action.

Financial support: Kashan University of Medical Sciences, Faculty of Medicine, Deputy of Research.

Conflict of interest: The authors have no conflict of interest.

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Introduction

Bleeding is still the major cause of mortality and morbidity in post-partum period. World health organization (WHO) has reported 585000 deaths for pregnancy each year. Twenty five percent of cases die from post-partum bleeding[1]. Mean amount of blood lost is 500 ml during normal vaginal delivery (NVD), 1000 ml in cesarean section (CS), and 3500 ml during CS with emergency hysterectomy[2,3].

Four per cent of NVD's and 6% of CS are accompanied with significant bleeding or more than 10% drop in hemoglobin level mandating blood replacement[4,5]. Control of blood loss during CS will prevent morbidity associated with blood transfusion. Although routine use of oxytocin may result in decreased blood loss[6,7], however it is not a safe drug for use in pre-eclampsia, heart diseases, and cesarean section after prolonged labor. It has negative inotropic, anti-platelet, and anti-diuretic effects, and may result in increased heart rate[8,9,10].

Misoprostol is a prostaglandin E1 (PGE1) analogous with stimulating effects on pregnant uterus through prostanoid EP2, and EP3 receptors[11]. The effect of oral, sublingual, and rectal misoprostol on post-partum hemorrhage in comparison with oxytocin has been documented[12-16].

Some studies showed that oral or sublingual misoprostol is more effective than oxytocin in preventing hemorrhage during cesarean section[17,18]. Due to impossibility of oral use of misoprostol during general anesthesia, difficulty in spinal anesthesia for its nausea and vomiting, and based on pharmacological studies proving that misoprostol holds the same blood level while being administrated whether rectally or orally[19,20], therefore , rectal misoprostol can be considered as an alternative to oxytocin.

In this study we compared the effects of rectal misoprostol and oxytocin on intra-operative bleeding, hemoglobin level, and hemodynamic changes in parturients undergoing elective cesarean section.

Methods

One hundred pregnant women candidate of elective cesarean section class 1 or 2 of American Society of Anesthesiology (ASA), admitted to Shabihkhany hospital of Kashan University of Medical Sciences (KAUMS), during 2009, were enrolled to this clinical trial. Cases of twin pregnancy, fetal distress, pregnancy induced hypertension, oligo- or polyhydramnious, macrosomy, more than three deliveries, HELP syndrome, sensitivity to prostaglandins, coagulation disorders, asthma, heart, lung, and liver diseases, previous more than one cesarean section, myomectomy, or any other abdominal operations, and patients with febrile diseases were excluded from the study.

After approval by the ethics committee of the university, and obtaining written informed consent, patients were allocated to one of the two study groups using a table of random numbers, receiving either 400 µg rectal misoprostol just before the incision[21,22], or infusion of 10 units of oxytocin in 500 ml of normal saline for 30 minutes after delivery of the baby up to the end of the operation. All of the procedures were performed by a surgeon with 10 years experience in this field.

In the operation room all of the patients were monitored and received 10 ml/kg Ringer solution before spinal anesthesia with 10-15 mg of Bupivacaine injected to L4/L5 space with a gauge 25 spinal needle. If the block was failed or blood pressure dropped below 90 mmHg the patient was excluded from the study, and replaced with another patient.

During the operation an isolated suction was used for evacuation of amniotic fluid through a small incision over the uterus, and another one used for collection of blood. Every small gauze soaked with blood was considered to contain 20 ml, and every large one 50 ml of blood, and every gram increase in the patients gown weight considered 1 ml of blood. These items added to the amount blood collected in suction and calculated as the total amount of blood loss.

Hemoglobin level was measured before and 24 hour after the operation. Blood pressure and pulse rate was measured before operation, 3 minutes after and every 5 minutes during the procedure. Shivering, number of nausea and vomiting along the operation and up to 2 hours after it ,was recorded. Oral temperature was also recorded in 20, 40, and 60 minutes after

the operation. Temperature above 40 degrees was considered as hyperpyrexia.

On the base of previous studies the mean amount of blood loss with the use of oxytocin during a CS is 600 cc, and misoprostol can reduce it by 200 ml[17]. So considering 90% power and 5% error the sample size was determined to be 50 cases in each group. Data was analyzed with SPSS software using chi-square and T-tests.

Results

There was no difference between the groups in age, duration of pregnancy, duration of operation, and number of pregnancies (table 1).

Table 1

Mean ± SD of age, number and age of pregnancy, and duration of operation in the two study groups

Variable	Misoprostol group	Oxytocin group	P-value
Age	26.6±5.4	27.1±5.3	0.64
(year)			
Duration of pregnancy	38.65±0.58	38.66±0.85	0.94
(week)			
Duration of operation	38.5±5.8	40.42± 6.1	0.11
(min)			
Number of pregnancies	1.85±.092	1.91±0.86	0.73

There were no differences in preoperative and postoperative hemoglobin concentration as well as the amount of intraoperative blood loss between the two groups (table 2).

Table 2

Mean ± SD of amount of intra-operative bleeding, and mean pre-, and post-operative hemoglobin level in the two study groups

Variable	Misoprostol group	Oxytocin group	P-value
HB preoperative	12.35±1.02	12.29±0.62	0.72
(g/dl)			
HB postoperative	11.32 ±0.83	11.19±0.58	0.36
(g/dl)			
Intra-operative	578±185	620±213	0. 39
Bleeding (ml)			

HB=Hemoglobin

There was no significant change in the mean arterial pressure before (82.4 ±15.5 mmHg) and after (78.3 ± 14.8 mmHg) (p=0.24) administration of rectal misoprostol while there was a statistically significant drop before (83.3 ±13.3 mmHg) and after (75.1 ± 11.5 mmHg) (p=0.003) intravenous administration of oxytocin. The heart rate of patients in oxytocin group significantly increased from 104 ± 17 beats/min to 122 ± 21 beats/min (p=0.005). There was no change in the heart rate in the patients who received rectal misoprostol (96 ± 21 vs. 99 ± 18; p= 0.48).

Comparison of the side effects revealed that shivering in misoprostol and respiratory distress in oxytocin group were significantly different from the other group. The difference of other side effects was not significant (table 3).

Table 3

The comparison of side effects during and after operation in the two study groups

Variable	Misoprostol group	Oxytocin group	P-value
Transfusion	0	0	N.S
Nausea	5	7	N.S
Vomiting	2	3	N.S
Shivering	8	1	0.03
Hyperpyrexia (>40 c)	4	1	N.S
Chest pain	1	7	0.03

N.S = No Significant

The incidence of shivering was statistically higher in the misoprostol group while the incidence of chest pain was statistically higher in the oxytocin group. Other side effects were not statistically different between the two groups (table 3).

Discussion

In this study there is no significant difference between intra-operative bleeding and post-operative hemoglobin level in patients receiving either rectal misoprostol or intravenous oxytocin.

Vimala et al[5] in their study on comparison of 400 µg sublingual misoprostol with oxytocin found

that intra-operative bleeding was more significant in oxytocin group, although post-operative hemoglobin level was not different. In another study by Hamm[7] comparing 200 µg buccal misoprostol with oxytocin, there was no difference between intra-operative bleeding and 24 hour post-operative hemoglobin level in the two groups. In Lapaire[6] study with 800 µg oral misoprostol, the amount of bleeding and hemoglobin levels 24, and 48 hours post-operative were similar with oxytocin group. In Chaudhuri et al[20] study with 800 µg rectal misoprostol, although post-operative hemoglobin level was not different in the two groups, the intra-operative bleeding was significantly lesser in misoprostol group.

Although in different studies intra-operative blood loss was equal between the two groups but intra-operative blood loss with the use of misoprostol has a wide ranged from 500 ml[20] to 1000 ml[5]. This wide range of blood loss may be due to differences in the dose, route, and timing of administration of misoprostol. Chaudhuri[20] used 800 µg rectal misoprostol before making incision on the uterus followed by infusion of 6 units of oxytocin in half an hour, but Vimala used 400 µg of sublingual misoprostol and 2 units of oxytocin in half an hour. On the other hand, in these studies, a similar method has not been used to estimate the amount of amniotic fluid and its admixture with blood which may result in inaccurate estimation of blood loss, for example Chaudhuri has used amniotic fluid index (AFI) for estimation of the amount of amniotic fluid, but it has shown that AFI is not a reliable index for this purpose[23,24,25].

In measuring hemoglobin level the aforementioned factors are less likely effective and so its changes are almost similar in different studies, e.g. in spite of 500 cc difference in amount of intra-operative blood loss in Chaudhuri and Vimala studies the difference in hemoglobin changes is only 0.3 mg/dl (0.411 versus 0.1 mg/dl respectively). The rate of bleeding and the hemoglobin changes found in our study was similar to most others studies[6,7]. The differences between our study and that of Chaudhuri may be due to the lower dose of rectal misoprostol (400 versus 800 µg) and higher dose of oxytocin in our study.

Changes in blood pressure and heart rate are side effects of oxytocin. In our study decrease in mean arterial blood pressure and increase in heart rate were significantly more common in patients receiving oxytocin. Several studies have been done on hemodynamic changes resulting from the use of oxytocin. Langesaeter[9], Svanström[10] and co-workers showed that oxytocin reduces mean arterial blood pressure and peripheral vascular resistance, increases heart rate and creates ST-segment changes and consequently will lead to chest pain. This study showed that the oxytocin receiving group had significantly more decrease in blood pressure and increase in heart rate than misoprostol group and dyspnea and chest pain were more common in this group as well. These similar changes are reported in many other studies[26,27,28].

Shivering is a side effect of misoprostol and is dependent to the kind of anesthesia, temperature of the operation room, and fluids used during the procedure[5,6,19,29]. We used fluids with 37 degrees of centigrade (either IV or irrigation) and room temperature was 25 centigrade in the other hand epidural anesthesia was not used in our study because shivering is more common in epidural anesthesia[19]. Oral use of misoprostol results in higher blood level of the drug and higher incidence of shivering. Vimala has reported shivering in 26% of patients with 400 µg of sublingual misoprostol, and 4% in oxytocin group[5]. In Lapaire study with 800 µg of misoprostol, the incidence of shivering was 36% in comparison with 8% in oxytocin group[6]. Chaudhuri reported 8.3% and 1.1% in the misoprostol and oxytocin groups respectively[20]. Shivering was seen in 16% of our patients in misoprostol group and 2% in oxytocin group. These findings are comparable to previous studies.

The difference of nausea and vomiting in the two groups was not significant. Similar findings were reported in previous studies[5,20], despite that for its metallic taste misoprostol when used orally or sublingually was associated with higher frequency of nausea and vomiting[29].

Hyperpyrexia was seen in 8% of patients who received misoprostol and 2% with oxytocin. The difference was not significant. Previous studies have reported similar findings[5,20].

Conclusion

Rectal misoprostol is an appropriate alternative for intravenous oxytocin in patients undergoing cesarean section, with lesser side effects and longer duration of action.

Acknowledgment

The researcher wishes to thank all the honorable personnel working at Shabihkhany Hospital for their generous cooperation.

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CHANGES IN INTRAOCULAR PRESSURES DURING LAPAROSCOPY: A COMPARISON OF PROPOFOL TOTAL INTRAVENOUS ANESTHESIA TO DESFLURANE-THIOPENTAL ANESTHESIA

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Abstract

The aim of the study was to examine intraocular pressure (IOP) changes during laparoscopic cholecystectomy performed under either desflurane-thiopental anesthesia or propofol total intravenous anesthesia (TIVA).

36 patients who will undergo elective laparoscopic cholecystectomy were enrolled in the study. The patients were randomly divided into one of two groups: desflurane (Group D, n=18) or propofol (Group P, n=18). All patients received fentanyl 2 micro/kg IV, and then breathed 100% oxygen for 3 minutes prior to induction of anesthesia. Anesthesia was induced by using thiopental 5 mg/kg IV in Group D and 2 mg/kg IV propofol in group P. Neuromuscular block was achieved with rocuronium 0.6 mg/kg IV. Anesthesia was maintained with desflurane 3-6% in group D and propofol infusion 5-10 mg/kg/h in group P. Desflurane and propofol concentrations were adjusted to maintain mean arterial pressure witihin 20% of the preinduction value. During anaesthesia, fractionated doses of fentanyl 0.5-1 μg /kg IV and maintenance doses of muscle relaxants were used. In both groups, the the mixture 60% nitrous oxide and 40% oxygen was administered used. Arterial pressure, heart rate, $ETCO_2$, SpO2 and IOP were recorded at the predefined time points.

Creation of pneumoperitoneum resulted in a significant increase in IOP which remained elevated throughout the operation in both groups. Also, we recorded a similar IOP changes with both techniques except at five minutes after pneumoperitoneum in 15° reverse Trendelenburg position during desflurane-thiopental anesthesia.

In conclusion, desflurane-thiopental anesthesia maintains the IOP at least at similar levels compared to propofol TIVA anesthesia.

Key words: intraocular pressure (IOP), laparoscopy, desflurane, propofol.

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Introductıon

Compared to traditional open surgery, laparoscopic surgery (LS) is associated with less postoperative pain, less scaring, less trauma, fewer complications, shorter hospital stays and reduced risk of infection[1]. Despite these advantages, LS is associated with an increase in intraperitoneal pressure and many other physiological changes that tend to increase the intraocular pressure[2,3]. Despite the fact that the use of propofol and the new low solubility inhalation anesthetics lead to faster induction and recovery[4], propofol was found to reduce the intraocular pressure in an independent way from the changes in arterial blood pressure or heart rate[5].

Our purpose was to investigate IOP changes during laparoscopic cholecystectomy (LC) under either desflurane-thiopental or total IV propofol anesthesia (TIVA).

Methods

After the study protocol had been approved by the local ethical commitee, writen informed consent was obteined from 36 ASA physical status I or II inpatients aged 18-65 yr scheduled to undergo elective laparoscopic cholecystectomy. Patients with previous eye disease, ophthalmic surgery, history of diabetes mellitus, hypertension, known allergy to the anesthetic drugs and anticipated difficult intubation were excluded. All patients were premedicated with 0.04 mg/kg of IV midazolam 3 minutes before the start of anesthesia.

The patients were randomly divided into one of two groups: desflurane (Group D, n=18) or propofol (Group P, n=18). All patients received fentanyl 2 micro/kg IV, and then breathed 100% oxygen for 3 min prior to induction of anesthesia. Anesthesia was induced by using thiopental 5 mg/kg IV in Group D and 2 mg/kg IV propofol in group P. Neuromuscular block was achieved with rocuronium 0.6 mg/kg IV. Controlled mechanical ventilation was applied to maintain endtidal CO_2 between 35-45 mmHg. Anesthesia was maintained with desflurane 3-6% in group D and propofol infusion 5-10 mg/kg/h in group P. Desflurane and propofol concentrations were adjusted to maintain mean arterial BP witihn 20% of the preinduction value. During anesthesia, fractionated doses of fentanyl 0.5-1 µg /kg and maintenance doses of muscle relaxants were used. In both groups, the mixture 60% nitrous oxide and 40% oxygen was administered using a semiclosed flow circle system. The flow rate of fresh gases was 3 L/ min. Lactated Ringer's solution 4-6 ml/kg/h was given IV throughout surgery.

The abdomen is insufflated with CO_2 to achieve a pneumoperitoneum pressure of 15 mmHg while the patient in the supine position. Patients were then placed in the 15° reverse Trendelenburg (head up) position. Systemic arterial pressure including the systolic, diastolic and mean arterial pressure (MAP), heart rate, SpO2, Et CO_2 and IOP (using a Shioetz tonometer) were recorded at the following points of time:

T1: One minute after endotracheal intubation.

T2: Five minutes after pneumoperitoneum in supine position.

T3: Five minutes after pneumoperitoneum in 15° reverse Trendelenburg position.

T4: 10 minutes after pneumoperitoneum in 15° reverse Trendelenburg position.

T5: 20 minutes after pneumoperitoneum in 15° reverse Trendelenburg position.

T6: After the pneumoperitoneum resolution in supine position.

T7: Just before tracheal extubation.

IOPs were measured with a Schiotz tonometer. The tonemeter was calibrated before each reading. In each patient, IOP was measured by 5.5 scale of Schiotz tonometer, and the average of the two measurements was calculated for each eye; the mean of the IOPs for both eyes was used as the patient's IOP.

A preliminary estimate of sample size was based on the previous studies, which was defined as the IOP. Using data from the previous studies, we calculated that a sample size of 16 patients per group would have 90 % power at 5% significance level to detect a difference in IOP of 3 mm Hg among groups with two sided significance testing. We planned to include 36 patients in this study to allow for dropouts.

Statistical analysis of our study was made by using SPSS 13 software. Wilcoxon Signed Ranks test was used for intra-group comparisons, and Mann

Whitney U test for inter-group comparisons. P<0.05 was considered to be significant.

Results

Four patients were withdrawn from the propofol group: two because the proposed laparoscopic cholescystectomy surgery was converted to open cholecystectomy and two because the standard anesthetic protocol was not followed. Aside from these four patients, 32 patients completed the anlysis.

Demographic profile, duration of surgery and anesthesia were similar in the both groups (Table 1). There was no statistically significant difference between both groups regarding mean arterial pressure, systolic blood pressure, diastolic blood pressures and end tidal carbon dioxide (Table 2 and Table 3). Figure 1 demonstrates the IOP changes between and within the two groups at measurement points. No significant differences in IOP changes were found between the groups except at time T3: IOP was significantly higher in Group P than in Group D (Group P versus Group D, P <0.05) (Figure 2). After the creation of pneumoperitoneum, IOP increased and remained significantly elevated at time points T2, T3, T5 compared with T1 in each group (p<0,05). IOP at T6 and T7 were also significantly higher than T1 in both groups.

Table 1

Demographic data, duration of surgery and anesthesia

	Desflurane Group n=18	Propofol Group n=14	P Value
Age (year)	46.33±11.32	49.57±9.93	0.404
Duration of surgery (minute)	52.83±27.47	50.50±29.63	0.819
Duration of anesthesia (minute)	61.50±29.827	59.92±24.11	0.874
Sex (F/M)	13/5	8/6	-

Data are mean±SD

* Abbreviations used are: T1, 1 min after endotracheal intubation; T2, 5 min after pneumoperitoneum; T3, 5 minutes after tilting into 15° reverse Trendelenburg position; T4, 10 min beginning of 15° reverse Trendelenburg position; T5, 20 min after the beginning of 15° reverse Trendelenburg position;T6, after the pneumoperitoneum resolution; T7, just before tracheal extubation; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; $ETco_{2,}$ end tidal carbon

Table 2

Hemodynamic Changes Of Poropofol Group During Laparoscopic Surgery

Time	T1	T2	T3	T4	T5	T6	T7
MAP, mmHg	100±19	107±21	106±11	103±16	105±11	102±17	108±18
SBP, mmHg	138±22	146±32	141±24	136±23	142±24	139±29	146±27
DBP, mmHg	83±18	89±17	88±9	84±15	86±9	82±15	90±14
$ETco_2$, mmHg	35±0.4	35±4	36±5	35±4	36±5.8	36±4.2	40±5

Hemodynamic changes were measured in Propofol Group. Data are mean±SD.

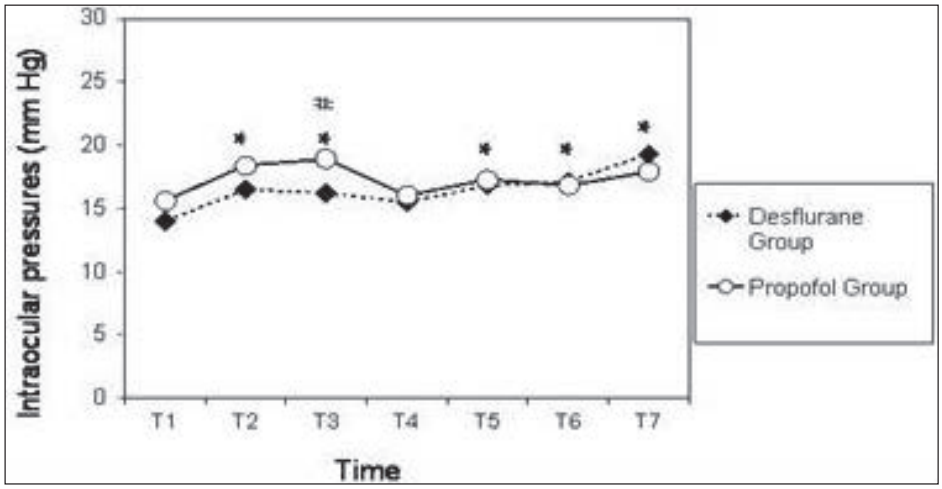
Table 3

Hemodynamic Changes Of Desflurane Group During Laparoscopic Surgery

Time	T1	T2	T3	T4	T5	T6	T7
MAP, mmHg	105±15	102±19	104±16	103±16	103±16	100±14	104±14
SBP, mmHg	141±21	141±29	140±24	139±23	138±25	137±24	144±17
DBP, mmHg	89±15	87±16	85±15	84±15	82±13	78±11	88±15
$ETco_2$, mmHg	35±2.4	36±4	37±5	35±4	37±4	36±3	36±7

Hemodynamic changes were measured in Desflurane Group. Data are mean±SD.

Fig. 1
Changes in intraocular pressure in the desflurane and propofol groups



dioxide.

* Abbreviations used are: T1, 1 min after endotracheal intubation; T2, 5 min after pneumoperitoneum; T3, 5 minutes after tilting into 15° reverse Trendelenburg position; T4, 10 min beginning of 15° reverse Trendelenburg position; T5, 20 min after the beginning of 15° reverse Trendelenburg position;T6, after the pneumoperitoneum resolution; T7, just before tracheal extubation; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; ETco$_{2,}$ end tidal carbon dioxide.

Intraocular pressures were measured in the both groups, 1 min after endotracheal intubation (T1), 5 min after pneumoperiotoneum (T2), 5 minutes after tilting into 15° reverse Trendelenburg position (T3), 10 min (T4) and 20 minutes (T5) after the beginning of 15° reverse Trendelenburg position, after the pneumoperitoneum resolution (T6), just before tracheal extubation (T7).

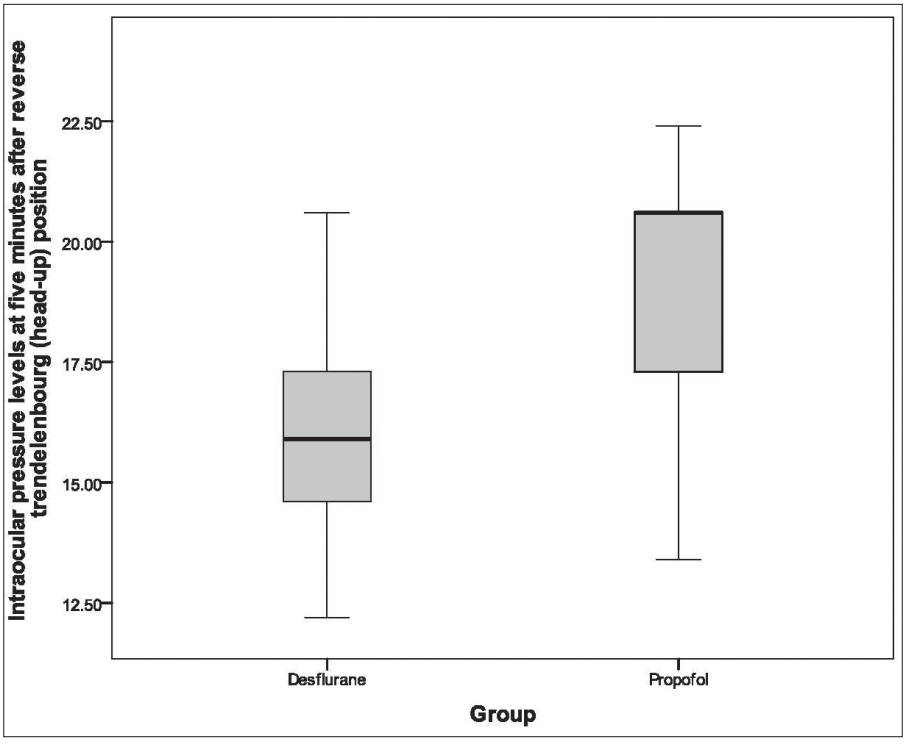
* P<0.05, as compared to T1 within the groups.

# P<0.05, between the groups.

Discussıon

We conducted a prospective, randomized clinical study to compare the effects of desflurane and propofol on IOP in patients undergoing LC. As

Fig. 2
Intraocular pressure levels at 5 minutes after reverse trendelenburg (head-up) position



the results showed, creation of pneumoperitoneum resulted in a significant increase in IOP and remained elevated throughout the whole operation regardless of anesthetic techniques used. Also, we recorded a similar IOP changes with both techniques except at time T3, which might be an advantage of desflurane-thiopental anesthesia. This could be due to the long duration of action of thiopental induction compared to propofol induction.

We used thiopental and desflurane in group D since thiopental induction and maintenance with an inhalational agent is one of the most widely used anesthetic regimen. Also, desflurane is a volatile anesthetic with a low blood-gas solubility coefficient. Recovery is more rapid[4] than other potent inhalation anesthetic agents and comparable with propofol[6]. Limited data suggest that it is also useful as propofol for the maintanence of IOP during anesthesia[6]. To our knowledge, there have been no pubished studies assesing the influence of desflurane on IOP in humans undergoing LC.

IOP is influenced by many factors. Coughing, straining, vomiting, laryngoscopy, intubation, extubation can lead to an increase in IOP[7,8]. In fact, the major factor in determining IOP changes acutely is the episcleral pressure, which is determined by central venous presseure (CVP)[8]. Laparoscopic surgery tend to a further increase in IOP resulting from intrathoracic pressure increase and postural changes, which lead to rise in CVP[2]. In addition to CVP, blood pressure, ETCO2, pneumoperitoneum are also the other factors that seem to have a clear impact on IOP rise[9]. However, most induction agents and all inhalation anesthetic agents reduce IOP in poroportion to the depth of anesthesia, by mainly central control mechanism[6,8]. Its well known that propofol decreases IOP by inhibiting somatodendritic AVP release from the supraoptic nucleus during laparoscopy[2]. Previous studies have shown decrease in IOP between 65% and 29% whether propofol alone or in combination with remifentanil and succincylcholine[7]. Reader J.C. et al. found that desflurane provides less expensive and faster recovery in cholecystectomy operations. However, propofol was found to cause less pain and nausea in the recovery unit[10].

A principal criticism of our study is that we did not include any measurement of IOP before the induction of anesthesia (because of ethical constraints), so that we accepted the baseline values of IOP as one minute after the intubation. It could be argued that the increases in IOP we observed were caused by the decrease of IOP due to induction of anesthesia. We believe this to be unimportant because, the purpose of this study was to ascertain to compare desflurane-thiopental anesthesia versus propofol anesthesia on IOP during LC.

In conclusion, desflurane- thiopental anesthesia appears to be a useful alternative to propfol-tiva anesthesia for maintenace of IOP during LC.

Acknowledgment

The study was approved by the Ethics Comittee of Antalya Education and Research Hospital (Reference No:85/15/06).

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DEXAMETHASONE ADDED TO BUPIVACAINE PROLONGS DURATION OF EPIDURAL ANALGESIA

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Abstract

Background: Different additives have been used to prolong regional blockade. We designed a prospective, randomized, double-blind, controlled clinical trial to evaluate the effect of dexamethasone added to bupivacaine-fentanyl on the duration of postoperative analgesia via epidural catheterization.

Methods: Seventy two adult patients scheduled for elective abdominal or thoracic surgery under epidural anesthesia were randomly allocated into two groups to receive either bupivacaine (0.5%) - fentanyl (50µg) and dexamethasone (8 mg) in lumbar or thoracic epidural anesthesia (Dexa group, n=36), or bupivacaine-fentanyl and saline normal (control group, n=36) via epidural catheter. Duration of analgesia, postoperative pain score and IV analgesic use at first 24 hours were recorded and compared.

Results: Two patients were excluded (one in each group) due to unsuccessful blockade. Age, gender and duration of surgery were similar in the two groups ($p>0.05$). The duration of analgesia (372±58.1vs. 234.6±24.3 min) was significantly longer and pain score and pentazocine use were less in the Dexa than the control group (37.1± 19.7 mg v.s. 73.1 ± 17.6 mg, respectively; $p=0.001$).

Conclusions: This study revealed that dexamethasone added to bupivacaine-fentanyl solution in epidural analgesia prolongs the duration of analgesia in abdominal or thoracic surgery.

Key words: Epidural, Analgesia, Dexamethasone, Bupivacaine, Fentanyl.

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Introduction

Uncontrolled perioperative pain may potentiate some of pathophysiologies and increase morbidity and mortality for patients. Attenuation of postoperative pain may decrease perioperative morbidity and mortality[1]. Analgesia delivered through an indwelling epidural catheter is a safe and effective method for management of postoperative pain[2].

Increasing the duration of local anesthetic action is often desirable because it prolongs analgesia. Different additives have been used to prolong regional blockade. Two of the more studied adjuvants are epinephrine and clonidine[3,4]. Epidural neostigmine and ketamin also were used as adjuvant drugs[5-6]. Some studies have demonstrated the analgesic effect of local spinal and systemic corticosteroids in combination with bupivacaine[7].

Dexamethasone is a high-potency, long-acting glucocorticoid with little mineralocorticoid effect that has been used for prophylaxis of postoperative nausea[8]. Dexamethasone microspheres have been found to prolong the block duration in animal and human studies[9-10], and adding methylprednisolone and dexamethasone to local anesthetic increases the duration of axillary brachial block[11]. Biodegradable microcapsules containing bupivcaine and dexamethasone have been tested in humans and found to produce analgesia for several days in intercostal block[12]. Epidural steroids were effective in the treatment of low back pain[13]. A double-blind study demonstrated postoperative pain reduction and analgesic requirements after epidural dexamethasone injection[14]. Nevertheless, the time of analgesia was not cleared in this study.

The safety of epidural steroid injections has been demonstrated[15]. Thomas et al. showed that epidural dexamethasone reduced postoperative pain and analgesic requirements in patients undergoing laparoscopic cholecystectomy[16]. Hanan et al. demonstrated efficacy of epidural dexamethasone on postoperative analgesia in patients undergoing lower abdominal surgeries[17].

The aim of the current study is to evaluate the effect of dexamethasone added to bupivacaine on the duration of epidural analgesia for postoperative pain management in patients undergoing lower and upper abdominal and thoracic surgeries.

Methods

After institutional approval, written, informed consent was obtained from each patient before inclusion in the study. Seventy-two ASA physical statuses I-II patients aged 23-79 years scheduled for elective abdominal or pelvic surgery were included in the study. Power analysis was done on the basis of authors' assumption that adding dexamethazone to epidural analgesia by bupivacaine prolongs the time of post-operative analgesia (240±45 min) up to 30 minutes; considering α=0.05 and desired power=80% and using online power analysis software; URL: http://www.stat.ubc.ca/~rollin/stats/ssize/n2.html.

Each group included 36 patients.

Exclusion criteria were history of peptic ulcer disease, hepatic or renal failure, psychological disease, allergy to narcotics, a contraindication to an epidural catheter, and use of any premedications (including opioids, benzodiazepines, and clonidine).

On arrival to the operating room, standard monitoring was established (pulse oximetry, electrocardiography, and noninvasive blood pressure monitoring). Patients were randomly divided into two groups (each n=36) using a table of random digits generated by a computer. The study was conducted as double-blinded manner so the patients were anesthetized and were unaware of drug choice. Anesthesia technician prepared the drugs and anesthesiologist only injected the coded-labeled syringes to the patients.

Before the induction of anesthesia, an epidural catheter was placed at the T10-11 or L3-4 intervertebral spaces (for thoracic and lumbar epidural catheter respectively), and correct positioning was confirmed by an injection of 3 ml of 2% lidocaine with 1:200,000 epinephrine. Patients that were under lumbar epidural catheterization in "Dexa group" received 15 ml of 0.5% bupivacaine, 50 µg (1ml) fentanyl, and 8mg (2ml) dexamethasone, and patients in "control group" received 15 ml of 0.5% bupivacaine, 50 µg (1ml) fentanyl, and 2ml of isotonic saline solution via

epidural catheter. Patients that were under thoracic epidural catheterization in Dexa group received 8 ml of 0.5% bupivacaine, 50 µg (1ml) fentanyl, and 4 mg(1ml) dexamethasone, and patients in control group received 8 ml of 0.5% bupivacaine, 50 µg (1 ml) fentanyl, and 1 ml of isotonic saline via epidural catheter. Epidural anesthesia was performed using epidural catheter in patients who underwent (lower or upper) abdominal surgeries. Epidural catheters were inserted via L4-L5 intervertebral space in abdominal surgeries and through T6-T7 intervertebral space in patients undergoing thoracic surgeries. Epidural catheter insertion was performed with 19-gauge Tuohy needle by hanging-drop method. General anesthesia was combined with epidural technique in patients undergoing thoracotomy. General anesthesia was induced with fentanyl 1 µg/kg, lidocaine 1 mg/kg, propofol 2 mg/kg, and atracurium 0.5 mg/kg, and patients were intubated.

All local anesthetic solutions and adjuvant drugs were prepared by an anesthesiologist not involved in performance of epidural catheterization, patient care, or data collection.

Postoperative pain management was performed via epidural catheter, and duration of analgesia and analgesic drug usage (if needed) was recorded. Intravenous pentazocine 10 mg bolus as analgesic drug was used if needed. Visual analogue scale (VAS) was used for estimate of pain degree in patients at 3, 6, 12 hours after surgery. Application of VAS was explained to the patients before operation.

Collected data were analyzed using SPSS statistical package v.17.0 (SPSS Inc. Chicago, IL, USA). For statistical analysis of demographic data and for comparison of groups, chi- square test and independent samples t-test were used. Level of significance considered $p \leq 0.05$.

Results

In this study, 72 patients were evaluated. Two patients were excluded from the study because of unsuccessful blockade. Demographic data and duration of surgery are presented in Table 1. There were no significant differences between the two groups with respect of age, gender, ASA physical status and surgery duration. There was no significant difference between groups regarding lumbar or thoracic epidural catheterization (p=0.49). The duration of analgesia (372±58.1 min in Dexa group vs. 234.6±24.3 min in control group) was significantly longer in the Dexa than in the control group (Table 2).

Table 1

Background parameters in the two study groups

Variables	Dexa group (n=35)	Control group (n=35)	P value
Age (year)	56.2 ± 13.1	52.8 ± 10.4	0.24
Gender (male/female)	17 / 19	17 / 19	0.60
ASA class (I/II)	19 / 17	24 / 12	0.22
Surgery duration (min)	124 ± 32.4	125.8 ± 35.6	0.82

Visual analogue scale (VAS) at 3, 6 and 12 hours after surgery were lower in dexamethasone group than control group. Pentazocine use for pain control in first 24 hours after surgery was lower in dexamethasone group(37.1± 19.7 mg) than control group (73.1 ± 17.6 mg) (Table 2).

Table 2

Clinical parameters in the two study groups

Variables	Dexa group (n=35)	Control group (n=35)	P value
Analgesia duration (min)	372 ± 58.1	234.6 ± 24.3	0.001
VAS* after 3 hours	0.51 ± 0.1	2.1 ± 0.3	0.001
VAS after 6 hours	1.4 ± 1.1	3.6 ± 1.3	0.001
VAS after 12 hours	2.2 ± 0.6	4.4 ± 1.37	0.001
Pentazocine use (mg) in first 24 hour after surgery	37.1 ± 19.7	73.1 ± 17.6	0.001

* VAS = Visual analogue scale.

Discussion

The results of current study indicate that the addition of dexamethasone (8mg, 4mg in lumbar and thoracic epidural catheterization, respectively) to bupivacaine and fentanyl for post-operative epidural analgesia, results in a significant increase in duration of analgesia.

Previous studies demonstrated that the addition of corticosteroid microspheres to local anesthetic prolonged duration of blockade of the peripheral nerves[9-10]. In one study, a prolonged percutaneous blockade of sciatic nerve in rat using bupivacaine-dexamethasone microspheres was demonstrated[9]. It was also reported that the intercostal injection of dexamethasone containing bupivacaine microcapsules produces a prolonged duration of anesthesia and analgesia[10]. Other preliminary data suggest methylprednisolone can increase the duration of sensory and motor block[21]. The authors concluded that the applicability of these findings to clinical practice should be verified in a randomized prospective clinical trial.

In one study (Thomas S, 2006) the addition of corticosteroid to epidural local anesthetic, demonstrated that dexamethasone reduced post-operative pain and analgesic requirements[14] but this study was performed in laparoscopic cholecystectomy. In another study, Hanan et al. demonstrated the efficacy of epidural dexamethasone on postoperative analgesia in patients undergoing lower abdominal surgeries[16].

However, in our study, both lumbar and thoracic epidural catheterization and postoperative analgesia were performed and applied for both lower and upper and thoracic surgeries. The mechanism of the analgesia induced by corticosteroids is not fully understood. However, this effect is suspected to be mediated by their anti-inflammatory or immune- suppressive effects[22-23]. Corticosteroids cause skin vasoconstriction effects on topical application. The vasoconstriction effects of topical steroids are mediated by occupancy of classical glucocorticoid receptors rather than by nonspecific pharmacological mechanisms[24-25]. According to the traditional theory of steroid action, steroids bind to intracellular receptors and modulate nuclear transcription.

In our study, dexamethasone produced a relatively rapid effect, which cannot be explained by the above mechanism[26]. Therefore, vasoconstriction, the presumed mechanism of action for epinephrine's adjunctive effect on local anesthetics, is probably not responsible for block prolongation by dexamethasone. Corticosteroids may have a local effect on the nerve and the dexamethasone effect may be related to this action[27].

Some authors believe that analgesic properties of corticosteroids are the result of their systemic effect[28]. Because of our positive results, the question of whether these results were attributable to a local or systemic effect warrants further investigation.

The safety of dexamethasone use in intrathecal or epidural injections may raise some concerns. In one study, after approximalely 2000 intrathecal injections of dexamethasone (8 mg) in 2000 patients for treatment of posttraumatic visual disturbance, no neurological disorders were found at 1- month follow up[29].

We used a dose of 8 mg dexamethasone in lumbar epidural and 4 mg in thoracic epidural cases because administration of this dose seems to be safe in adults. Advers effects with a single dose of dexamethasone are probably extremely rare and minor in nature, and previous studies have demonstrated that short-trem (<24 hours) use of dexamethasone was safe[30-31]. Adding a steroid to local anesthetic solution may not be indicated for all patients. For example, diabetic patients may experience hyperglycemia and patients with a continuing infectious process may be detrimentally affected by the anti-inflammatory effects of steroids. This study led us to hypothesize that dexamethasone may be useful in situations in which epinephrine must be used with caution (e.g., hypertension, ischemic heart disease).

In conclusion, the addition of dexamethasone to bupivacaine solution in epidural postoperative analgesia prolongs the duration of blockade. Further studies are needed to evaluate the optimal dose of dexamethasone to be used for prolonged epidural analgesia as well as the mechanism of this effect.

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THE EFFECTIVENESS OF PATIENT-CONTROLLED EPIDURAL ANALGESIA WITH ROPIVACAINE 0.165% WITH FENTANYL 2.0 μG/ML OR LEVOBUPIVACAINE 0.125% WITH FENTANYL 2.0μG/ML AS A METHOD OF POSTOPERATIVE ANALGESIA AFTER MAJOR ORTHOPAEDIC SURGERY

KARIS BIN MISIRAN* AND LENIE SURYANI BINTI YAHAYA**

Abstract

This prospective randomized single-blinded study was conducted to determine whether there were differences in consumption, demand dosing and postoperative analgesia quality between PCEA using ropivacaine and levobupivacaine. Seventy patients with ASA classification I and II aged 18 to 80 years old scheduled for elective total knee replacement or total hip replacement were studied. All patients received CSE and then were randomly allocated to receive either ropivacaine 0.165% (Group A) or levobupivacaine 0.125% (Group B) both added with fentanyl 2.0μg/ml via epidural route. PCEA regime was offered for 48 hours with additional standard orthopaedic practice of oral analgesia (etoricoxib 120mg OD and paracetamol 1.0gm QID) on the second postoperative day. Basal infusion of PCEA was at 3.0ml/hour and discontinued after 24 hours following started of PCEA. The consumption of local anaesthetics used within the first 24 hours (basal + demand) and 48 hours (total basal + total demand) were recorded. The VAS pain score, sedation score, side effects and vital signs (blood pressure, heart rate and respiratory rate) were also recorded every four hours for 48 hours. This study showed that the total volume of drug used was significantly higher in Group A (163.31±29.01ml) than Group B (142.69±30.93ml) ($p<0.01$). The mean dose of Group A for the first 48 hours after surgery was 251.43±70.02mg and was significantly greater than the mean dose of Group B (178.91±42.33mg) ($p<0.01$). The numbers of PCEA boluses delivered (D) and PCEA attempts (A) were higher in the Group A (22.37±7.32 and 27.66±9.12) in contrast to Group B (17.63±7.71 and 24.40±11.51) but the differences were not statistically significant. The ratio D/A showed significantly higher in Group A (0.83±0.13) than Group B (0.74±0.15) ($p<0.02$). The VAS pain score was similar for both groups. One patient in Group B had vomiting and there was no sedation, hypotension, pruritus or motor block recorded in both groups. In conclusion this study showed that both PCEA using ropivacaine 0.165% with fentanyl 2.0μg/ml and levobupivacaine 0.125% with fentanyl 2.0μg/ml provided effective postoperative analgesia within the first 48 hours of major lower limb orthopaedic surgery despite clinically significant dose difference. There was no hypotension, pruritus, sedation or motor block recorded in both groups.

Key words: patient-controlled epidural analgesia, major lower limb orthopaedic surgery, VAS pain score.

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Introduction

At the present time, the use of epidural infusion of local anaesthetics with or without patient-controlled epidural analgesia (PCEA) to provide postoperative analgesia is becoming more popular. The benefits of PCEA over epidural infusion alone include avoidance of potential drug over-dosage, elimination of the "waiting time" and "peaks and valleys" of nurse-administered analgesics and the involvement of the patient in his/her own healthcare[1].

The high quality of postoperative pain relief is the main concerns for the patients. It is also the ultimate goal of both national health policy and the specialty of anaesthesiology. Nevertheless, postoperative pain relief is often inadequate[2]. Several studies have shown that epidural analgesia with local anaesthetics combined with opioid provides better postoperative analgesia than epidural analgesia or systemic opioid alone and improves the surgical outcome[3-5]. Initial reports suggest that PCEA may improve the quality of analgesia[6], patients' satisfaction and safety compared with conventional epidural infusion or bolus techniques despite lacking and limited experience concerning the efficacy and safety of this method[7].

Study done by Camorcia et al showed that ropivacaine and levobupivacaine were both less potent than bupivacaine and ropivacaine appeared to be 20% less potent than levobupivacaine[13]. However Polley et al reported that similar ED_{50} value for ropivacaine and levobupivacaine in parturients with cervical dilatation of up to 7 cm[14]. Two other studies performed in 1999 suggested that ropivacaine was 40% less potent than bupivacaine[10,11] whereas this difference was only 2% for levobupivacaine[12]. Casati et al[8] and De Cosmo et al[9] showed that lumbar and thoracic epidural catheter placement with levobupivacaine 0.125% provided satisfactory intraoperative and postoperative analgesia for major orthopaedic surgery and thoracotomies respectively.

Combining the benefits of better analgesia with the advantages of patient control; it appears therefore that PCEA might offer the best option for postoperative analgesia. Currently PCEA is mainly used in obstetrics and the technique is not widely used outside this unit. However, a study done by Smet et al which used ropivacaine 0.165% plus sulfentanil 1.0μg/ml versus levobupivacaine 0.125% plus sulfentanil 1.0μg/ml in total knee and total hip arthroplasty suggested the volume consumed was higher in ropivacaine group than levobupivacaine group[15]. This study suggested either a potency difference between both local anaesthetics of more than 25% or a different duration of action. Therefore, it is going to be extremely difficult when performing comparative studies to decide what concentrations of local anaesthetics to select to give optimal analgesic care for post-operative patients.

General Objective

The purpose of this study was to determine whether there were differences in consumption, demand dosing and postoperative analgesia quality between PCEA using ropivacaine 0.165% with fentanyl 2.0μg/ml and levobupivacaine 0.125% with fentanyl 2.0μg/ml within the first 48 hours of major lower limb orthopaedic surgery.

Methods

This prospective single-blinded randomized study was conducted following approval by the Dissertation Committee of the Department of Anaesthesiology and Intensive Care, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and by the Research and Ethics Committee of UKMMC (Project Code: FF-288-2009).

Following written informed consent, seventy patients with ASA I and II aged between 18 to 80 years old scheduled for elective unilateral total knee replacement (TKR) or total hip replacement (THR) surgery were studied. Exclusion criteria included contraindications to central neuroaxial block (e.g. bleeding disorders), allergies to any drugs used and patients who had difficulty in understanding PCEA. Intra-operatively, all patients received combined spinal-epidural anaesthesia (CSE) under aseptic technique at level L_3/L_4 or L_4/L_5. The spinal component consisted of 3.0ml of hyperbaric bupivacaine 0.5% with fentanyl 25μg. If the spinal block proved insufficient for the surgery, epidural lignocaine 2% supplement was allowed to be given a maximum of 10ml, after which

the patients were put under general anaesthesia and were excluded from the study.

After CSE had been performed all the patients were then randomly allocated to Group A (ropivacaine 0.165% + fentanyl 2.0µg/ml) or Group B (levobupivacaine 0.125% + fentanyl 2.0µg/ml). Post-operatively, once the Bromage score had decreased to zero on the non-operated side, the PCEA regimen was started. This PCEA delivered 3.0ml/hr basal infusion for the first 24 hours with additional demand doses of 4.0ml with a lockout time of 20 minutes. After the first 24 hours, the basal infusion was stopped but the demand doses continued as required.

Every four hours, the ward nurses recorded the following variables: heart rate, arterial blood pressure, respiratory rate, Visual Analogue Scale (VAS) pain scores on a scale 0-10, sedation score (Ramsay score) and evidence of side effects (e.g. nausea, vomiting, pruritus) while the Acute Pain Service (APS) staff nurses assessed Bromage score twice daily. The observer recorded the volume of the local anaesthetic used within the first 24 hours (basal + demand) and 48 hours (total basal + total demand). The observer also recorded the number of successful PCEA boluses delivered (D) and the number of PCEA attempts made (A) and the ratio (D/A) for 48 hours was then calculated. All the epidural catheters were removed 48 hours after the start of the PCEA infusion.

After 24 hours, all patients were given supplementary analgesia in the form of oral etoricoxib 120mg OD and oral paracetamol 1.0gm QID. For patients who had insufficient analgesia, additional drug such as tramadol 50mg or opioids (e.g. morphine and pethidine) were given to the patients.

Statistical Analysis

Data calculated from previous study done by Smet et al[15] showed that sample of 70 patients who underwent major orthopaedic surgery were required to detect a 15% difference in the volume between the two groups. Thirty five patients were required in each group to obtain a study power of 0.85 with a '*p'* value of 0.05. Data was analyzed by using SPSS 17.0™ software (SPSS, Chicago, IL). ANOVA for repeated measures was used to compare VAS pain scores, heart rate and arterial blood pressure. Student's t-test was used to compare the volumes of epidural solution consumed, delivered/attempt (D/A) ratios, age and weight. A '*p'* value of < 0.05 was considered to be statistically significant.

Results

A total of 70 patients were enrolled in this study with 35 patients in each group. As shown in Table I, the two groups were comparable with respect to age, gender, eight, ASA classification and race.

Table I
Demographic and surgical data. Values expressed as mean ± SD and number (%) as appropriate

		Group A (n=35)	Group B (n=35)
Mean age (years)		63.3±11.4	66.1±8.0
Gender	Male	6 (17.1)	7 (20.0)
	Female	29 (82.9)	28 (80.0)
Weight (kg)		66±8.6	68±7.6
ASA	I II	15 (21) 18 (25)	20 (28) 17 (24)
Race	Malay	16 (45.7)	13 (37.1)
	Chinese	16 (45.7)	19 (54.3)
	Indian	1 (2.9)	2 (5.7)
	Others	2 (5.7)	1 (2.9)
Surgery	TKR THR	27 (38.6) 8 (11.4)	23 (32.9) 12 (17.1)

Table II shows that after 48 hours, the cumulative volumes of drugs used were higher in Group A compared to Group B and the difference was significant at 24 hours (*p<0.02*) and 48 hours (*p<0.01*). The mean

Table II
Volume and amount of drugs used, number of PCEA delivered (D), number of PCEA attempt (A) and ratio D/A. Values expressed as mean ± SD and number (n) as appropriate

	Group A (n=35)	Group B (n=35)	*p* value
Volume 24 hr (ml)	118.17±20.36	105.54±22.03	0.02*
Volume 48 hr (ml)	163.31±29.01	142.69±30.93	0.01*
Amount of drug used 48 hr (mg)	251.43±70.02	178.91±42.33	0.01*
PCEA bolus delivered (D)	22.37±7.32	17.63±7.71	0.19
PCEA attempts (A)	27.66±9.12	24.40±11.51	0.17
Delivered/Attempted	0.83±0.13	0.74±0.15	0.02*

* Significant '*p*' values.

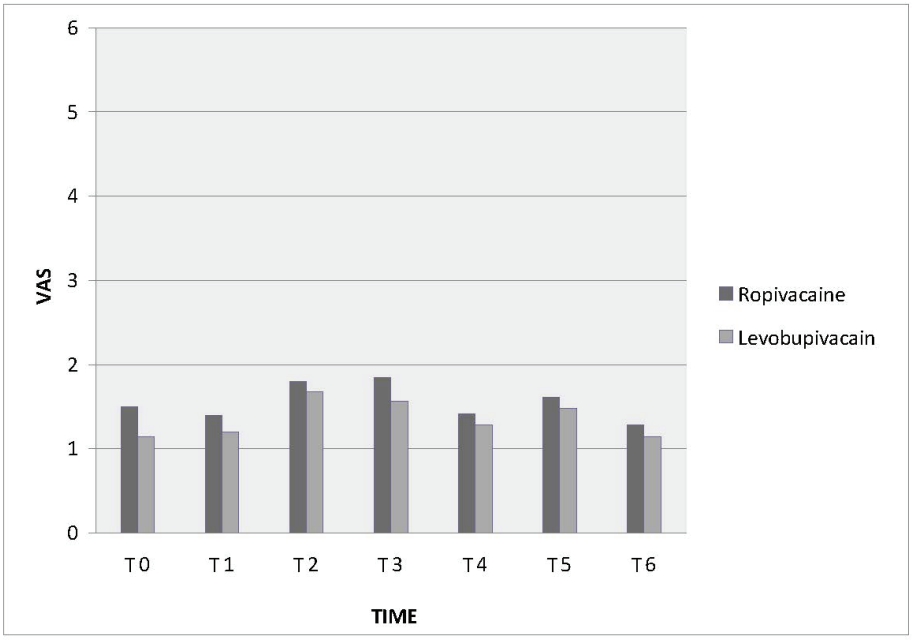
± SD dose of Group A for the first 48 hours after surgery was significantly ($p<0.01$) greater than the dose of Group B.

The numbers of PCEA boluses delivered (D) and PCEA attempted (A) were higher in the Group A in contrast to Group B but the differences were not statistically significant. However the delivered/attempt ratio (D/A) was significantly higher in Group A ($p<0.02$) than Group B.

Figure 1 shows VAS pain scores presented as means ± SD at different time intervals for both drugs. T_0 at the start of PCEA, T_1 at 8 hour, T_2 at 16 hour, T_3 at 24 hours, T_4 at 32 hours, T_5 at 40 hours and T_6 at 48 hours. There were no statistically significant differences.

None of the patient developed hypotension or sedation. There was only one incidence of vomiting occurred in one patient in Group B. Other incidences such as pruritus and motor block were not detected in this study.

Fig. 1
VAS pain score at different time intervals. Values expressed as mean ± SD and number (n) as appropriate



Discussion

Patient-controlled epidural analgesia provides us with a valuable and informative research tool in terms of comparing the efficacy of various concentrations of different local anaesthetics, either alone or in combination with opioids. Varying lockout periods, bolus and infusion dose with PCEA may also provide useful information for managing pain in acute setting.

There were several studies comparing ropivacaine and levobupivacaine for postoperative epidural analgesia. Casati et al compared PCEA ropivacaine 0.2% with levobupivacaine 0.125% (with baseline infusion rate 5.0ml/hour) for intraoperative and postoperative analgesia for major orthopaedic surgery and concluded that the quality of analgesia was similar for both local anaesthetics but

their study observation was only for the first 12 hours after surgery[8]. In our study we found that PCEA ropivacaine 0.165% or levobupivacaine 0.125% provided effective postoperative analgesia. However in our study, fentanyl 2.0 µg/ml was added to the local anaethetics and our observation was done up to 48 hours.

A nearly similar study done by Smet et al found that both PCEA ropivacaine 0.125% and levobupivacaine 0.125% (sufentanyl 1.0µg/ml was added to both local anaesthetics but no basal infusion was given) provided effective analgesia for major orthopaedic surgery. Smet et al chose sulfentanil whereas in our study we used fentanyl because it's availability, widely used and cost-effective[15]. The addition of an opioid may have affected local analgesic quality and duration. However, there is no evidence that opioid added to local anesthetic solution would alter the potency difference between them[16].

Our study showed significantly larger volumes and doses of ropivacaine were used than levobupivacaine during 48 hours of PCEA regime. The mean volume of ropivacaine was 13% greater than that of levobupivacaine. The boluses delivered/attempted ratio was also greater in ropivacaine group. In Smet et al study, the volume and dose used was 25% higher in those receiving ropivacaine than levobupivacaine[15]. The volume and dose difference may suggest different population studied and additional standard oral analgesic given. Therefore the higher amount of ropivacaine used probably reflects the potency difference between the two local anaesthetics.

Possible explanation for higher requirement of ropivacaine in both studies may be due to shorter duration of action of ropivacaine. However it would be unwise to believe that a higher dose can be explained entirely by a difference in duration of action alone. Furthermore, the ideal combination of local anaesthetic and opioid for PCEA is yet to be discovered.

In another study conducted by Senard et al using PCEA levobupivacaine 0.1% and ropivacaine 0.1% (both were combined with an epidural infusion morphine 0.1mg/hour) they did not find any difference in terms of postoperative pain relief between PCEA these two drugs in which was added morphine background infusion over a 48 hours period. However this study was conducted on patients undergoing abdominal surgery[17].

There were no side effects documented except for one patient in levobupivacaine group who had vomited twice within 24 hours postoperative without episode of hypotension observed. In a study by Smet et al[15], the incidence of hypotension and vomiting were very low, but mild pruritus was reported by 13% and 10% of patients in the ropivacaine and levobupivacaine groups respectively. Lack of side effects is probably related to the potency of the drug. The previous studies done by Capogna et al[11] and Lyon et al[12] showed that ropivacaine was 2% less potent than levobupivacaine but Camorcia et al[13] reported that ropivacaine was 20% less potent than levobupivacaine. Despite different potency described from these studies, there were no differences in analgesic qualities.

The other aspect of the study design needs further discussion. A background infusion may not be useful for epidural opioid alone[16] but with combination of both local anaesthetics and opioids, the use of basal infusion seems to be common practice, although there is lack of studies demonstrating benefit from this. In this study, a basal infusion was used for the first 24 hours. We found this basal rate infusion was beneficial during the first 24 hours after surgery when patients were not yet familiar with the PCEA pump. It was also noted, frequent additional demands had been observed despite of basal infusion of local anesthetic to obtain

optimum pain control. However, frequent demands may affect patient satisfaction and sleep quality.

Conclusion

This study showed that both PCEA using ropivacaine 0.165% with fentanyl 2.0µg/ml and levobupivacaine 0.125% with fentanyl 2.0 µg/ml provided effective postoperative analgesia within the first 48 hours of major lower limb orthopaedic surgery despite clinically significant dose difference. There was no hypotension, pruritus, sedation or motor block recorded in both groups.

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POSTOPERATIVE SORE THROAT IN CHILDREN: COMPARISON BETWEEN PROSEAL™ LMA AND CLASSIC™ LMA

Azlina Mazzita Mohamed Mokhtar*
and Choy Yin Choy**

Abstract

Background: Postoperative sore throat after minor pediatric surgery although uncommon and the symptoms are mild, the incidence may be affected by several factors. This study was designed to compare the frequency and severity of post operative sore throat in children undergoing elective surgery following the use of proseal LMA (PLMA) compared to classic LMA (cLMA).

Methods: Two hundred children, 6 to 12 years old undergoing general anesthesia were selected and randomly divided into two groups which involved the use of the PLMA and the cLMA respectively. Induction of anesthesia was done with fentanyl 1mcg/kg and propofol 2-3mg/kg or sevoflurane 8% depending on the preference of the clinicians. Postoperatively, airway devices were removed when patients were fully awake and given supplemental oxygen via face mask.

Results: At 6 hours postoperatively, the incidence of sore throat was lower in the Proseal LMA group ($p<0.001$).

Conclusion: The incidence of sorethroat was lower in the Proseal LMA group compared to Classic LMA at 6 hours postoperatively.

Key words: Anaesthesia, LMA, sore throat, children, anesthesia.

Sources of financial support: Hospital Universiti Kebangsaan Malaysia.

Conflict of interest: No financial relationships between authors and commercial interests with a vested interest in the outcome of the study.

Introduction

Postoperative sore throat, a minor complaint after general anesthesia is of multifactorial etiology. There are few published studies on postoperative sore throat in children. Furthermore, assessing discomfort and pain in children is more difficult than in adults. In children, Splinter et al. reported an overall incidence of postoperative sore throat of 9% following the use of the Classic™ Laryngeal Mask Airway (cLMA™) compared to the use of the endotracheal tube (ETT), and the

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difference between the groups was not statistically significant[1]. They concluded that postoperative sore throat after minor pediatric surgery is uncommon, symptoms are mild and the incidence is unaffected by the choice of an LMA or ETT.

Increasingly the ETT is being replaced by the LMA as it offers an effective method of airway management due to ease of insertion and cost effective considerations. Once it has been properly positioned, it provides an adequate seal around the laryngeal inlet, thereby able to act as a reliable airway, and at the same time minimizes contamination of the environment from leakage of anesthetic gases.

The Proseal LMA (PLMA) has a modified cuff to improve the seal around laryngeal inlet. An esophageal drain tube is available through which a gastric tube can be inserted to empty the stomach thus reduce the risk of gastric aspiration and overcome inadvertent stomach insufflation during mechanical ventilation. In addition, it allows insertion of a bougie to assist in insertion thus it results in a higher success rate of insertion of the device[2]. Studies in adults have also found that PLMA forms a better seal without exerting any higher pressure on the mucosa, as was demonstrated by a higher airway leak pressure compared with the cLMA[2,3,4,5]. However, the standard recommended technique of insertion is association with a higher failure rate at first attempt and has resulted in airway trauma leading to postoperative sore throat in some patients[6]. The pediatric PLMA is available in sizes 1.5, 2 and 2.5 which, and unlike the adult sizes, do not have an additional dorsal cuff. As a result, insertion following the standard recommended technique, the PLMA has been found to be easier. Unlike in adults, bougie-guided technique is seldom required in children to facilitate insertion and proper position of PLMA[2].

This study was designed to compare the frequency and severity of post operative sore throat in children undergoing elective surgery following the use of PLMA (The Laryngeal Mask Company (M) Sdn, Bhd, Kulim, Kedah, Malaysia) compared to cLMA (The Laryngeal Mask Company (M) Sdn, Bhd, Kulim, Kedah, Malaysia). The roles of several factors such as type of airway, technique and multiple attempts at insertion, experience of the anesthetic personnel and duration of surgery were also evaluated.

Methods

This was a randomized controlled clinical trial. The study protocol was approved by the Ethics Committee. Written and informed consent was obtained from the parents. This was a prospective randomized, independent observer study with involvement of multiple operators carried out at Institute Paediatric Hospital Kuala Lumpur and UKMMC.

Two hundred patients aged between 6 to 12 years old with the physical status of ASA I-II and weighing 20-50 kg undergoing general anesthesia for elective non oral surgery were recruited in this study. Exclusion criteria included patients with risk of aspiration, potential difficult airway, communication problems and patients who were considered unsuitable for the use of PLMA or cLMA and smaller children who were unable to self report pain using a four-point categorical pain scale.

Patients were randomized into two groups of 100 patients each to either the PLMA group or cLMA group for airway management. Each patient was allocated to one of two groups using a concealed random number generator. All patients were monitored using an electrocardiogram, pulse oximeter, gas analyzer, non-invasive blood pressure monitor, capnograph, tidal volume monitor and airway pressure monitor during anesthesia.

Anesthesia was induced with intravenous propofol 2-3 mg/kg or inhalational induction with sevoflurane 8% and intravenous fentanyl 1mcg/kg according to the preference of the clinician. Following induction, the patients were ventilated manually using sevoflurane 2-4% in oxygen to achieve MAC of 1.3 and until condition are suitable for airway insertion indicated by presence of apnea, loss of eyelash reflex and lack of response to jaw thrust. The sizes of both devices were selected according to the manufacturer's recommendation.

The PLMA were inserted according to manufacturer's instructions using the introducer tool with the cuff fully deflated. Prior to insertion, lubricant was applied to both PLMA and cLMA. Upon insertion of the PLMA into the pharynx, the cuff was inflated with air until effective ventilation was established or the maximum recommended

inflation volume was reached. Correct positioning of the PLMA was determined by the presence of a square wave capnograph tracing, air bubble formation after placing lubricant over the proximal end of the drain tube and auscultating for esophageal air leak with the adjustable pressure limiting, valve set at 35 cmH_2O with gas flow of 3L/min. Effective ventilation for both LMA was judged by observation of adequate chest wall excursion, $SpO_2 > 97\%$ and a square-wave capnograph trace. Three attempts were allowed before insertion is considered a failure and a rescue device was used. The total number of attempts were noted and recorded. Between attempts, the patient's lungs were ventilated using the face mask with sevoflurane 2-4% in oxygen. Once insertion is successful, using the digital manometer, the intra cuff pressure was set at 60 cmH_2O based on the recommended upper limit recommended in the study by Schloss et al.[7] Anesthesia was maintained with 2-4% sevoflurane in 50% oxygen and 50% air and patient was allowed to breathe spontaneously.

At the end of the procedure, the anesthetic agent was discontinued and patient was given 100% oxygen and during this period the patient was not disturbed. Oropharyngeal suction was done carefully to minimize trauma. The LMA was removed when patient was fully awake. Following removal of LMA, supplementary oxygen was given via a regular face mask.

Patients and their parents were interviewed in recovery room 6 hours after surgery and before discharge. An independent observer asked patients about self assessment for the presence of sore throat (constant pain, independent of swallowing). A four-point categorical pain scale used in the investigation was explained to patients and parents. Grading of severity is as follow: sore throat is rated as 0 = none, 1= mild, 2 = moderate and 3 = severe. Any adverse events such as evidence of trauma to oropharyngeal structure, stridor, hiccup, laryngospasm and biting of the LMA during removal and drop of SpO_2 were recorded.

We are planning a study of independent cases and controls with 1 control(s) per case. Prior data indicate that the incidence of sore throat among controls is 0.42. If the true incidence for experimental subjects is 0.21 (50% less), we will need to study 85 experimental subjects and 85 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use a continuity-corrected chi-squared statistic or Fisher's exact test to evaluate this null hypothesis[8].

Demographic data were analyzed using the Student t test while the Chi-square test was used to analyze the incidence of sore throat between PLMA and cLMA. A p value of < 0.05 was considered statistically significant.

Results

The demographic data of the patients are shown in Table I. There were no significant differences between the two groups in terms of age, sex, weight, and ethnic group but there was a statistically significant longer duration of surgery in PLMA group compared to cLMA ($p < 0.001$).

Table I
Demographic data of patients in both groups.
Data are mean ± standard deviation (SD)

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	Classic LMA™ (n = 100)	Proseal LMA™ (n = 100)
Age (year)	9.2 ± 2.0	9.1 ± 2.0
Weight (kg	33.2 ± 8.2	30.6 ± 8.0
Gender :		
Male	51	46
Female	49	54
Ethnic group :		
Malay	57	58
Chinese	28	25
Indian	13	15
Others	2	2
Duration of surgery (min)	34.5 ± 11.9	46.4 ± 19.58

Fig. 1
Pain scores in the immediate postoperative period in recovery room and 6 hours later

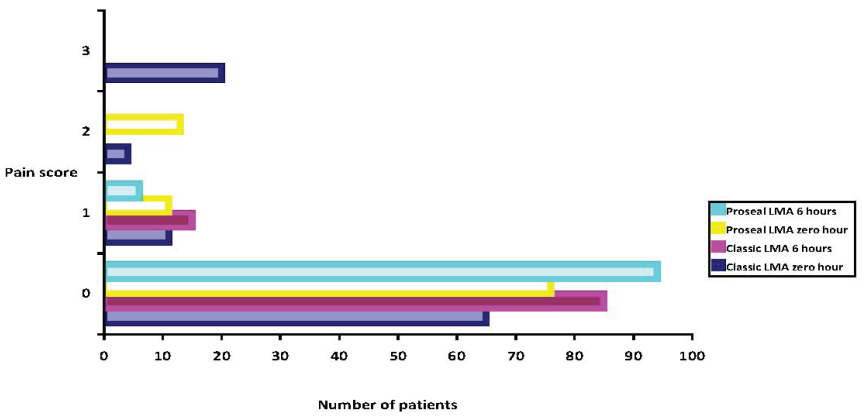

Figure 1 shows the pain scores between the two groups at immediate postoperative period in recovery room and 6 hours later. Table II shows the incidence of sore throat in recovery room and 6 hours postoperatively. Classic LMA™ and Proseal LMA™ had no statistically significant difference in the incidence of sore throat in immediate postoperative period (P=0.09). However at 6 hours later, the incidence of sorethroat was lower in the Proseal LMA group (p<0.001). None of the patient had dysphonia and dysphagia.

Table III shows the numbers of attempt taken for insertion of the device and the difference sizes of airway used among the two groups. There was no statistically significant difference in the number of attempts (P=0.471) when using Classic LMA™ and Proseal LMA™. Regarding the size of airway used, 61% of patients used size 2.5 Proseal LMA™ as compared to 58% of patients used size 3 Classic cLMA™.

Table II
Incidence of sore throat

	Classic LMA™	Proseal LMA™
Incidence of sore throat (%)	(n=100)	(n=100)
Recovery room	35	24
6 hours postoperative	15	6

Table III
Number of attempts of insertion of the device and airway sizes used

	Classic LMA™	Proseal LMA™
Number of attempt	(n=100)	(n=100)
1	79	83
2	20	16
3	1	1
Airway size		
2.5	32	51
3.0	68	49

Discussion

In this study the incidence of sore throat was lower in the Proseal LMA group at 6 hours postoperatively. Of interest was the lower incidence of sore throat observed after PLMA insertion in children and this could be attributed to the differences in laryngopharyngeal anatomy and physiology between children and adults. Under-reporting by children and/or parents may also have contributed to the lower reported incidence of sore throat.

In the case of the pediatric PLMA, the lack of a dorsal cuff may be significant as it results in lesser fold over as the cuff is pushed into the mouth, and this may facilitate insertion of the device. However, we did not find any difference in terms of the number of attempts required to achieve successful insertion.

This study demonstrated that the use of a slightly larger LMA^T was not associated with a higher incidence of sore throat compared to a smaller size airway used in the PLMA group. Grady et al found a fourfold increased risk of developing sore throat when a larger LMA was used in adult patients[9,10,11,12]. Originally, the manufacturer of the LMA recommended insertion of a size 3 LMA in children and small adults weighing more than 30 kg, a size 4 LMA in normal adults and a size 5 LMA in large adults. More recently, Brain and other investigators have recommended the routine use of a larger LMA. Many of these studies reported lower oropharyngeal leak pressure during positive pressure ventilation associated with the use of a larger LMA. However, a smaller LMA may be equally effective in spontaneously breathing patients, in whom a very good seal around the laryngeal inlet is less critical to achieve effective functioning of the LMA[10].

Postoperative sore throat ranges 22.7% vs. 41.8% of patients with LMS use[8]. In adults, the incidence of postoperative sore throat is similar in anaesthetized, non-paralyzed compared to intubated patients, probably both are equally affected by a combination of trauma on insertion and pressure exerted by the cuff against the pharyngeal mucosa[6,9,10].

Grady et al. identified longer surgical procedure as being a factor predictive of higher incidence of sorethroat[11]. The longer duration of operation in the PLMA group that can theoretically result in higher incidence of sore throat was not reflected in this study.

Williams el al studied 400 children and found that, thirteen children (3.3%) developed sore throat after LMA. Using a laryngeal mask airways with a polyvinyl chloride (PVC), material was associated with a higher risk for sore throat compared with an LMA with a silicone material (P = 0.0002). They concluded that, with controlled low cuff pressures, the incidence of sore throat was low and the use of an introducer device did not affect the rate of sore throat[12].

This study had several limitations. First, multiple operators with different length of experience were involved in using the devices. All the devices were inserted by personnel with relatively short period of experience of use of these airway devices and the data obtained in this study may not be applicable to those which involved very experienced personnel. Secondly, this study did not use a standard questionnaire to evaluate the severity of sore throat, there were differences among individual assessor and patient in the definition of sore throat. It has been shown for example that direct questioning results in a significantly higher incidence of sore throat than indirect questioning[13,14].

In conclusion the incidence of sore throat was lower in children ventilated using the Proseal LMA compared to the Classic LMA group at 6 hours postoperatively.

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SPINAL ANAESTHESIA FOR PELVIC SURGERY: LOW CONCENTRATIONS OF LIGNOCAINE AND BUPIVACAINE ARE EFFECTIVE WITH LESS ADVERSE EVENTS

JYOTSNA PUNJ* AND R.M. KHAN**

Abstract

Background: The aim of this study was to compare the clinical efficacy of 5% lignocaine, 2.5% lignocaine, 0.5% bupivacaine and 0.25% bupivacaine in subarachnoid block for pelvic surgeries.

Methods: 80 adult ASA grades I and II patients of either sex between the ages of 18-60 yrs, undergoing routine pelvic surgery of short duration were included in this prospective, randomized double blind study. Patients were allotted by computer generated random number table into 4 groups of 20 patients each.

Group A (n = 20): injected with 2 ml of 0.5% hyperbaric bupivacaine

Group B (n = 20): injected with 2 ml of 0.25% hyperbaric bupivacaine

Group C (n = 20): injected with 5% hyperbaric lignocaine

Group D (n = 20): injected with 2.5% hyperbaric lignocaine

The following parameters were measured every five minutes till 60 minutes and then every 15 minutes till recovery.

1. Onset of sensory block assessed by pin prick method bilaterally at middle of the shin. Maximum height of sensory block noted.

2. Onset of motor block assessed by inability to raise the leg.

3. Duration of sensory block judged as time to first postoperative analgesic requirement by the patient.

4. Duration of motor block assessed by return to Bromage scale of 1.

5. Non invasive blood pressure (NIBP) and Heart Rate-

6. Complications if any were noted

-nausea, vomiting, headache, transient neurological symptoms

Statistical analysis was done with Kruskal-Wallis, Mann-Whitney tests and ANOVA test.

Results: The groups were comparable with respect to age, weight and male to female ratio ($p < 0.05$).

Time to onset of sensory block in seconds in groups A, B, C and D was 79.5 ± 52.26, 104.24 ± 24.53, 33.6 ± 14.98 and 62.50 ± 25.05 respectively. 5% lignocaine was observed to have statistically

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significant shortest onset of sensory block compared to other three groups ($p < 0.05$).

The mean onset of motor block in seconds was 137.25 ± 60.92, 240.75 ± 73.31, 62.30 ± 24.56, 119.5 ± 56.51 sec in Groups A, B, C and D respectively with 5% lignocaine observed to have statistically significant fastest onset of time compared to the other groups ($p < 0.05$).

The upper dermatomal height reached was T8 or T9 in groups A, C & D. However in group B, the upper dermatomal height reached was T 10.

Duration of sensory block in minutes was 172.5 ± 49.64, 146 p.00 ± 35.87, 105.9 ± 31.68 and 133.6 ± 17.68 in groups A, B, C & D respectively. 0.5% bupivacaine was observed to have the longest duration of sensory block compared to both the groups of lignocaine ($p < 0.01$).

The duration of motor block in minutes was 159.25 ± 53.49, 137.4 ± 15.71, 100.5 ± 21.81, 110.0 ± 27.76 respectively in groups A, B, C & D. The duration of motor blockade with 0.5% bupivacaine was significantly more as compared to 5% and 2.5% lignocaine ($p < 0.005$).

Nine, one, twelve and four boluses of intravenous boluses of ephedrine were required in Groups A, B, C & D respectively. Most of the boluses were required after 30 minutes in Group A as compared to 5% lignocaine wherein the doses were required in the initial 30 minutes post spinal.

Four boluses each of intravenous atropine 0.3 mg were required in 0.5% and 0.25% bupivacaine which was not statistically significant amongst the four groups.

Significantly more patients in 0.5% bupivacaine required intravenous boluses of ondansetron 4 mg; five in Group A, one each in Group B and C and none in Group D ($p < 0.05$).

None of the patients showed transient neurological symptoms till 5 days postoperatively.

None of the patients of this series developed post spinal headache at any time till discharge of the patient from the hospital (8-10 days).

Conclusion: For subarachnoid block for pelvic surgeries longer than two hours 0.25% bupivacaine is a better choice as compared to 0.5% bupivacaine. However for short duration surgeries lasting up to one hour, 2.5% lignocaine is a better choice as compared to 5% lignocaine as the lower concentrated solutions of bupivacaine and lignocaine are more haemodynamically stable compared to their higher concentrations and with similar duration of sensory and motor block.

Keywords: bupivacaine, lignocaine, spinal anaesthesia

Key message: 0.25% bupivacaine and 2.5% lignocaine are more haemodynamically stable with similar profiles of duration of sensory and motor block as compared to their higher concentrations (0.5% bupivacaine and 5% lignocaine).

Introduction

August Bier in 1899 performed planned spinal analgesia for surgery and thus introduced a method of painless surgery without making the patient unconscious. Spinal anesthesia is a well established technique for pelvic surgery and is considered to be a technique of choice in many patients. A combination of 5% lignocaine and 0.5% bupivacaine, with or without adjuncts, has been traditionally used for this purpose[1-8]. However this is associated with extensive motor block. A prolonged motor block extending to the post operative period is undesirable as it requires urinary catheterization and delayed immobility of the patient causing discomfort and delayed discharge in day care surgeries.

Attempts have been made to reduce the intensity of motor block without sacrificing the sensory block necessary for surgical procedure. As such, some authors have studied low dose and/or low concentrations of bupivacaine and lignocaine in subarachnoid block (SAB)[9-18]. To our knowledge no studies have compared the clinical efficacy of 5% lignocaine, 2.5% lignocaine, 0.5% bupivacaine and 0.25% bupivacaine in patients undergoing pelvic surgery in a single study protocol.

The aim of this study was to identify any significant clinical benefit and thus to conclude from this study the local anesthetic with quickest onset of action with minimal motor but optimal sensory block

of reasonable length of time.

Methods

After approval by our local research committee and ethical clearance from the Institute Review Board, 80 adult ASA grade I and II patients of either sex between the ages of 18-60 yrs, undergoing routine pelvic surgery of short duration were included in this prospective, randomized double blind study.

Exclusion criteria were unwilling patients, coagulopathies, cardiac disease, hypertensive patients, shock, neurological disorders, spinal deformity and patients with skin infection of back at the site of lumbar block.

Premedication consisted of 10 mg of oral diazepam and prophylactic antibiotics.

In the operating room, routine monitors of NIBP, ECG and pulse oximeter were attached to the patient. All patients were preloaded with 500 ml of a balanced salt solution. Under all aseptic precautions, after infiltrating the skin with local anesthetic, subarachnoid block (SAB) was performed with 24 G quincke needle at L4-5 subarachnoid space in the sitting position by an expert anesthesiologist.

Eighty patients were randomized to either of the four groups by a computer generated random number table into 4 groups of 20 patients each. The solutions were made in the OT by an anesthesiologist not involved in the study. The anesthesiologist performing the spinal anesthetic was blinded to the solution being injected. The four groups were:

Group A (n = 20): injected with 2 ml of 0.5% hyperbaric bupivacaine; Group B (n = 20): injected with 2 ml of 0.25% hyperbaric bupivacaine; Group C (n = 20): injected with 5% hyperbaric lignocaine; and Group D (n = 20): injected with 2.5% hyperbaric lignocaine.

Dilutions to 0.25% bupivacaine and 2.5% lignocaine were done with normal saline available in sterile ampoules under aseptic precautions by an anesthesiologist other than the anesthesiologist performing the SAB who was blinded to the drug used. The final baricity of the diluted local anesthetic solutions was assessed as hyperbaric by the department of pharmacology before the study was initiated.

Intrathecal injections were performed during a 30 sec period in all groups. After completion of spinal anaesthesia block patients were immediately placed in supine position.

The following parameters were measured every five minutes till 60 minutes and then every 15 minutes till recovery.

1. Onset of sensory block assessed by pin prick method bilaterally at middle of the shin. Maximum height of sensory block noted.

2. Onset of motor block assessed by inability to raise the leg. Intensity of motor block assessed using modified Bromage scale: (0- no block,1- inability to raise extended leg, 2- inability to flex the knee, 3- inability to flex the ankle joint or first digit of foot)

3. Duration of sensory block judged as time to first postoperative analgesic requirement by the patient.

4. Duration of motor block assessed by return to Bromage scale of 1.

5. Non invasive blood pressure (NIBP) and Heart Rate-

1. Fall in more than 20% systolic blood pressure from baseline treated with a bolus of intravenous ephedrine 6 mg and fall in HR of more than 20% from baselines treated with intravenous bolus of atropine 0.3 mg. The doses were repeated if necessary.

6. Complications if any-

1. -nausea, vomiting, headache

2. transient neurological symptoms noted everyday for first five postoperative days

Nausea/vomiting in the perioperative period was treated with IV ondansetron 4 mg.

Patients were advised to lie flat in bed for 24 hours postoperatively with no pillow and plenty of oral fluids were given after return of bowel movements. Vital parameters were monitored during this time.

Statistical Analysis

The size of the sample was based on the results of a pilot study, and the intention was to show a

Table 1
Demography

	Group A (n =20) 0.5% bupivacaine	Group B (n =20) 0.25% bupivacaine	Group C (n =20) 5% lignocaine	Group D (n =20) 2.5% lignocaine
Age (in years)	46.60 ± 16.81	45.30 ±15.84	49.25 ±22.42	44.25 ±14.35
Sex (M:F)	12:8	12:8	11:9	10:10
BMI (kg/m^2)	32.03 ± 2.55	30.73 ± 2.35	31.01 ± 2.65	31.02 ± 2.35
Durtn of surgery (min)	65 ± 25	73 ± 23	67 ± 22	71 ± 21

P >0.05
Values given as mean ± SD

significant difference in spread of anesthesia of 2 or 3 dermatomes with a SD of 2 dermatomes, with an a risk at 0.05 and a p risk at 0.20. Comparisons between groups for onset time of sensory and motor blockades and cephalad spread of sensory blocks were performed using Kruskal-Wallis and Mann-Whitney tests. The ability to obtain a complete motor blockade was compared using a contingency table between isobaric and hyperbaric solutions. MAP changes were compared using analysis of variance (ANOVA) for repeated measurements; ephedrine and crystalloid requirements and frequency of hypotension were compared using a contingency table. The significance level was set at p <0.05.

Results

The groups were comparable with respect to age, weight and male to female ratio (p <0.05). (Table 1).

Time to onset of sensory block in seconds in groups A, B, C and D was 79.5 ± 52.26, 104.24 ± 24.53, 33.6 ± 14.98 and 62.50 ± 25.05 respectively. 5% lignocaine was observed to have statistically significant shortest onset of sensory block compared to other three groups (p <0.05). 0.25% bupivacaine had statistically slower onset compared to both concentrations of lignocaine (p <0.005). (Table 2).

The mean onset of motor block in seconds was 137.25 ± 60.92, 240.75 ± 73.31, 62.30 ± 24.56, 119.5

Table 2
Onset and duration of sensory and motor block in the four groups

	Onset Sensory block (in seconds)	Onset Motor block (in seconds)	Duration Sensory block (in minutes)	Duration Motor block (in minutes)
Group A (n =20) 0.5%bupivacaine	79.5 ±52.26	137.25 ±60.92	172.5 ±49.64 **	159.25 ±53.49 **
Group B (n =20) 0.25%bupivacaine	104.3 ±24.53	240.75 ±73.31	146.00 ±35.87	137.4 ±15.71
Group C (n =20) 5% lignocaine	33.6 ±14.98 *	62.30 ±24.56 *	105.9 ±31.68	100.5 ±21.81
Group D (n =20) 2.5% lignocaine	62.5 ±25.05	119.5 ±56.51	133.6 ±17.68	110.0 ±27.76

* fastest onset of sensory and motor block (p <0.05)
** longest duration of sensory and motor block (p <0.05)
Values given in mean ± SD

± 56.51 sec in Groups A, B, C and D respectively with 5% lignocaine observed to have statistically significant fastest onset of time compared to the other groups ($p < 0.05$). 0.25% bupivacaine had statistically slowest onset of motor block ($p < 0.001$) amongst all the groups. (Table 2).

The upper dermatomal height reached was T8 or T9 in groups A, C & D. However in group B, the upper dermatomal height reached was T 10. Time to reach the upper dermatomal height was not noted.

Duration of sensory block in minutes was 172.5 ± 49.64, 146.00 ± 35.87, 105.9 ± 31.68 and 133.6 ± 17.68 in groups A, B, C & D respectively. 0.5% bupivacaine was observed to have the longest duration of sensory block however it was statistically longer only compared to both the groups of lignocaine ($p < 0.01$). 5% lignocaine had the shortest duration however only statistically significant compared to both the groups of bupivacaine ($p < 0.005$). (Table 2).

The duration of motor block in minutes was 159.25 ± 53.49, 137.4 ± 15.71, 100.5 ± 21.81, 110.0 ± 27.76 respectively in groups A, B, C & D. The duration of motor blockade with 0.5% bupivacaine was significantly more as compared to 5% and 2.5% lignocaine ($p < 0.005$). 5% lignocaine had statistically shortest duration of motor block as compared to both concentrations of bupivacaine ($p < 0.005$). (Table 2).

Mean prespinal pulse rate and MAP was not significantly different between the 4 groups.

Nine, one, twelve and four boluses of intravenous boluses of ephedrine were required in Groups A, B, C & D respectively. Most of the doses were required after 30 minutes in Group A whereas most of the doses with 5% lignocaine were required in the initial 30 minutes post spinal. (Table 3).

Four boluses each of intravenous atropine 0.3 mg were required in 0.5% and 0.25% bupivacaine which was not statistically significant amongst the four groups. (Table 3).

Significantly more patients in 0.5% bupivacaine required intravenous boluses of ondansetron 4 mg; five in Group A, one each in Group B and C and none in Group D. (Table 3).

None of the patients showed transient neurological symptoms till 24 hours postoperatively.

None of the patients of this series developed post spinal headache at any time till discharge of the patient from the hospital (8-10 days).

Discussion

Study of patients undergoing various surgical procedures of different body regions are associated with variable blood loss making it difficult to associate changes in hemodynamics to the local anaesthetic agents alone. It was this which prompted us to include patients undergoing only pelvic surgery, thereby making a more conclusive cause and effect relationship

Table 3

Total number of doses of ephedrine, atropine and ondansetron required

	Ephedrine bolus	**Atropine bolus**	**Ondansetron**
Group A (n = 20) 0.5% bupivacaine	9**	4	5*
Group B (n = 20) 0.25% bupivacaine	1	4	1
Group C (n = 20) 5% lignocaine	12**	0	1
Group D (n = 20) 2.5% lignocaine	4	1	0

* 0.5% bupivacaine required significantly more boluses of ondansetron ($p < 0.05$)

** higher concentrations of both bupivacaine and lignocaine required more boluses of ephedrine as compared to their dilute concentrations ($p < 0.05$)

between hemodynamic changes and the effect of spinal analgesia with different local anaesthetics.

A comparative analysis of duration of sensory block with different concentrations and volume of bupivacaine and lignocaine by different workers is variable with different studies. This is secondary to difference in methodology like volume and concentration of local anaesthetic used and methods of assessing the onset and duration of sensory and motor block.

The onset time of sensory block reported by Veering et al with 0.5% bupivacaine 3 ml was 3.7 min in 20-55 years group and 3.9 min in >55 yrs group nearly twice to that of the results obtained in this study. This could be because they sought onset of sensory block till it reached L1 in contrast to our sensory block assessment as the loss of pinprick sensation at mid shin which is L4[13].

The onset time of sensory block of 0.25% bupivacaine as recorded by Chung et al as assessed by pin prick method to level of T 6 was 7.7 min when working with 3.2-3.6 ml 9 8-9 mg) of 0.25% bupivacaine which was considerably longer than this study (1.74 min). This could be attributed to recording of onset of sensory block of the drug to T 6 by Chung et al as compared to our level at L4[19].

The onset time of sensory block of 0.5% bupivacaine as reported by Williams et al was 9 min which is significantly longer than ours i e 79.5 sec (1.33 min). This could be attributed to the difference in methodology of assessing the sensory block. Williams et al used ethyl chloride spray in place of needle pricks and waited till sensory block reached T 10 which was recorded as the onset time of sensory block[20].

Ewart MC et al in 1987 found similar duration of sensory and motor block of 0.5% bupivacaine and 5% lignocaine at thoracic level whereas longer duration of sensory and motor block was found in sacral and lumbar segments with 5% lignocaine[21]. Though Pradhan 2010 didn't comment on the onset of the similar concentrations of these drugs, he found a similar duration of sensory and motor block with both these drugs[22]. However it is worthwhile to note that these authors have used different volumes of drugs as compared to our study.

In our study the hemodynamic parameters of 0.5% bupivacaine and 5% lignocaine were similar which is in accordance to study by Pradhan 2010 and Ewart MC 1987 who found similar hemodynamic parameters between both the groups.

In the study by Williams N et al in 1995, comparing 2% lignocaine and 0.5% bupivacaine, found a lower HR and MAP with 2% lignocaine, however volumes used were different than our study.

David B diluted 0.5% bupivacaine to final 4 different concentrations and found 0.25% bupivacaine 3 ml to be most hemodynamic stable as compared to 0.5% bupivacaine 3 ml and found it suitable for long duration of surgeries[23].

In our study subarachnoid blocks with both the lower concentrations of bupivacaine and lignocaine offered similar duration of motor and sensory block as compared to their higher concentration counterparts and were found to be more haemodynamically stable in pelvic surgeries compared to their higher concentrations of 0.5% bupivacaine and 5% lignocaine.

Though both concentrations of lignocaine had faster onset and duration of sensory and motor block as compared to both concentrations of bupivacaine. Also 0.5% bupivacaine caused more nausea and vomiting in the perioperative period compared to the other local anaesthetics.

Thus we conclude that in subarachnoid block for pelvic surgeries longer than two hours 0.25% bupivacaine is a better choice as compared to 0.5% bupivacaine. However for short duration surgeries lasting up to one hour, 2.5% lignocaine is a better choice as compared to 5% lignocaine as the lesser concentrated drugs of bupivacaine and lignocaine are more haemodynamically stable with similar profiles of duration of sensory and motor block.

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SCALP NERVE BLOCKADE REDUCES PAIN AFTER HEADFRAME PLACEMENT IN RADIOSURGERY: A DOUBLE BLIND, RANDOMIZED CLINICAL TRIAL

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Abstract

Background: Patients undergoing stereotactic headframe placement for radiosurgery report that discomfort associated with the headframe often lasts for the duration of the treatment day (approximately 6 hours). We hypothesize that blockade of scalp nerves prior to headframe placement reduces the incidence of moderate to severe head pain during the entire treatment day. We describe a randomized, double-blind, placebo-controlled study of awake patients having radiosurgery for intracranial pathology that examines whether scalp nerve blockade and local anesthetic infiltration results in superior patient comfort versus infiltration alone.

Methods: Twenty seven adult patients undergoing stereotactic radiosurgery were randomized to receive a nerve block with placebo or bupivacaine 0.5% with epinephrine. Supraorbital and greater occipital nerve blocks using blinded syringes were performed by the anesthesiologist in addition to subcutaneous infiltration of pin sites with lidocaine 1% by the surgeon. Pain was reported using 10 cm visual analog scales (VAS) at pre-specified time points during the treatment day. The primary outcome measure was the presence of pain scores classified as "zero to mild pain (VAS <4)" or "moderate to severe pain (VAS ≥4)".

Results: 27 patients were randomized to placebo (n = 14) and nerve block (n = 13) groups. The proportion of moderate to severe pain measurements were significantly less in the nerve block group than the placebo group (4.9% vs. 24.1%; odds ratio, 0.166; 95% confidence interval 0.029-0.955; p = 0.044). There were no adverse events.

Conclusion: Scalp nerve block significantly decreased moderate to severe head pain in radiosurgery patients throughout the treatment day.

Keywords: randomized controlled trial; nerve block; stereotactic radiosurgery; regional anesthesia; bupivacaine

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Introduction

Stereotactic radiosurgery, first introduced by Lars Leksell at the Karolinska Institute in the 1960s, is widely used to treat intracranial tumors and arteriovenous malformations. This technique uses tightly focused , relatively high doses of radiation directed to the lesion. A stereotactic head frame, which is attached to the patient's skull with pins, is utilized to ensure accuracy of treatment setup and delivery[1]. This ambulatory treatment starts with placement of a stereotactic head frame, followed by diagnostic imaging, planning and delivery of radiation treatment. The team includes an anesthesiologist, neurosurgeons, and a radiation oncologist. Immediately prior to headframe placement, the anesthesiologist administers intravenous sedation and the neurosurgeon administers local anesthetic via infiltration of the skin at the intended pin sites. For the remainder of the 4-8 hour treatment day, the anesthesiologist is generally not in attendance. Placement of the frame causes considerable discomfort in patients[2]. In our experience, this discomfort continues during the entire treatment day. We hypothesize that bilateral blockade of the greater occipital and supraorbital nerves will reduce the incidence of moderate to severe head pain during the entire treatment day.

In 2001, Watson et al investigated the efficacy of scalp nerve blockade versus local infiltration in patients undergoing placement of a headframe for functional neurosurgery[2]. Each patient received supraorbital and greater occipital blocks on one side of the head, and subcutaneous infiltration at pin sites on the contralateral side. The study demonstrated that while scalp nerve blocks provided improved analgesia for the subsequent ipsilateral administration of subcutaneous local anesthetic, blocks were not superior for ameliorating the pain of pin placement, and not superior after the first hour. However, this study was not blinded, and the analysis incorrectly treated the Visual Analog Scale (VAS) scores of pain as parametric variables with a normal distribution.

In this trial, we seek to answer the question of whether scalp nerve blockade is superior to usual care (subcutaneous infiltration with lidocaine) throughout the radiosurgical treatment day, not just during pin placement. Our study design includes blinding through the use of placebo nerve blocks, and uses a non-parametric outcome for greater statistical accuracy.

Scalp blocks have previously been shown to be safe and effective in craniotomy patients[3]. Additionally, although patients requiring radiosurgery may have lower seizure thresholds than other patients, both levobupivacaine and ropivacaine have been found to have safe plasma levels after scalp block[4,5]. Prior clinical trials of scalp blocks for craniotomy patients have found that a block is superior to placebo[6] and provides similar postoperative pain relief to intravenous morphine[7], with less stress response to surgical stimulation as measured by ACTH, serum cortisol, and hemodynamic changes[8].

Methods

This was a single-center, double-blind, placebo-controlled randomized trial conducted at a tertiary care hospital. Following institutional review board approval and written informed consent, patients over the age of 18 were recruited who presented for elective radiosurgery of an intracerebral lesion requiring headframe placement. Patients were excluded if they were unable to give informed consent, understand the Visual Analog Scale (VAS), had an allergy to local anesthetic, an incompletely healed craniotomy scar, or a known coagulopathy.

Assuming a 75% incidence of moderate to severe pain among controls and 15% among patients receiving treatment, a sample size of 26 patients is required to detect a difference in postoperative pain scores between placebo and control groups with a Type I error probability of 0.05 and a Type II error probability of 0.8. 27 patients were enrolled; 14 males and 13 females, with a mean age of 57 ± 14.8 years.

Prior to attachment of the headframe, and following sedation by the anesthesiologist, the neurosurgeon infiltrated 5 mL of 1% lidocaine subcutaneously at the pin sites using a 25 gauge needle. After the headframe was secured, the anesthesiologist (S.D. or I.O.) performed bilateral supraorbital and greater occipital nerve blocks using a syringe containing either normal saline or 0.5% bupivacaine with epinephrine.

Table 1
Demographic Data

	Saline placebo	Bupivacaine 0.5% with epinephrine	P-value
Number of patients	13	14	
Age (yr)	60.8 ± 12.8	53.4 ± 16.1	0.197
Male: Female (*n*)	4:9	10:4	0.057
ASA status			0.338
II	1	3	
III	10	11	
IV	2	0	
Diagnosis			0.222
Tumor	13	11	
AVM	0	3	
Duration in Study (hrs)	5.1 ± 1.3	4.7 ± 1.3	0.474

Data are presented as mean ± standard deviation or n. AVM = Arteriovenous malformation. P-value for age and duration in study computed using two-sample t-test; p-values for Gender, ASA, and Diagnosis computed using Fisher's exact test.

For the supraorbital nerve block, the supraorbital notch was identified by palpation. A syringe with a 25 gauge needle was inserted 1 cm medial to the supraorbital foramen, and 2 mL of study drug was injected. For the greater occipital nerve block, the occipital artery was identified and the needle was inserted medial to the artery. After negative aspiration, 3 mL of study drug was injected. The technique followed that described in the recent review article by Osborn[9].

Patients were assigned to the placebo or treatment group using a computer-generated randomized list with a block size of 3. Blinding was maintained by a research pharmacist who recorded the actual contents of each syringe in a secure location. Patients and investigators were both blinded to treatment assignment.

The patient recorded their head pain on a Visual Analog Scale (VAS) administered by a trained research assistant at 30 minutes, 1 hour, 2, hours, 4 hours, 6 hours, and 8 hours after headframe placement or until the headframe was removed. Patients were able to request supplementary analgesia in the form of lidocaine gel, lidocaine injections, or oral pain medication (acetaminophen, ibuprofen, or oxycodone/acetaminophen) as needed.

The primary outcome measure was the proportion of patients reporting a VAS score greater than or equal to 4, signifying "moderate to severe head pain". The primary outcome variable was analyzed with clustering by patient using the generalized estimating equations method. A secondary outcome measure was the median pain score within each group.

Inter-group differences in patient age and study duration were analyzed using a two-sample t-test. Differences in gender, ASA status, and diagnosis were computed using Fisher's exact test. P values less than 0.05 were considered to indicate statistical significance. Statistical analysis was performed with the geepack library and R statistical software, version 2.13.1[10,11]. Data visualization was performed with the ggplot2 R package[12].

Results

Recruitment occurred from July 2009 to February 2011, terminating once the desired sample size was reached. Of the 28 patients who were assessed, 27 were enrolled and one declined to participate. Of the 27 patients enrolled, 14 were randomized to placebo and 13 received local anesthetic for their nerve blocks. The demographics and diagnoses for the patients are described in Table 1. The placebo group had similar

Table 2
Results

	Saline placebo	Bupivacaine 0.5% with epinephrine	P-value
Median Pain Score (all times)	1.4 (3.8)	0.6 (1.9)	0.183
30 minutes after block	0.1 (1.3)	0.1 (0.8)	0.722
60 minutes	2.8 (3.7)	1.2 (2.1)	0.250
120 minutes	1.7 (4.6)	0.6 (1.1)	0.379
240 minutes	2.4 (3.8)	1.3 (2.3)	0.355
360 minutes	1.4 (2.7)	1.8 (1.3)	0.748
Percentage of pain scores ≥4 (all times)	24%	4.9%	0.003
30 minutes after block	7.7%	0%	0.481
60 minutes	23%	0%	0.098
120 minutes	31%	7.1%	0.165
240 minutes	38%	7.7%	0.160
360 minutes	17%	17%	1.000
Number of patients receiving first adjunct analgesia at any time point	5	7	0.704
60 minutes after block	4	3	0.678
120 minutes	1	0	0.481
240 minutes	0	2	0.481
360 minutes	0	2	0.481

Data are presented as median pain score (interquartile range), percentage of observations, or n. P-value for median pain scores computed using Mann-Whitney-Wilcoxon test; p-values for percentages with VAS ≥ 4 and patients receiving adjunct analgesia computed using Fisher's exact test.

age, gender ratio, and ASA scores compared to the treatment group ($p > 0.05$ for each category.) As only one procedure lasted more than 6 hours, pain scores after 6 hours were not included in the analysis. All patients received the assigned treatment, and all patients were included in the final analysis.

Patients from both groups requested supplementary analgesia, 5 from the placebo group and 7 from the treatment group. Four of the 7 patients in the treatment group asked for the first analgesic supplement at 4 hours after the nerve block, while four of the 5 patients in the placebo group asked for the first analgesic supplement at 1 hour after the nerve block. Two patients each in the placebo group asked for more than one dose of supplementary medication, versus no patients in the treatment group.

Only twelve patients out of the original 27 were still wearing the headframe at six hours, split evenly between placebo and treatment groups. No complications as a result of the nerve blocks were observed.

A total of 119 pain scores were collected, 58 in the placebo group and 61 in the treatment group. Table 2 shows the percentage of scores ≥4 and the median pain scores across all times and at individual time points. Fig. 1 displays the number of moderate to severe pain scores (VAS ≥4) within each group for each time period. The treatment group had fewer moderate to severe pain scores at every time point prior to 6 hours. The odds ratio of experiencing moderate to severe pain is less in the nerve block group than the placebo group, when clustered by patient (4.9% vs. 24.1%; odds ratio, 0.166; 95% confidence interval 0.029-0.955; $p = 0.044$).

Fig. 1

Moderate to Severe Pain Scores at Each Time Interval; Placebo vs. Treatment. Bars indicate number of moderate to severe pain scores at each time period for treatment versus placebo. Percentages represent the number of moderate to severe pain scores out of all pain scores within each time period and each group

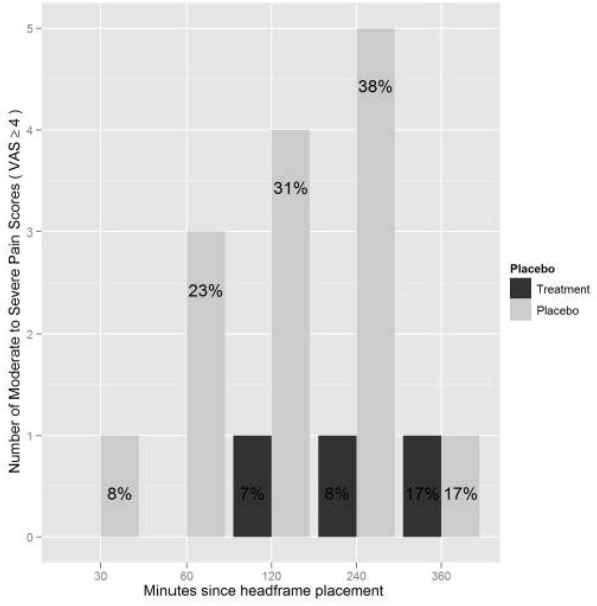

Fig. 2

Pain Scores; Placebo vs. Treatment. Box plot of VAS pain scores at all time points for treatment versus placebo. Whiskers extend to 1.5 times interquartile range

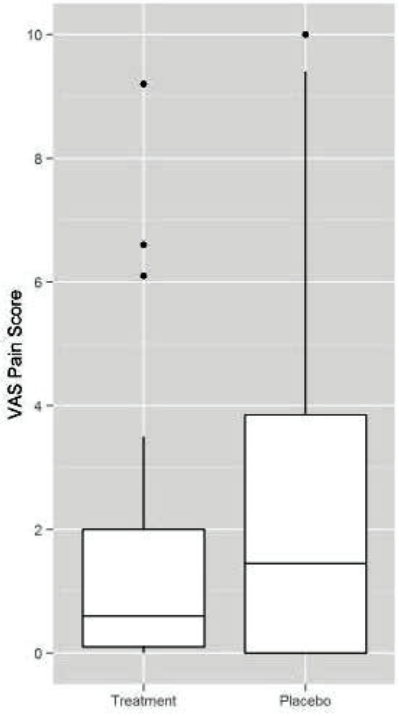

Fig. 2 shows a boxplot of the collected pain scores. The percentage of scores ≥ 4 across all times was 24% in the placebo group and 4.9% in the treatment group (p=0.003 using Fisher's exact test.) There was no significant difference in the median pain score between groups overall (1.4 in placebo group versus 0.6 in treatment group, p=0.183) or at any time point.

Discussion

Scalp nerve blocks significantly decrease moderate to severe pain in radiosurgery patients versus subcutaneous pin site infiltration alone for at least 4 to 6 hours after administration. While one could speculate that our study compared local anesthetics and not infiltration vs. nerve block, we observed a difference between pain scores at the earliest time point, suggesting an additional benefit of nerve blockade even when short acting local anesthetic is given via infiltration. As seen in fig. 2, the treatment group had fewer moderate to severe pain scores at every time point prior to 6 hours. There was no difference at the 6 hour mark, possibly due to the nerve block effect wearing off or the small number of patients that were still wearing the frame at the 6 hour point.

There is some precedent for our findings. Nguyen et al. examined the use of nerve block for craniotomy using a similar classification of moderate to severe pain vs. none. They found that 70% of placebo patients reported moderate to severe pain (defined as VAS >3), versus 20% in the treatment group[3]. In our study 62% of placebo patients and 14% of treatment patients reported a pain score greater than 3 at any time point. However, the Nguyen study used parametric statistics in parts of their analysis which limits its applicability to our results.

No patients in the treatment group requested more than one dose of supplementary analgesia. Most of the treatment group patients who did require supplementary analgesia first requested it at four hours after the block, while most placebo group patients

asked for supplementary analgesia within the first hour. While these results are not statistically significant, they support our hypothesis that scalp nerve blocks prolong the period of time that the radiosurgery patient does not require additional pain relief.

A limitation of this study is that all patients received subcutaneous injections of 1% lidocaine at the pin sites. It is not clear whether the block added longevity due to the local effect of bupivacaine or the scalp block technique. However, the fact that at time points prior to 6 hours the treatment group was less likely to have moderate or severe pain suggests that the technique has merit. This was a small pilot study, therefore the differences in pain scores are only statistically significant when clustered. Our pilot study suggests that a larger sample size would be required to demonstrate significance at individual time points. It is not clear if treatment group outliers who reported significant pain were due to block failure. Testing for nerve block success was not possible, as a successful test would have revealed that the patient was in the treatment group.

An important role of the anesthesiologist is to treat current and future pain in patients who arrive for prolonged outpatient procedures. As the anesthesiologist cannot remain at the patient's side the entire day, methods for long-lasting analgesia must be employed. Future studies can find if patient satisfaction improves with different nerve block agents and concentrations. Scalp nerve blocks can be studied in conjunction with patient controlled intravenous analgesia to identify its potential role in improving patient analgesia.

To the best of our knowledge, this is the first double-blind, randomized, controlled trial of nerve block versus placebo for stereotactic headframe pain. We believe our results demonstrate that the scalp nerves are a major contributor to the pain caused by the pins themselves and the overall weight of the headframe. Scalp nerve blocks significantly decrease moderate to severe pain in radiosurgery patients who are not under the continuous care of an anesthesiologist. Nerve blocks are an important tool to provide radiosurgery patients with pain relief throughout the course of the treatment day.

Acknowledgment

The authors wish to acknowledge Kathleen E. Maloney Lutz RN (Mount Sinai School of Medicine, Department of Neurosurgery) for her assistance in conducting this research. This research was supported by departmental funding only. The authors have no conflicts of interest.

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COMPARISON OF THREE METHODS OF PREVENTING ROCURONIUM INDUCED PAIN ON INJECTION USING VENOUS OCCLUSION TECHNIQUE

- A Randomized Prospective Double Blind Controlled Study –

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Abstract

Background: Intravenous administration of rocuronium bromide causes pain at the site of injection in most patients. The mechanism that leads to this side effect is still unknown and multiple drugs' pretreatments were used to prevent its occurrence with varying success rates.

Purpose: The study aimed to evaluate the effects of the pretreatment with lidocaine, fentanyl, and remifentanil using a venous occlusion technique in preventing pain caused by intravenous injection of rocuronium during induction of general anesthesia.

Method: Two hundred patients, ASA I-II, requiring various types of surgical procedures under general anesthesia with muscle relaxation and mechanical ventilation, were enrolled. Patients were pre-educated to report pain severity on rocuronium injection on a 4-point severity scale. Patients were allocated randomly using sealed envelopes method into one of four pretreatment groups: (Xylocaine group, 50), Remifentanyl group 50), (Fentanyl group, 50), and (Normal saline group, 50). After venous occlusion, study drugs were injected and the venous occlusion was maintained for one minute. Rocuronium was then administered and patients were asked to report their pain score.

Results: Compared to control group, all pretreatment drugs were effective in reducing pain on rocuronium injection. Xylocaine was the most effective (Mean difference-1.42, $P < 0.001$), followed by Remifentanil (Mean difference-1.32, $P < 0.001$) and Fentanyl (Mean difference-0.50, $P < 0.001$) in reducing pain on rocuronium injection. Remifentanil was statistically comparable to Xylocaine ($P = 0.820$) and both drugs were superior to Fentanyl in reducing pain on rocuronium injection.

Conclusion: Remifentanyl is a better choice of opioid in preventing pain on rocuronium injection using venous occlusion technique than fentanyl, with efficacy comparable to Xylocaine.

Keywords: Fentanyl; Lidocaine; Pain; Remifentanil; Rocuronium Bromide.

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Introduction

Pain on intravenous injection of rocuronium bromide during induction of general anesthesia is common and occurs in 50-80% of patients[1-4]. Unfortunately, the mechanism of this pain is not fully understood yet. Different modalities for the prevention of pain on injection of rocuronium have been tried with different rates of success; including the use of local anesthesthetic drugs[5,6], opioids[6], ondansterone[6], magnesium[7], ketamine[8], and ketorolac[9]. Dilution of rocuronium solution and slow injection rate were also suggested as effective techniques[10]. However the best modality to control pain on rocuronium injection is still controversial.

The aim of our study is to evaluate and compare the effect of pretreatments with Lidocaine, Fentanyl, or Remifentanil in preventing pain caused by intravenous rocuronium injection in patients during induction of general anesthesia using a 60-second venous occlusion technique.

Methods

This study was conducted at University of Jordan Hospital, Amman, Jordan, between September, 2008 and October, 2009. Ethical approval was provided by the Research and Ethics Committee at the Faculty of Medicine-University of Jordan (Institutional Approval Number 11/2006-2007). Verbal consent was considered adequate by the committee. Participation was voluntary and anonymity and confidentiality of patients were ensured. Adult patients scheduled for surgery under general anaesthesia and requiring muscle relaxation were considered for enrolment. A 4-point Likert scale of pain assessment was used to classify reported pain on Rocuronium injection as follows: 0 when there is no pain, 1 if the pain is mild, 2 for moderate pain, and 3 if their pain is severe. Two hundred patients, ASA I-II, were enrolled in the current study. Patients were allocated randomly using sealed envelopes method into one of four groups: the first group (n = 50) was given Remifentanil 1mcg/kg, the second group (n = 50) was given Fentanyl 1mcg/kg and the third group (n = 50) was given 2 ml of Lidocaine 2% (40 mg). All study drugs' solutions were prepared in normal saline in a total volume of 5 ml. The fourth (control) group (n = 50) was given normal saline 5 ml. Exclusion criteria included patients who were not cooperative, those with history of allergy to study drugs, patients having chronic pain, those who received analgesics in the pre-operative period, and patients with difficult intravenous access.

At the end of the preoperative assessment visit, volunteering for enrollment in the study was suggested to each patient after detailed explanation of its aims and procedural aspects. Consenting patients were educated and instructed in the following manner: the patients were told that after insertion of an intravenous cannula at the dorsum of the hand in the operating theatre, an inflatable tourniquet will be applied 5 cm proximal to the intravenous cannula and its pressure will be gradually increased until cessation of flow of the crystalloid solution. After that they will be given anesthetic drugs, and one of these drugs might cause discomfort or even pain at the site of injection. They were taught to quantify the severity of any pain they might feel according to the mentioned 4-point likert scale.

After arrival to the operating theatre and before induction of anesthesia, patients instructions were reviewed a second time. After establishment of monitoring an 18G Venflon® intravenous cannula (BD, Haryana, India) was inserted in one of the large veins at the dorsum of the hand or forearm. A Lactated Ringer's crystalloid solution was mounted and free flow through the venous catheter was ensured. The tourniquet was then applied as mentioned above. The study drug solutions were pre-prepared in 5-ml syringes and kept at room temperature. The drug solutions were unknown to the administering anesthetist who was instructed to inject the prepared drug over 5 seconds. Venous occlusion was released after 60 seconds. The room anesthetist was then asked to administer a 0.6 mg/kg dose of Rocuronium at rate of 0.5 ml per second. Immediately and while the patient is awake, the prime investigator asked the patient whether he/she suffered any pain on Rocuronium injection and to quantify it if any. Pain score was then registered and the anesthesthetic in charge of the patient was asked to proceed with the induction of anesthesia.

Table 1

Summary of Demographic characteristics of study sample

Pretreatment group	Age	Sex (M/F)	BMI
Remifentanyl	41.8 (16.55)	19/31	26.92 (5.41)
Fentanyl	46.4 (14.31)	20/30	26.88 (5.48)
Xylocaine	40.6 (14.65)	14/36	27.03 (4.33)
Normal saline	40.92 (13.20)	15/35	27.48 (4.88)

Values for Age and BMI are in mean (SD)

Statistical Analysis

An effect size of 0.3 reduction in pain score was considered clinically significant. At a study power (β) of 0.8 and statistical significance level (α) of 0.05, a sample size of 150 was found to be the minimum number of patients needed for the study[11]. Statistical analysis was performed using SPSS software (version 19.0.0; SPSS Inc., Chicago, Illinois, USA). Data were analyzed using descriptive statistics to summarize demographic characteristics of study participants using frequencies for categorical variables and mean ± *SD* for continuous ones. The occurrence of pain among different study groups was summarized using frequencies in terms of counts and within-group percentages and Pearson Chi-square test was used to test the differences between study groups. Analysis of variances with post hoc multiple group analysis was used to test the differences of mean pain scores between different pretreatment groups.

Results

Two hundred patients aged 18-70 years (132 females) were enrolled in the study. Study groups were comparable in their demographic characteristics Table 1. Summary of the distribution of study results is cross-tabulated in Table 2 based on ultimate occurrence of pain sensation. In total, 144 patients reported pain on Rocuronium injection: 30 in the Remifentanil group, 42 in the Fentanyl group, 23 in the Xylocaine group, and 49 in the saline group.

Results of specific pain scores in different drug groups are shown in Table 3. Freedom from pain on injection was highest in the Xylocaine group (54%)

Table 2

Summary count distribution of ultimate pain sensation frequencies based on drug group, gender and age group

	Age Group																
Drug Group	**18-40 yr**				**41-60 yr**				**>60 yr**				**Subtotals**				**Total**
	Pain		**No Pain**		**Pain**		**No Pain**		**Pain**		**No Pain**		**Pain**		**No Pain**		
	M	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	
Remifentanyl	7	8	2	9	4	5	1	3	2	4	3	2	13	17	6	14	50
Fentanyl	5	10	0	1	5	13	2	3	5	4	2	0	15	27	4	4	50
Xylocaine	2	8	3	15	2	8	1	3	3	0	4	1	7	16	8	19	50
Normal Saline	15	5	2	1	3	18	1	0	1	1	3	0	19	24	6	1	50
Total	29	31	7	26	14	44	5	9	11	9	12	3	54	84	24	38	200

Table 3
*Distribution of pain scores in different treatment groups**

		DRUG GROUP				Total
		Remifentanyl	Fentanyl	Xylocaine	Saline	
Pain Score	No Pain	20 (40%)	8 (16%)	27 (54%)	1 (2%)	56
	Mild Pain	21 (42%)	17 (34%)	13 (26%)	13 (26%)	64
	Moderate Pain	8 (16%)	11 (22%)	8 (16%)	15 (30%)	42
	Severe Pain	1 (2%)	14 (28%)	2 (4%)	21 (42%)	38
	Total	50	50	50	50	200

* Frequencies are within-group counts and percentages.

followed by Remifentanil group (40%), Fentanyl group (16%), and normal saline group (2%). Analysis of variance of pain scores among different drug groups shows that all drug groups were effective in reducing the incidence of pain on injection of rocuronium when compared to Normal saline (P <0.001) (Table 4). Xylocaine and Remifentanil were both superior to Fentanyl in reducing pain on rocuronium injection with a slightly greater effect of Xylocaine (Mean difference -0.92, P <0.001) than Remifentanyl (Mean difference -0.82, P <0.001). Xylocaine was not significantly different than Remifentanyl in reducing pain (Mean difference 0.1, P = 0.582). Patients in the Fentanyl group had the highest frequency of severe pain (28%) and lowest frequency of mild pain (16%) (Table 3).

Among different age groups, the incidence of pain on injection of rocuronium was highest in the middle age group (81%), followed by young (68%) and then old age group (66%) (Table 2). Despite this order of pain frequency, chi square test analysis showed the differences to be statistically non-significant (P = 0.126). When comparisons were made across different drug groups the P value continued to reflect statistical non-significance and was lowest in the Xylocaine group (P = 0.079).

There was no statistically significant difference

Table 4
*Analysis of variance of pain scores among different drug groups**

(I) DRUG GROUP	(J) DRUG GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
REMMIIFENTNYL	FENTANYL	-.820	.182	<.001	-1.18	-.46
	XYLOCAINE	.100	.182	.582	-.26	.46
	SALINE	-1.320	.182	<.001	-1.68	-.96
FENTANYL	REMMIIFENTNYL	.820	.182	<.001	.46	1.18
	XYLOCAINE	.920	.182	<.001	.56	1.28
	SALINE	-.500	.182	<.001	-.86	-.14
XYLOCAINE	REMMIIFENTNYL	-.100	.182	.582	-.46	.26
	FENTANYL	-.920	.182	<.001	-1.28	-.56
	SALINE	-1.420	.182	<.001	-1.78	-1.06
SALINE	REMMIIFENTNYL	1.320	.182	<.001	.96	1.68
	FENTANYL	.500	.182	.006	.14	.86
	XYLOCAINE	1.420	.182	<.001	1.06	1.78

* Values <0.05 are statistically significant.

between male and female genders in terms of pain sensation (P = 0.882). This statistical non-significance was still valid when the two genders were compared across all drug groups.

No patient suffered from any local or systemic drug reaction and all patients were hemodynamically stable throughout their operations.

Discussion

There are several theories about the cause of pain on injection of some anesthetic drugs. A common perception in all is that activation of polymodal nociceptors leads to the release of endogenous mediators such as kinin, histamine, and bradikinin that mediate the pain response. The stimulation of the pain receptors is proposed to be caused by the unphysiological osmolality or pH of these drugs solutions[5,12-14]. Although rocuronium preparation is isotonic it has a pH of 4 which may explain its association with pain on intravenous injection[12].

Techniques of administration of pretreatment drugs used to prevent pain on rocuronium injection included direct intravenous injection[7,8,15,16], or intravenous injection that was preceded by venous occlusion for one minute or so[6,17]. None of the studies that adopted the venous occlusion technique included remifentanil as a study drug. Thus our study may be to our knowledge the first that tests remifentanil as a possible pretreatment drug of rocuronium induced pain on injection using the venous occlusion technique.

By limiting central spread of drugs, the venous occlusion technique will retain them in the target vein and make any observed effects exclusively local. Our results agree with previous studies using this technique in showing local anesthetic effect of opioid drugs. Opioid receptors are distributed throughout the body including vascular epithelium[18]. However, the mechanism of local anesthetic action of opioids can be either receptor mediated or possibly through nonspecific membrane conduction blocking effects that are shared by many other compounds[19,20]. This second mechanism is supported by the fact that the local anesthetic actions of opioid drugs are not revered by naloxone[21].

The difference in the effectiveness between remifentanil and fentanyl in our study in favor of remifentanil can be explained by the one-minute venous occlusion technique we used. Remifentanil has an onset of action time of around 1 minute compared to fentanyl (3-5 minutes). This time limit was unfavorable for fentanyl to establish its local effect. At physiologic pH, remifentanil (pKa 8.4) is 90% non-ionized compared to 33% for fentanyl (pKa 7.09) which explains remifentanil's faster onset. Xylocaine use for prevention of pain on injection of some anesthetic drugs is well established in literature[5]. It has an onset time of action that is comparable to remifentanil (45-90 seconds), and so the venous occlusion technique is not expected to delay the onset of its action. It is anticipated that venous occlusion will limit the drug dilution by stopping venous blood flow and providing transient stagnancy of the administered doses thus enhancing any local drug effects. Studies comparing remifentanyl and fentanyl administered in the usual way showed inconsistent results about the superiority of remifentanil over fentanyl in controlling pain on rocuronium injection[22,23]. The inconsistency in results is likely to be due to different timing of rocuronium injection after the pretreatment drugs in different studies that affected the onset of their central analgesic effects. The venous occlusion technique adopted in our study tests the peripheral local anesthetic effects of these two opioid drugs within one minute of containment. However, increasing the venous occlusion time longer to accommodate the time for onset of action of Fentanyl may give equal effectiveness of both drugs. This needs to be tested in further studies.

Studies of gender factor in the perception of pain on rocuronium injection had shown that the incidence of this type of pain is significantly higher in females[16]. Our study showed no significant differences between the two genders of patients. The difference between males and females may actually be stemming from central perception of pain, a process that is likely to have been blocked by the local analgesic effect of our study drugs. The same argument can be applied for the lack of significant difference among different age groups in our study. However, these concepts need to be addressed in specially designed studies.

Although propofol is known to be associated

with pain on injection, the venous occlusion technique adopted in our study and the administration of rocuronium and assessment of its associated pain on injection before the administration of propofol excludes any interactive effects from both drugs in causing the pain. Movement of the limb on injection of drugs associated with pain on injection was found to correlate with pain sensation[24]. As our patients were still conscious on administration of rocuronium, we did not include this assessment modality or other surrogate variables (e.g., heart rate and blood pressure) to test pain on rocuronium injection and relied on conscious reporting of pain sensation which we believe provides more objective assessment of pain. Surrogate variables are nonspecific and are also common in stage II anesthesia.

In conclusion, our study showed consistent results with previous studies regarding the effectiveness of xylocaine, fentanyl, and remifentanil in preventing pain on rocuronium injection. We have introduced the possible safe use of remifentanil for this purpose using the venous occlusion technique in a dose of 1mcg/kg with efficacy comparable to xylocaine. Further studies are encouraged to further test the validity of our results.

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A COMPARISON OF TWO DIFFERENT DOSES OF BUPIVACAINE IN CAUDAL ANESTHESIA FOR NEONATAL CIRCUMCISION. A RANDOMIZED CLINICAL TRIAL

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Abstract

Background: We aimed to compare the analgesia quality of caudal block of low volume, high concentration bupivacaine to the conventionally used volumes and concentrations of the drug in neonates undergoing circumcision with sole caudal anesthesia.

Methods: Fifty neonates, undergoing circumcision were randomly assigned to low volume high concentration (group LVHC, n=25) and control groups (group C, n=25). Both groups received a caudal injection: Group LVHC 0.5 ml/kg bupivacaine 0.375% (1.875 mg/kg) and group C 1 ml/kg bupivacaine 0.25% (2.5 mg/kg). Hemodynamic parameters, block onsets and analgesia periods were compared among the groups. Pain scores were evaluated hourly for 3 hours postoperatively with NIPS (neonatal infant pain score). Statistical analyses were performed with Student's *t*-test for continuous variables. X^2 and Mann–Whitney U-tests were used for nominal and/or categorical variables.

Results: Demographic, hemodynamic data, block onset time (group LVHC and C values were 4.9 ± 1 vs 5.2 ± 2 mins, respectively; p=0.53) was similar and postoperative median NIPS (a median value of 0 at postoperative 1, 2, and 3. hours) were identical among the groups (p=0.7, p=0.9, p=1). None of the neonates required additional analgesic for the first 24 hours following the surgery; therefore postoperative analgesic requirement was similar among the groups (p>0.1).

Conclusions: Low volume high concentration caudal bupivacaine provided a similar perioperative analgesia quality, time and safety profile compared to conventional bupivacaine doses in awake neonates undergoing circumcision. Low volume, high concentration bupivacaine may be used to reduce the risk of local anesthetic toxicity in outpatient neonates.

Key words: Neonatal caudal anesthesia, bupivacaine, circumcision.

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Introduction

Caudal epidural anesthesia is one of the most commonly performed regional block for postoperative analgesia in pediatric surgery[1] and is often used to provide perioperative analgesia in neonates and infants[2]. Sole caudal block may be a safe alternative to general anesthesia in this population[3]. However, there are only few studies and case reports evaluating caudal anesthesia alone in neonates[3-7].

Local anesthetics used for pediatric caudal anesthesia are bound to serum proteins, mainly to alpha-1 acid glycoprotein (AAG). As the plasma concentration of AAG is decreased, the risk of local anesthetic toxicity would be higher in infants[8]. The commonly used bupivacaine dose for caudal anesthesia in small infants for infra-umblical surgery is 2.5 mg/kg. However, it was reported that following caudal administration of a single dose of L-bupivacaine (2.5 mg/kg), the highest Cmax level in children younger than 3 years was found to be close to the toxic threshold of adult patients[9]. Therefore, in neonates and infants, the dose of the local anesthetic during regional anesthesia should be reduced for safety reasons.

In this study we hypothesized that, low volume, high concentration (0.5 mL/kg, 0.375%) caudal regional block with bupivacaine (1.8 mg/kg) provides as effective and prolonged analgesia as the conventionally used volumes and concentrations (1 mL/kg; 0.25%; 2.5 mg/kg) in neonates undergoing circumcision with sole caudal anesthesia.

Methods

This was a single-centre, balanced randomised [1:1], double-blinded, parallel-group study conducted at Yeditepe University Hospital (Istanbul, Turkey) between March and November 2011. After obtaining Ethical Committee approval (01.02.2011/N^{o} 073; chair-person Professor Recep Serdar Alpan, MD) and parental consent, 50 full-term neonates undergoing elective circumcision were enrolled in this study. Exclusion criteria were coagulopathy, sepsis, infection at the puncture site, anatomic abnormality in the caudal region or parental refusal.

Patients did not receive a sedative or an analgesic drug before the caudal block. Preoperative laboratory tests included prothrombin time, partial thromboplastin time and complete blood count. All the neonates were born at our hospital and routinely received vitamin K. Neonates were randomly assigned to low volume high concentration group (group LVHC, n=25) and to control group (group C, n=25) using a computer generated randomization table by a pediatric surgeon who did not participate in the study. Patients were fasted for 4 hrs before caudal anesthesia.

Intravenous access was obtained prior to caudal block. Children received 5% dextrose in 0.45% saline at a rate of 4 ml/kg/h until feeding was restarted. Heart rate (HR), noninvasive blood pressure (NIBP) measured on the upper limbs, and oxygen saturation by pulse oximetry (SpO_2) were monitored and recorded during the procedure at 5 minutes intervals.

All neonates were placed in the left lateral position and caudal block was performed using an aseptic technique and a 25 G caudal needle (Epican; BBraun Melsungen, Germany). Aspiration test was used to detect blood or cerebrospinal fluid. Patients in group LVHC received a caudal injection of 0.5 ml/kg bupivacaine 0.375% (1.875 mg/kg), while the patients in group C received a caudal injection of 1 ml/kg bupivacaine 0.25% (2.5 mg/kg). All the caudal blocks were performed by two anesthesiologists experienced in the neonatal caudal block at least for 4 years. The patients were positioned for surgery after the procedure. Adequacy of the block was assessed with the absence of hemodynamic response, facial grimace and aversive response to a manual pinprick test. Caudal block level was evaluated by the absence of facial grimace or crying to a pinch test. Circumcisions were performed using a standardized technique. An intraoperative successful blockade was defined as no hemodynamic reaction (heart rate or mean arterial pressure >20% compared with the baseline) and absence of crying in response to surgical stimulus. All the neonates were awake during the procedure.

Postoperative pain was assessed with neonatal infant pain scale (NIPS)[10] every hour for 3 hours postoperatively. When the score was >3, 15 mg/kg rectal paracetamol was considered as a rescue analgesic. Side-effects encountered during the study period were also recorded. Block onset time, block level, the time

Table 1
Demographic and surgical data, caudal block onset and discharge time

	Group LVHC (n=25)	Group C (n=25)	p value
Age (days)	19 ± 7	19 ± 8	0.9
Weight (gr)	3766 ± 492	3684 ± 643	0.6
Height (cm)	51 ± 1	51 ± 2	0.8
Block onset time (mins)	4.9 ± 1	5.2 ± 2	0.5
Duration of surgery (mins)	13.2±2	13.3±3	0.8
Discharge time (mins)	230±23	231±25	0.9

Abbreviations: Group LVHC; low volume high concentration local anesthetic group.
Group C; control group.

required for the first analgesic drug administration and postoperative total paracetamol dose were recorded and compared between the two groups. Caudal block failure rate was also recorded. No attempt was made to assess the degree of motor block because of its subjectivity in neonates. Postoperative evaluation was done by pediatric nurses who were blinded to the study.

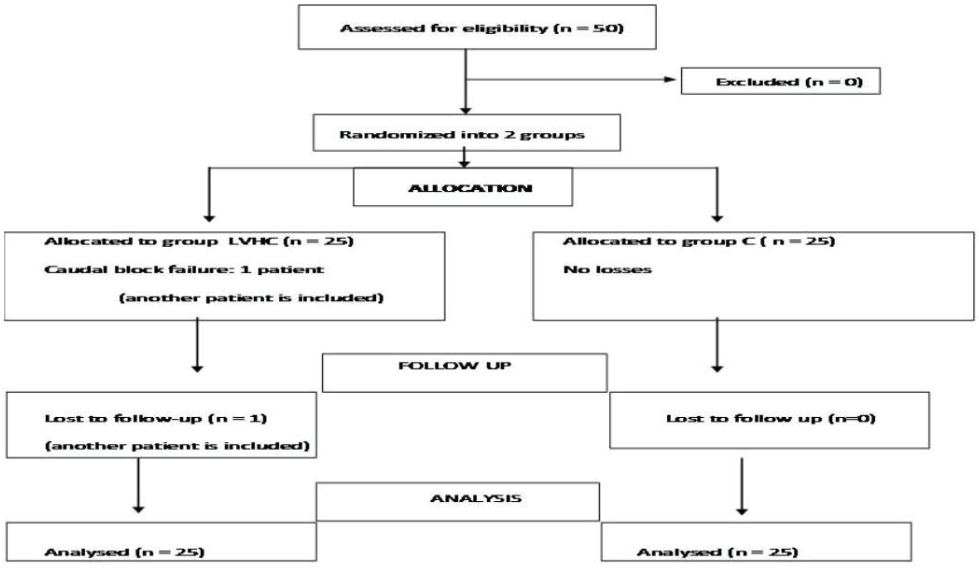
All the neonates were discharged from the hospital on the same day of the surgery. Home discharge was decided according to absence of the surgical bleeding and adequate breast feeding. Parents were educated and asked to evaluate the same pain scale to give rectal paracetamol suppository (15 mg/kg) if the neonates have pain. The parents were called by an anesthesiologist who was blinded to the groups for postoperative pain evaluation and the need for paracetamol twenty-four hours after the surgery.

Statistical analysis

The data obtained are presented as the mean (±SD) and median, where appropriate.

We determined the number of the patients participated in our study according to the previous studies performed on the topic[11,12]. Statistical analyses were performed with Student's *t*-test for continuous variables. X^2 and Mann-Whitney U-tests were used for nominal and/or categorical variables. We considered a p value less than 0.05 for statistical significance.

Fig. 1
Flow chart of the study



Results

One child in group LVHC was excluded from the study due to caudal block failure. Therefore, another child was added to the group. During the follow up period one patient in the same group was given paracetamol suppository due to postoperative fever. This patient was also replaced by another neonate. A total of fifty children participated and completed this study. Flow chart of the study is shown in Figure 1.

Demographic and surgical data are given in Table 1. There were no differences between the groups.

Heart rate and the mean arterial blood pressure values recorded during the anesthesia period were similar between the groups (Figures 2 and 3).

Fig 2.

Variations in the heart rate values throughout the study period. None of the comparisons reached statistical significance between the groups (p>0.05). Abbreviations; bpm, beat per minute, group LVHC, low volume high concentration group; group C, control group

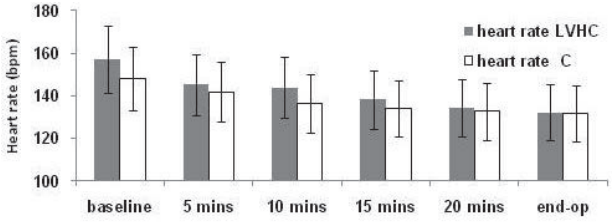
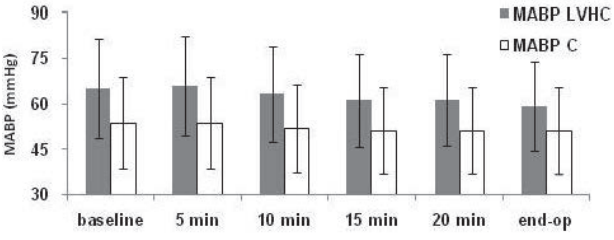


Fig. 3

Variations in the mean arterial blood pressure values throughout the study period. Abbreviations; MABP, mean arterial blood pressure, group LVHC, low volume high concentration group; group C, control group



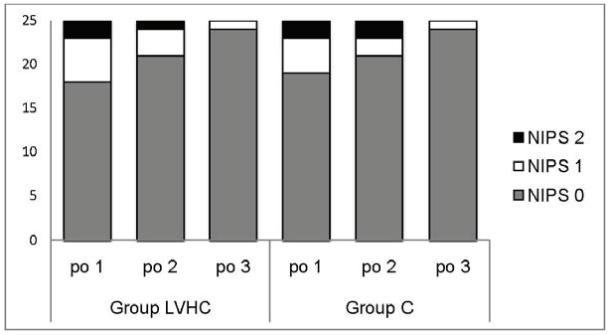
Caudal block onset time was not statistically different between the groups. (LVHC and Control group values were 4.9 ± 1 vs 5.2 ± 2 mins: 95% CI (-1.17-0.6), respectively; p=0.53, Table 1). None of the neonates in both groups required additional analgesic for the first twenty four hours following the surgery (p>0.1).

Sensorial block level after caudal block in group C was T 4-6, and L 1 - T 12 in group LVHC.

None of the neonates had a NIPS score of > 3 throughout the study period. Postoperative median NIPS (a median value of 0 at postoperative 1, 2, and 3 hours) were identical among the groups (p=0.7, p=0.9, p=1) (Figure 4).

Fig. 4

NIPS pain scores for the groups. Comparison of LVHC group versus control group did not reach statistical significance (p>0.05). Values are given as the number of the patients. Abbreviations; group LVHC, low volume high concentration group; group C, control group; po 1, 2, 3; postoperative hours 1, 2, 3



There was no difference among the groups regarding the hospital discharge times (group LVHC 231±23 mins vs group C 231±25 mins; p=0.9).

No complications or drug-related side effects were observed during the study. None of the neonates developed acute urinary retention in the postoperative period.

Discussion

Uguralp et al demonstrated that caudal anesthesia is a safe, effective, inexpensive anesthetic technique and superior alternative to general anesthesia in premature infants and neonates when performed by experienced anesthesiologists. The authors did not observe any complications in their study[13]. Findings

of our study are parallel with the aforementioned paper. All the caudal blocks were performed by two experienced anesthesiologists in our study.

Hoelzle et al demonstrated that caudal anesthesia is feasible in patients ≤5 kg and technically easier and less dependent on immobility in awake infants compared to the spinal anesthesia[14]. Caudal epidural anesthesia alone has been recommended for neonates to reduce the risk of postoperative complications[15], as it obviates the necessity for general anesthesia and endotracheal intubation.

The quality and level of the caudal block is dependent on the dose, volume and concentration of the local anesthetic drug[1]. The analgesia duration has been shown to depend on the level of cranial spread of local anesthetic drug injected to caudal epidural space in children[16]. There are some attempts to reduce the dose, prolong the analgesia time and decrease the risk of motor block during the procedure by using high volume (1.8 mL/kg) and low local anesthetic concentrations[1]. When high volumes of local anesthetic agents are used for neonatal caudal anesthesia, cranial spread of ≥ T12 (up to T3) is likely[17]. However, a block level limited to the sacral dermatomes is enough for the circumcision procedure and transient motor block is not a major concern in neonates. Furthermore, recommended dose of bupivacaine for caudal anesthesia as a sole anesthetic method in infants is 1-1.2 mL/kg of 0.25% bupivacaine[18]. This caudal injection provides a bupivacaine dose of 2.5 mg/kg. Despite being safe this dose is reported to be close to the toxic threshold of adult patients in children younger than 3 years old[9]. Therefore, we used high local anesthetic concentrations (0.375%) along with a reduced volume providing a decreased local anesthetic dose (1.875 mg/kg). Caudal anesthesia with 0.375% bupivacaine was shown to be safe in neonates[19]. The reason for the similar postoperative analgesia time among the groups despite using different volume and concentrations, is probably due to the blockade of the A alpha nerve fibers more satisfactorily when increased concentration of the local anesthetic agent is used[20]. This theory may also explain the prolonged postoperative analgesia obtained in LVHC group neonates considering the low block levels (L1-Th12). A study by Schrock CR et al. has shown that, increased local anesthetic volume did not increase the duration of postoperative analgesia when the aforementioned caudal local anesthetic volumes were compared (0.7 vs 1.3 mL/kg)[21]. Therefore, volume alone may not explain the prolonged analgesic effect as is the case in our study.

Epidural or even high spinal block causes minimal hemodynamic changes in children up to the age of 6-8. The reason is low basal sympathetic tone in this age group. We did not observe any hemodynamic change in both groups in our study[18].

We did not observe any complications related to the caudal block, a finding correlated with a previous study[22], probably due to the appropriate management of the neonates by experienced anesthesiologists with maximal precaution.

Study limitations: Lack of the assessment of the local anesthetic plasma levels is a limitation of our study. However most of the families did not permit us to do extra punctures for blood sampling.

In conclusion, low volume, high concentration bupivacaine solution used during caudal anesthesia provides a similar perioperative analgesia quality, postoperative analgesia time and safety profile compared to the conventionally used doses in neonates undergoing circumcision procedure awake. Therefore, we recommend using low volume, high concentration bupivacaine in outpatient neonates to reduce the risk of local anesthetic toxicity.

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CASE REPORTS

REMIFENTANIL INFUSION PROLONGS SPINAL ANESTHESIA

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Abstract

Spinal anesthesia was given to a patient undergoing transurethral resection of prostate (TURP). A total of 3.2 ml of bupivacaine 0.5% mixed with fentanyl 20 mcg were used. The patient started experiencing sensation after 150 min. Remifentanil intravenous infusion prolonged the duration of anesthesia for an additional 105 minutes.

Key words*:* TURP, spinal, anesthesia, remifentanil.

Case Report

A 56 years old male, ASA III class, with a history of chronic prostatitis was scheduled for TURP/open prostatectomy. The patient was assessed in the ward the night before surgery where a history, examination and investigations were performed. The patient was a heavy smoker, smoking 40 cigarettes a day for 36 years, and occasionally consumed alcohol. The patient suffered from COPD (chronic bronchitis), coronary artery disease, and occasional chest pain with the last attack 2 days before surgery and an old MI 3 years ago. The patient was evaluated by a cardiologist who confirmed, after undergoing echocardiography showing acceptable EF of 58% and a negative treadmill test that the patient cardiac state was stable. There was also a history of gastro-esophageal reflux disease and an allergy to sulfa. The patient underwent varicocelectomy in 1983 and 1985 in addition to a few recent uneventful cystoscopies under GA. Recent investigation results were as follows: ECG; normal sinus rhythm, CXR; increased bronchovascular markings, Blood work; Hb 13.9, Ht 42.3, platelets 219, WBC 20.5, BUN 5.1, creatinine 6.8, Na 134, K 4.2, Cl 104, PT 10.2, PTT 32.3, INR 0.9. Anesthesia plan and consent for spinal with back up general anesthesia were reviewed and documented.

In the operative theatre, standard monitors were attached which included, non-invasive blood pressure, pulse oximetry and ECG. Uneventful spinal anesthesia was induced in the sitting position using strict aseptic technique; local lidocaine 2% 2 ml was injected into the skin and subcutaneous

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area and then a 27G Whitacre spinal needle was advanced in the midline at the L3-L4 level, till clear CSF was obtained. A mixture of 0.5% bupivacaine 3.2 ml and fentanyl 20 mcg were injected slowly after careful barbotage. The patient was then turned to supine position which was adjusted to get a bilateral T10 level. A simple oxygen face mask at 5 liters per minute was used and end-tidal carbon dioxide catheter was applied under the mask. Thereafter, a screen was applied and the patient was put in the lithotomy position. Midazolam 2mg IV injection was given for sedation and surgery was done with the patient in lithotomy position. Bipolar resectoscope was used for surgery and normal saline for irrigation. Around 150 minutes after the subarachnoid injection, the patient started to feel movement at the surgery site and some mild pain. Remifentanil intravenous infusion was started and titrated according to pain sensation, respiratory rate and sedation level until the end of the operation 105 minutes later. A two-way Foley's catheter was used for continuous irrigation.

A total of 1500ml of intraoperative fluids (crystalloids) were given: 1000ml Ringers Lactate and 500ml normal saline (NS) with a blood loss of around 500 ml. Furosemide 5mg IV was injected and NS was used for irrigation during the procedure instead of glycine. Intraoperative vital signs were stable. The patient received paracetamol 1gm intraoperatively, 30 min after starting remifentanil, then morphine 9mg in the recovery room 50 min after the end of the remifentanil infusion. Postoperative analgesic medications in the ward included pethidine 50 mg IM twice a day PRN if VAS $\geq$ 40, paracetamol 1gm every 6 hours PRN if VAS $\geq$ 30 and diclofenac sodium 75 mg IM twice a day PRN if VAS $\geq$ 30. Postoperative vital signs were stable and the postoperative investigations and clinical course of the patient were satisfactory.

Discussion

By reviewing the literature, we could not find similar case reports to date. TURP patients often have multiple co-morbidities and spinal anesthesia is usually safer than general anesthesia as it assures better cardiorespiratory stability, decreases blood loss, and allows for monitoring of the patient's conscious level as a warning sign of TURP syndrome in addition to providing early postoperative analgesia[1]. Following the frequently used 1.5% glycine irrigation, hyponatremia and increased blood glycine levels contribute to development of TURP syndrome. The increased time of the operative procedure could predispose patients to more blood loss or more absorption of glycine, in addition to hyponatremia, hypothermia and the need for extended anesthesia time[2].

It is an anesthetic challenge to be obliged to induce general anesthesia to overcome patient pain complaint especially if his medical state is not suitable for that. The combination of fentanyl with heavy bupivacaine 0.5% for subarachnoid injection increases the duration of spinal block[3]. In our case, the patient started to feel movement of surgical instruments in addition to pain after 150 minutes of subarachnoid injection. Asking the surgeon about the expected time to finish, he said he needed only a few minutes to control bleeding. Remifentanil infusion was started to help analgesia and sedation for the remaining expected short time. Remifentanil dose was titrated according to respiratory rate and sedation level and to our surprise, the patient was comfortable, answering questions up to the end of the whole procedure, which lasted for an additional 105 minutes. The patient complaint of the sensation of surgical instruments followed by pain was relieved by the effect of remifentanil infusion. This allowed an additional 105 min which saved the patient the risk of general anesthesia. In our case, isotonic sodium chloride (0.9% NaCl) was used instead of glycine for irrigation. Even when glycine 1.5% (15 mg glycine/ml) is used for irrigation, the use of remifentanil infusion does not add to the problem. The remifentanil formulation contains only 15 mg glycine per 1 mg remifentanil powder[4]. Remifentanil is a potent ultra-short acting mu-agonist which has been used for analgesia and sedation and as a component of balanced anesthesia. It has also been recently used as a sole analgesic for patient controlled analgesia during labor[5]. With proper titration, the sedative effect of remifentanil is mild and patients can cooperate and answer questions during the procedure[6]. There is no cumulative effect with remifentanil and it has been used to supplement multiple loco-regional anesthetic techniques[7-9]. Remifentanil possibly will not mask the TURP syndrome; however, careful monitoring is needed to guard against overdosage and

potential respiratory depression. Being an ultra-short acting narcotic, remifentanil's context-sensitive half-life remains at 4 minutes after a 4 hour infusion and its possible side effects will disappear rapidly once the infusion is stopped[10].

Nonetheless, this is the first time remifentanil been report to show value in prolongation of spinal anesthesia. Further prospective controlled studies are still needed for stronger validation of use of remifentanil in spinal anesthesia prolongation. We think this case report will encourage us and others to try this technique with more patients and various operative procedures done under loco-regional anesthesia.

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INFRACLAVICULAR BRACHIAL PLEXUS BLOCK IN WILSON'S DISEASE

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Abstract

Wilson's disease (WD) is characterized by progressive copper accumulation with hepatic and neurological impairment. Anesthesia and surgical practices may exacerbate WD and liver damage, and even cause life-threatening liver failure. Due to this existing liver damage, anesthetic management is important in WD cases in terms of drug choice, dose, and technique used. This study reports an emergency surgical procedure for trauma in a 24-year-old WD patient suffering the disease for 18 years. The operation was planned under infraclavicular brachial plexus block because of a right supracondiller/proximal humerus fracture. The selected type of anesthetic technique and agents in WD is specific. The pharmacokinetic changes in these cases are difficult to predict and require attention to drug choice and dose.

Key words: Wilson's disease, plexus block, regional, anesthesia.

Introduction

Wilson's disease (WD), also known as hepatolenticular degeneration, is a rare autosomal recessive disorder which typically occurs in older children or young adults. A reduction in the synthesis of the copper transporter protein (ceruloplasmin) leads to impairment of copper excretion into bile from lysosomes in hepatocytes, due to mutations in the ATP7B gene on chromosome 13 in patients[1]. As a result, copper cannot be removed by the bile duct and accumulates in various organs and tissues, particularly the liver[2]. It also accumulates in the liver, brain, kidney, and cornea, impairs organ function, and has toxic effects by creating free radicals[3,4]. In 40% of patients, the first sign is liver disease, varying in type from asymptomatic with only biochemical abnormalities to acute liver failure or chronic liver disease leading to cirrhosis[5]. The most common clinical signs are neurological (dysarthria and gait disturbance) and psychiatric (personality disorders and depression) changes[6,7].

Due to this existing liver damage, anesthetic management is important in WD cases in terms of technique, drugs, and doses[8]. This case report will discuss the anesthesia protocol used during an emergency surgical procedure for trauma in a WD patient, and experiences in the perioperative and postoperative periods.

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Case Report

The 24-year-old male patient had suffered WD for 18 years. He was 68 kg in weight. The operation was planned following a right supracondiller/ proximal humerus fracture. The patient had difficulty in walking, speech, and had tremor and involuntary muscle contractions on preoperative examination. In addition, he had complaints of double-vision and Kayser-Fleischer ring in both eyes. There was no hepatosplenomegaly. Blood biochemical analysis was normal. The patient underwent 750 mg/day penicillamine therapy for about three years, and continued a low copper diet (<1 mg/day of copper) for three years. The patient was taken to the operating room, underwent standard monitoring (non-invasive blood pressure, ECG and pulse oximetry), and given 1 mg of midazolam i.v for premedication.

For the infraclavicular brachial plexus block, the patient was placed in a supine position and the skin over the coracoid process was disinfected. Local anesthetic (0.25% 30 mL plain bupivacaine) was injected at 2.0 cm medially and 2.0 cm caudally to the center of the coracoid process. Subsequently, the needle attached to the nerve stimulator (B.Braun, Melsungen, Germany), and the syringe containing local anesthetic penetrated the skin at the same point. Once the optimal motor response in the range of 0.3-0.5 mA was achieved, 0.25% 30 mL plain bupivacaine was administered as a single injection followed by aspiration. Onset of the sensory block was assessed by cold test using an alcohol-soaked swab. The cutaneous dermatomes of the four major nerves of the upper limb were assessed and compared with the opposite side. This evaluation was repeated every 5 minutes for 20 minutes. To quantify the sensory block, the level of sensation of the alcohol-soaked swab and needle was graded as 0 (no sensation), 1 (hypoesthesia sensation), or 2 (normal sensation). We defined successful block as a lack of sensation (score of 0) in all four areas of innervations after 20 minutes, or a block that failed to provide appropriate surgical anesthesia and required supplementary anesthesia/analgesia. For evaluation of motor block, the patient was asked to make specific movements from which the physicians assessed the block of specific muscles. Thumb abduction was used to evaluate radial nerve, thumb adduction for ulnar nerve, thumb opposition for median nerve, and elbow flexion in supination and pronation for the musculocutaneous nerve. It was assessed at 5, 10, 15, and 20 minutes after injection of local anesthetic. No sedation was added and oxygen therapy 1 L/min *via* a nasal cannula was administered. Surgery lasted 110 minutes. Afterwards the patient did not complain of any pain at the surgical or tourniquet sites. Oxygen saturation ($Sp0_2$) remained in the range of 96% to 98%. The patient was discharged from the post-anesthesia care unit one hour postoperatively. The sensory and motor blocks lasted 20 hours.

Discussion

WD initially occurs as a liver disease in children[8]. Although clinical course varies among patients, neurological symptoms are usually the most common symptoms[6]. In early diagnosis, histological changes on liver biopsy, high and low serum ceruloplasmin level and 24-hour urine copper excretion are valuable. The goal of treatment is to prevent progression of the disease by reducing the accumulation of copper tissue and organs. For this purpose, D-penicillamine is used[5].

Very few publications related to the anesthetic management of WD have been reported. There is no clear consensus on the safest anesthetic technique and agent[8,9]. It has been expressed that general anesthetic agents such as hypnotics, narcotics, and muscle relaxants may aggravate neurological and psychiatric problems, increase existing hepatic damage, and affect the central nervous system in the postoperative period. It has also been expressed that patients are more sensitive to muscle-relaxing agents than normal patients due to use of d-penicillamine[10]. Systemic blood pressure, hepatic blood flow, and tissue perfusion are decreased due to hemodynamic changes that occur during general anesthesia. The decreased blood flow in WD with failed hepatic function may increase existing hepatic damage and adversely affect drug metabolism.

Despite all these negative anesthetic effects, the literature has also reported smooth application of general anesthesia[8-10]. However, this may be due to patients in the pediatric age group. Because general anesthesia may aggravate current disease, we decided to apply a regional anesthesia to our patient who has

clinical complaints and 18-year history with WD. After varicocelectomy under general anesthesia, aggravated cases of WD have been reported in the literature[11]. Anesthesia and surgical practices may exacerbate WD and liver damage, and even cause life-threatening liver failure[12]. As many agents used in general anesthesia are metabolized by the liver, the effect duration of these drugs can increase in WD. When choosing the method of anesthesia in patients with WD, the method which causes less effect to the liver must be chosen.

Electrophysiological changes in patients with WD are typically seen in the central nervous system[13]. However, some studies have found that the effect of the chelators used to treat WD caused polyneuropathy in the peripheral nerves[13,14]. Myelin loss and axonal degeneration in peripheral nerve biopsies have also been observed[15]. For this reason, the literature has shown that the peripheral nerves of patients with WD are more sensitive to local anesthetic agents. This may be so; however our patient did not require any additional analgesic in the 12 hours period after the block.

In sum, it should be considered that in a patient with WD showing hepatic or neuropsychiatric findings, general anesthesia may aggravate existing disease. If possible, regional anesthesia techniques and decreased local anesthetic dose are preferred.

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REPORT OF A CASE OF ULTRASOUND GUIDED CONTINUOUS THORACIC PARAVERTEBRAL BLOCK FOR POST THORACOTOMY ANALGESIA IN A CHILD

Mohammed Arshad Ali* and Aslam Sher Khan Akbar**

Case Report

We report a case of ultrasound guided thoracic paravertebral block for post thoracotomy analgesia in a child.

A six year old female child, weighing 13 kg was posted for patent ductus arteriosus ligation by a left lateral thoracotomy approach. The planned anesthetic was general anesthesia and placement of a continuous paravertebral block at the end of surgery for post operative analgesia. The patient was induced with propofol 30 mg i.v, fentanyl citrate 25 µg i.v and atracurium 7 mg i.v to facilitate endotracheal intubation, and maintained with sevoflurane in oxygen and air. After skin closure, ultrasound scanning in the transverse plane was done with 25 mm 6-13 MHz broadband linear array probe on a Sonosite micromaxx (Sonosite Inc, Bothwell, MA, USA) at the level of the skin incision just lateral to the thoracic spine. The transverse process of the vertebra, internal intercostal membrane, pleura and the wedge shaped paravertebral space were clearly identified. A 5 cm, 19 G Tuohy epidural needle was inserted inplane from the lateral to the medial side. 1.25 $mg.kg^{-1}$ of 0.25% bupivacaine was injected in incremental aliquots and the thoracic paravertebral space was observed to distend with the pleura moving ventrally. A 0.63mm OD end hole catheter was inserted. After initial resistance, the catheter passed easily with slight rotation of the needle bevel. The catheter was tunneled and fixed with the tip 2 cm in the paravertebral space. The patient was extubated and shifted to the recovery room and an infusion of 0.125% bupivacaine was started at $0.25mg.kg^{-1}.hr^{-1}$. Rescue analgesia consisted of pethidine 13 mg i.m and promethazine 6.5 mg i.m. The need for rescue analgesia was assessed by nursing staff not otherwise connected with the care of the patient. The patient was comfortable, slept well the night of surgery and did not receive any rescue analgesia during the 48 hr observation period.

The parents, ward nurses and surgeons were satisfied with the analgesic regimen. The most efficacious methods of post operative analgesia following thoracotomy are continuous thoracic epidural and continuous thoracic paravertebral blocks. Continuous thoracic epidural under sonographic guidance has been described[1]. This technique requires extensive experience

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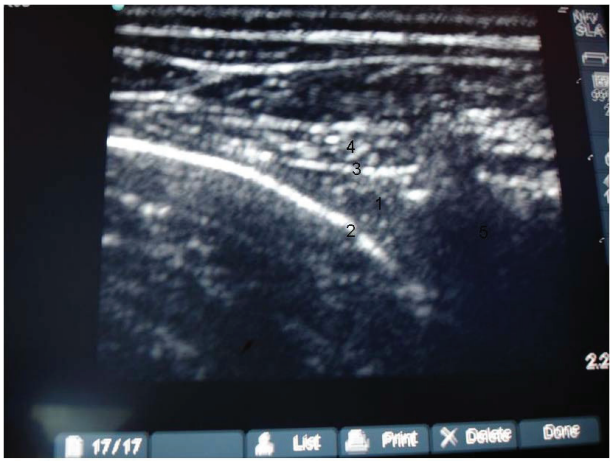
for safe conduct. Continuous paravertebral blocks using landmarks and loss of resistance to saline as end point[2,3] and surgical placement of catheters during thoracotomy have previously been described[4,5,6]. Real time ultrasound guided thoracic paravertebral blocks have been described in adults for analgesia following thoracotomy and breast surgery[7,8,9]. To date there have been no published report of thoracic paravertebral block in children with ultrasound guidance. Our technique is based on the technique described by Shibata et al[7]. In children, the visualization of the space is better and tracking the needle is easier because of the shorter skin to paravertebral space distance. Real time needle guidance has the potential to decrease the risk of pleural puncture and vascular injection[10]. This technique merits further evaluation in children for post operative analgesia following thoracotomy.



1 Thoracic paravertebral space
2 Pleura
3 Internal intercostal membrane
4 External intercostal muscle
5 Edge of transverse process

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CONTINUOUS INTRAOPERATIVE TEE MONITORING FOR A CHILD WITH FONTAN PATHWAY UNDERGOING POST SPINAL FUSION

Ibrahim S. Farid*, Abelash Reddy**, Judith Lewis***
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Abstract

The following case report describes a very challenging surgical case where the use of intraoperative, continuous TEE monitoring in the prone position was crucial for the anesthetic management (diagnosis and treatment) of a patient with single ventricle physiology. The use of TEE monitoring enabled the anesthesia team to continuously assess hemodynamic stability and respond immediately to hypotension and bradycardia in our patient, thereby providing optimal anesthetic care of the intraoperative spinal fusion patient with Fontan physiology.

Introduction

Improvement in the treatment of congenital heart disease has led to a rise in survival rates of patients with cardiac anomalies, thus patients are presenting more frequently for complex noncardiac surgical procedures. The following case report, with written parental consent, describes the continuous intraoperative use of transesophageal echocardiography in an adolescent with a Fontan circulation undergoing posterior spinal fusion for idiopathic thoracic scoliosis.

Case Description

A 15-year-old, 25 kg girl, with a history of idiopathic thoracic scoliosis (53 degree curve), presented for posterior spinal fusion T1-T10 with history of congenital hypoplastic left heart syndrome corrected by fenestrated Fontan procedure at 3 years of age.

In the OR, a 5-lead ECG was used to monitor ST segment changes. Anesthesia was induced with propofol 2 mg/kg followed by atracurium 0.5 mg/kg for intubation. She was intubated with a 6.0 oral endotracheal tube. An 18g peripheral IV, a 22g right radial arterial line, and a right IJ 5 french 12cm triple lumen catheter were inserted. Initial central venous pressure (CVP) reading

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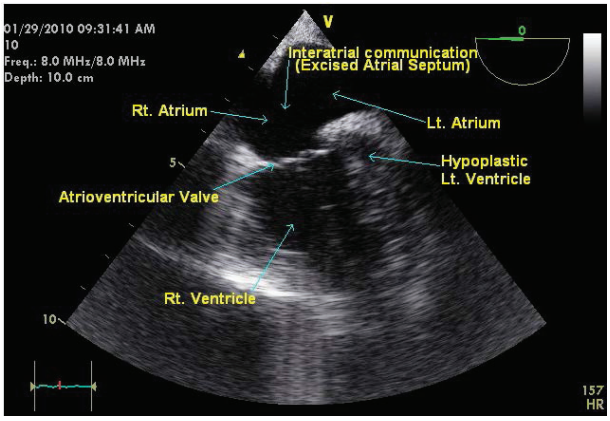
was 13-15 mmHg. A transesophageal echocardiogram (TEE) probe (9T/9T-RSTEE) was placed through an endoscopic bite block (Inoris). Baseline readings showed good filling volumes of the right atrium (RA), well-functioning Fontan baffle with small fenestration, normal tricuspid valve function without regurgitation, and good right ventricular (RV) size and function (fig. 1). Anesthesia was maintained with O2/Air with FiO2 0.5 Sevoflurane 1%.

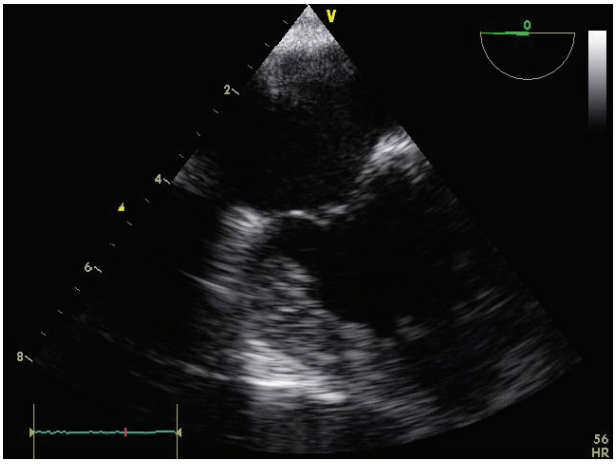
Fig. 1



The patient was placed prone with longitudinal bolsters. Chest and abdominal excursion, and TEE placement were confirmed. Heart function was assessed prone, which demonstrated no change from initial study. Vital signs remained stable, CVP reading was 18-20 mmHg, and surgery commenced.

For evoked potential monitoring, sevoflurane was reduced to 0.6%. Remifentanil (0.1 mcg/kg/min) and propofol (50 mcg/kg/min) were started. Blood pressure dropped to 85/45 mmHg and heart rate dropped from 110 to 80bpm 2-3 minutes later. Despite reduction in sevoflurane to 0.2%, and infusion of dopamine at 5 mcg/kg/minute, blood pressure and heart rate further dropped to 60/40mm Hg and 60bpm. Heart function was assessed via TEE, showing dilated RA and RV, mild tricuspid valve regurgitation, and poor global RV contractility (fig. 2). Dopamine was increased to 10 mcg/kg/min Epinephrine was started at 0.05 mcg/kg/min, titrated to 0.15 mcg/kg/min. Remifentanil was held, and propofol discontinued. Phenylephrine 80 mcg increased BP to 96/57 mmHg. Arterial blood gases remained normal.

Fig. 2



Once blood pressure returned to 80/40 and heart function improved (TEE monitoring), dopamine was weaned to 3 mcg/kg/min and epinephrine was weaned to 0.04 mcg/kg/min. Fluid volume was titrated to maintain CVP readings of 18 mmHg. Once blood pressure stabilized to 90/50 mmHg, remifentanil was restarted at 0.1 mcg/kg/min. Estimated blood loss was 200 cc.

At closure, remifentanil, dopamine and epinephrine were weaned and discontinued. The patient was placed in the supine position and morphine was titrated for analgesia. TEE readings showed good volume status, tricuspid valve function and RV size and function. The TEE probe was removed. The patient became responsive, with good tidal volumes, and moved her extremities, and was extubated to 2L/min oxygen.

Discussion

Improved treatment of congenital heart disease has given patients opportunity to present as adolescents and adults for noncardiac surgical procedures. Idiopathic scoliosis occurs in 2-4% of the general population[1]; though four times increased incidence in patients with cyanotic heart conditions[2]. The anesthetic management of these patients presenting for spinal fusion and instrumentation can be very challenging. Only few cases have been reported describing their perioperative management. Patients who underwent a Fontan operation with palliations of their cardiac disease may present with significantly diminished

cardiac and pulmonary reserve[3].

Patients undergoing spinal fusions lose nearly half of their blood volume intraoperatively, with the average blood loss estimated to be 800-1200 ml[1]. This blood loss can result in significant hypotension and hemodynamic instability. Contributing factors for this substantial blood loss have been attributed to surgical technique, surgery duration, number of vertebral levels to be fused, and/or arterial pressure[1]. Positioning the patient prone transmits pressure from the intrabdominal cavity to the epidural veins and increases bleeding; however, prone positioning with longitudinal bolsters relieves the sternal compression of the heart and limits subsequent increase in blood loss and hypotension[1,4]. Fontan patients have potential for excessive blood loss secondary to elevated venous pressure[1].

Fontan patients possess a very fragile hemodynamic profile. They specifically require special attention to preload, contractility, cardiac output, and pulmonary vascular resistance (PVR)[5]. Since the systemic return directly enters the pulmonary circulation, preload is vital for pulmonary blood flow and cardiac output. Pulmonary vascular blood flow may be impeded by hypothermia, hypoxia, hypercarbia, and sympathetic stimulation leading to increased PVR and decreased cardiac output[3]. Sluggish blood flow from the lack of pulsatile flow through pulmonary circulation poses a risk of thromboembolism[6]. However, preoperative thromboprophylaxis may contribute to blood loss[7].

TEE provides a real time evaluation of preload, contractility, AV valve function, and cardiac output. Continuous qualitative evaluation utilizing the four chamber view can determine cause of hypotension. During blood loss, dynamic visualization of cardiac function and venous return enabled the maintenance of intravascular volume to maintain pulmonary blood flow and cardiac output. TEE is an effective adjunct to anesthesia monitoring. TEE enabled the anesthesia team to ascertain hemodynamic tolerance of positive pressure ventilation, administration of volatile agents and prone positioning.

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POSTOPERATIVE HYPOTENSION ASSOCIATED WITH AMLODIPINE

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Abstract

Continuation of anti-hypertensive drugs peri-operatively and their influence on intra-operative hemodynamic is a major concern among anesthesiologists. Amlodipine is often favored clinically over other calcium channel blockers for its vascular selectivity and relative lack of negative ionotropy, once daily dosing and prolonged duration of effect. A post renal transplant patient who was on amlodipine for control of blood pressure was scheduled for laparoscopic cholecystectomy under general anesthesia. He developed severe post-operative hypotension which required intensive monitoring and vasopressor support.

Introduction

The causes of post-operative hypotension are multi-factorial, including hypovolemia, anesthetic overdose, anaphylaxis, pre-operative anti-hypertensive use, sepsis and myocardial depression. We report a case in which a patient presented with severe hypotension in the post-operative period which persisted for many hours and did not respond to vasopressors.

Case report

A 58 year old post renal transplant patient with gall bladder calculi was scheduled for laparoscopic cholecystectomy. Post transplantation he had a creatinine of 1.5 mg/dl and a good urine output. He was on Amlodipine 5 mg once daily for control of blood pressure. All investigations including CBC, RBS, creatinine, electrolytes, electrocardiogram, echocardiography, chest x-ray and liver function tests were normal.

He had taken his usual dose of Amlodipine in the morning four hours before the surgery. In the operation theatre his pulse was 76/min and blood pressure was 120/80 mm Hg. After applying all the monitors he was pre-medicated with glycopyrrolate 0.2 mg, ranitidine 50 mg, ondensetron 4 mg and fentanyl 3 μg/kg intravenously and was induced with thiopentone sodium 7 mg/kg and succinylcholine 2 mg/kg. Trachea was intubated with 8.5 mm portex cuffed endotracheal tube and anesthesia was maintained with O_2 + air + Isoflurane + atracurium. Monitoring included ECG, NIBP, SpO_2, $EtCO_2$ and peripheral nerve stimulator.

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About an hour after induction, towards the end of the surgery at the time of extubation the blood pressure decreased from 120/80 mm Hg to 90/60 mm Hg. The patient was extubated. Post-operatively the blood pressure further fell to 86/60 mm Hg. One litre of normal saline was infused rapidly followed by incremental doses of ephedrine and 500 ml of Gelofusin, without much improvement in blood pressure. Dopamine infusion was started and gradually increased to 20 µg/kg/min. Later on, nor-adrenaline and vasopressin infusions as high as 0.4 µg/kg/min and 6units/hr were added sequentially which did not produce any significant benefit. A central line for CVP monitoring and arterial line for invasive blood pressure monitoring were inserted. The CVP was 8 mm of Hg. With all the three vasopressors his blood pressure was still 70/40 mm Hg.

He was shifted to ICU where a sonography of the abdomen was done to rule out hemorrhage. An arterial blood gas (ABG) sample showed mild metabolic acidosis with normal electrolytes (pH 7.2, PCO_2 32, BE -12). Simutaneously a complete blood count was done which revealed total and differential WBC counts to be within normal limits. A bedside ECG, echocardiography and cardiac enzymes assay did not reveal any abnormality. He was on high dose ionotropic support with normal CVP (10 mm Hg) and a blood pressure of 80/50 mm Hg. There was a drop in his hourly urine output because of compromised renal perfusion pressure.

About eight hours after the initial episode of hypotension, the patient started improving hemodynamically. ABG at this time showed improvement in acidosis with normal electrolytes levels (pH 7.32, PCO_2 31, BE-8). Over the next 5-6 hours the inotropic support was tapered gradually and then stopped altogether. Thereafter he was stable hemodynamically with a pulse of 88/min and a blood pressure of 130/80 mm Hg. On the next day he had a slightly elevated creatinine of 2.6 mg/dl but the hourly urine output was improved. His CBC, Chest x-ray, ECG, ABG and electrolytes were normal. He was shifted from the ICU on third day with stable hemodynamics, creatinine of 1.5 mg/dl and a good urine output.

Discussion

The reasons for severe post-operative hypotension can be myocardial infarction, septicemia, anaphylaxis or anaphylactoid reaction to drugs used, hypovolemia, valvular heart disease and hyper-responsiveness to pre-operative anti hypertensives.

In our patient, the cardiac enzymes and echocardiography in the immediate post-operative period were normal which ruled a cardiac cause of hypotension. Post-operatively, an ultrasound of the abdomen was done and hemorrhage as a cause of hypovolemia was ruled out. Septicemia can also be one of the causative factors for hypotension especially in immunocompromised patients, however the patient's total and differential WBC counts before and after the surgery were within normal limits. His body temperature was normal. Anaphylactic reactions during anesthesia can also cause severe refractory hypotension, but that seemed unlikely in our case because the patient did not give any history of allergic reaction and neither were signs of anaphylactic reaction like skin redness, wheezing, hives, swelling of face and eyes or angiodema noted intra-operatively. The next probable cause of hypotension was considered to be the exaggerated response of antihypertensive medication. Pre-operatively he had taken the usual dose of amlodipine on the morning of the surgery.

Amlodipine, a dihydropyridine calcium channel blocker inhibits transmembrane influx of calcium ions into vascular smooth muscles and cardiac muscles by binding to voltage gated calcium channels causing decreased cardiac output and vasodilatation of blood vessels, thus decreasing blood pressure[1]. Unlike diltiazem or nifedipine, amlodipine can also induce nitric oxide dependent vasodilatation in coronary and peripheral arteries and may inhibit the angiotensin converting enzyme itself[2]. Peak plasma concentrations occur 6-8 hours after dosing and return to baseline at 24-72 hours. While there is no clear consensus on whether the drug needs to be withheld on the day of surgery, it is generally believed that most of the calcium channels blockers (CCB) can be continued in the peri-operative period[3]. There are innumerable case reports citing severe hypotension after CCB overdose[4,5], but the same with therapeutic dosage is scarcely reported[6].

Though the time of peak plasma concentration of Amlodipine occurred intra-operatively, the blood pressure did not fall drastically during surgery. It may have been maintained by increased endogenous catecholamine concentration due to sympathetic stimulation during laparoscopy[7]. At the completion of surgery, catecholamine concentration may have decreased to a level at which hypotension resulted. Hypotension did not respond to any of the vasopressors. The blood pressure slowly started increasing 8 hours after the initial fall, which co-incides with the terminal elimination half-life of Amlodipine. Omitting the morning dose of amlodipine could have avoided or at least decreased the severity of hypotension in this patient.

Conclusion

We conclude that careful titration of anti-hypertensive treatment in the peri-operative period is necessary till definite guidelines on peri-operative anti-hypertensive therapy are drawn. Blood pressure should be monitored carefully intra-operatively and it should be continued in the post-operative period as well when the stimulation of surgery has ceased.

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SUB-DURAL HEMATOMA FOLLOWING SPINAL ANESTHESIA TREATED WITH EPIDURAL BLOOD PATCH AND BURR-HOLE EVACUATION

- A Case Report -

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Abstract

The appearance of a subdural hematoma (SDH) following spinal anesthesia is a serious and rare complication which mandates prompt diagnosis, although the treatment modalities are not well codified. Patients with post-dural puncture headache (PDPH) non-responsive to conservative measures and/or those patients with a change of the character of the headache should be considered seriously. In symptomatic patients, evacuation of SDH is essential but epidural blood patch should be strongly considered as it can prevent reappearance of SDH by sealing the dural defect.

Keywords: Spinal anesthesia; Post dural puncture headache; subdural hematoma; epidural blood patch

Competing Interests: NIL

Introduction

The post-dural puncture headache (PDPH) is a known complication of spinal anesthesia, characterized by headache, commonly triggered by assuming upright posture[1]. The appearance of a subdural hematoma (SDH) is a serious and rare complication of spinal or epidural anesthesia with an accidental dural puncture which mandates prompt diagnosis, although the treatment modalities are not well codified[2].

We report a case of bilateral SDH presented with severe PDPH following spinal anesthesia, treated with simultaneous evacuation of the SDH and a lumbar epidural blood patch.

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Case report

A 49 year old gentleman presented with severe headache for three months and visual disturbances since one week. He underwent inguinal hernia surgery under spinal anesthesia three months ago, when subarachnoid block was performed successfully with 25G Quincke type spinal needle through L4-L5 inter-space, but with multiple attempts. The surgery was uneventful. Following the surgery he complained of mild headache not associated with any neurological signs, which became severe on the second post-operative day. He was treated with conservative measures: bed rest, postural adaptations, intravenous fluids and analgesics. The severity of headache decreased from the fourth post-operative day, and he was discharged on the seventh post-operative day. However the headache reappeared after 3 days, and over the next 3 months its intensity increased gradually. The nature of headache was holocranial, intermittent, not associated with vomiting, increased while standing and partially relieved on lying down. The patient also complained of visual disturbances since one week before presentation. The patient was not having any other co-morbid illnesses and was not receiving any anticoagulant medication. Computed Tomography (CT) scan on admission showed bilateral SDH over fronto-parietal region (6.8 mm on the right and 9 mm on the left). A Magnetic Resonance Imaging (MRI) taken simultaneously confirmed late sub-acute SDH. In addition it showed generalized patchy enhancements and dropping of the posterior fossa structures (Fig. 1). Considering the extent and symptomatology of SDH, a decision was made to drain the more affected side (left). Since the clinical history suggested a high possibility of an iatrogenic SDH following spinal anesthesia, an epidural blood patch was also considered to seal the dural vent which was possibly causing the persistent CSF leak, at the same time with the burr-hole evacuation of the SDH. Pre-op laboratory investigations were within normal limits.

Patient was shifted to the operation theatre and general anesthesia was administered with standard monitoring. After endotracheal intubation, an arterial catheter was inserted in the right radial artery for continuous blood pressure monitoring and also for an easy aspiration of blood for epidural blood patch administration. SDH on the left side was drained with burr-hole evacuation. Thereafter patient was placed in left lateral position, and a 16G Tuohy type epidural needle was placed through L3-L4 inter-space and

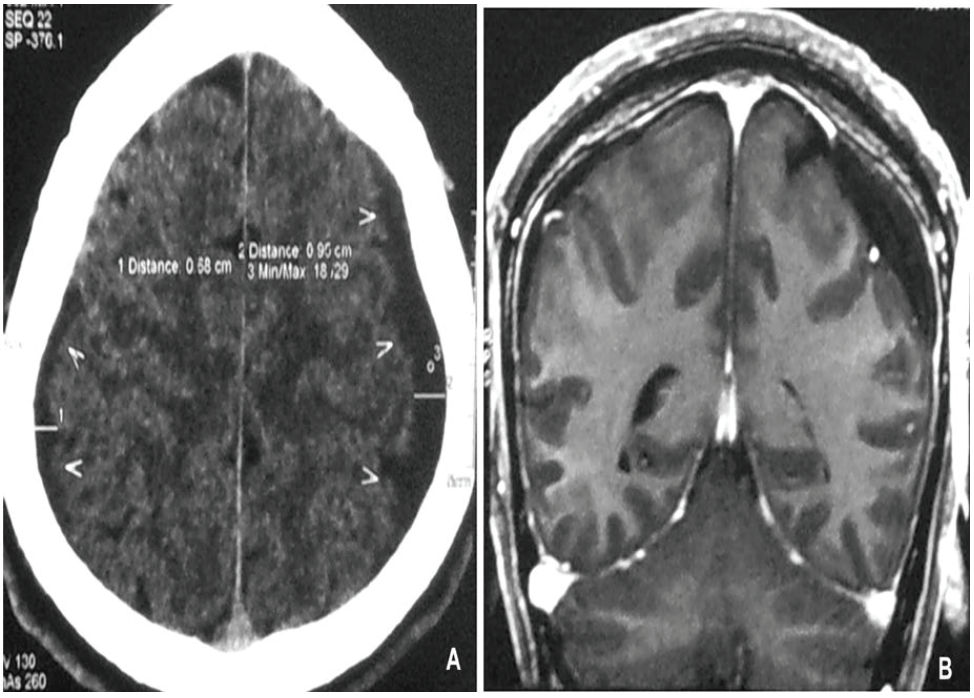

Fig. 1
Axial tomography scan (A) and coronal T1 weighted gadolinium enhanced magnetic resonance image (B) of the patient showing presence of bilateral frontoparietal chronic subdural hematomas (left > right)

carefully positioned in the epidural place. Twenty milliliters of blood was drawn from the arterial line and injected into the epidural space through the needle. The needle was carefully withdrawn and the puncture site was sealed. Patient was again turned supine, anesthetics were discontinued, and he was reversed and extubated. Following extubation the patient was conscious, alert and did not complain of headache. He reported complete relief of the residual pain from second post operative day. A CT scan performed on post-op day 5 did not show any SDH in the operated side and insignificant volume of SDH on the opposite side.

Discussion

PDPH remains a major complication of spinal anesthesia. In majority of patients this subsides within a few days with conservative measures. SDH is rare, but it can be a lethal complication following spinal or epidural anesthesia. Because of the relative rarity of this complication, it is difficult to precisely identify contributing factors. Previous studies focused on Cerebrospinal Fluid (CSF) leakage[3]. Most of the reported patients were symptomatic at diagnosis and having focal neurological signs. In those cases, the treatment was surgery; however, an epidural blood patch has a definite role in patients with PDPH without any neurological signs, when presented early. Epidural blood patch decreases the risk of SDH by preventing the reduction of CSF volume and subsequent intracranial hypotension. A recent literature has shown that 80% of patients with SDH following spinal anesthesia required surgery and the mortality rate was 20%[3]. Another series has reported the incidence of SDH as 3.5% with a mortality of 67% in patients following CSF drainage through the lumbar route[4].

The postulated mechanisms of PDPH and SDH are similar. They involve continuous leakage of CSF through the dural vent causing a reduction in CSF volume, lowering intraspinal CSF pressure and subsequently leading to intracranial hypotension. This results in caudal movement of the brain and the spinal cord, which in turn stretches the pain sensitive structures, dura, cranial nerves and the bridging veins. Following a spinal anesthesia, a dural fistula may remain patent for weeks, and the volume of CSF loss could well exceed the normal rate of production[5]. Excessive leakage of CSF leads to collapse of the ventricles, which tends to detach the brain from the dura, ultimately causing rupture of the bridging veins resulting in SDH.

In our patient, the delay in diagnosis was mainly because of the insidious onset of symptoms. The precise time of formation of SDH cannot be concluded. Once SDH develops, the intracranial pressure is increased, which can be associated with non-postural headache, disorientation and more serious neurologic symptoms. A change in headache characteristics from postural to non-postural should always be considered as a warning sign. It is evident that intracranial hypotension syndrome might be a prodrome of future development of SDH following a dural puncture.

Conclusion

Patients with PDPH non-responsive to standard conservative measures and/or those with a change of the character of the headache should be considered seriously. Systematic brain imaging might aid in detecting SDH early, considering that in majority of such patients, SDH remains unnoticed. In symptomatic patients, evacuation of SDH is essential but epidural blood patch should be strongly considered as it can prevent reappearance of SDH by sealing the dural defect.

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UNEXPECTED BRADYCARDIA AND CARDIAC ARREST UNDER SPINAL ANESTHESIA:

- Case Reports And Review Of Literature -

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Abstract

Spinal anesthesia has been regarded as safe and simple technique since its introduction into anesthesia practice. Bradycardia and hypotension under spinal anesthesia is a known phenomenon. However sudden unexpected bradycardia and cardiac arrest under spinal anesthesia is considered as rare and uncommon manifestation. On the contrary, as per current reviews, severe bradycardia and cardiac arrest under spinal anesthesia occurs more frequently in healthy, young and vagotonic patients. It is often associated with higher mortality. However, appropriate risk stratification, careful monitoring and structured management plan will have favorable outcome in these patients. We report successful management of two cases of unexpected cardiac arrest under spinal anesthesia and briefly reviewed the literature.

Key words: Spinal anesthesia, unexpected bradycardia, sudden cardiac arrest

Conflict of Interest: The authors report no conflict of interest.

Introduction

Ever since August Bier administered first clinical spinal anesthesia more than a century ago, it has become an integral part of the modern day anesthesia practice. Although considered simple to perform and relatively safe technique, life threatening complications do occur under spinal anesthesia. Bradycardia and cardiac arrests during spinal anesthesia are described as very rare and unexpected, but are not uncommon. As per current literature the incidence of cardiac arrest under spinal anesthesia (neuraxial blockade) varies from 1.3 to 18 per 10,000 cases[1].

We report occurrence of severe bradycardia followed by asystole under spinal anesthesia in two patients, who were otherwise young and healthy. This communication is to emphasize the importance of vigilant monitoring and protocol based treatment in the management of severe bradycardia and cardiac arrest under spinal anesthesia.

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Case 1

23yrs old healthy male weighing 60kg was scheduled for left inguinal hernia repair. Routine preoperative assessment was done. Patient denied any medical illness and the laboratory reports were unremarkable. Anesthetic plan was discussed and patient consented for spinal anesthesia. He was advised overnight fasting and premedicated with oral midazolam 7.5mg.

Upon arrival to the operating theatre, the patient was calm and adequately sedated (Ramsay sedation score 2). Baseline blood pressure of 140/80mmhg, heart rate 72/min and oxygen saturation 97% on room air were recorded. Intravenous access (18G cannula) was obtained and preloading was done using 15ml/kg of lactated Ringers solution. Spinal anesthesia was performed under strict aseptic technique with the patient in the sitting position. Through L3/4 interspace, hyperbaric bupivacaine 12.5mg and fentanyl 20mcg was injected into the subarachnoid space using 25 G Whitacre-type spinal needle. Block level was assessed using pinprick and sensation for cold. At 10 min, maximum sensory block up to T6 was noted. Patient was continuously monitored. In the first 20 min, blood pressure and heart rate remained stable. While patient was verbalizing with the anesthetist, and without any prodromal symptoms he developed sudden bradycardia (heart rate <30/min). Subsequently, intravenous (IV) atropine 0.5mg was administered. Intravenous fluid was also given as rapid infusion. Suddenly patient became unresponsive with asystole. Immediately IV ephinephrine 1ml (1:10000) was given and cardiopulmonary resuscitation (CPR) initiated as per ACLS (American Heart Association) guidelines. After 2 min of CPR, patient was successfully revived without any residual effect. The surgical procedure was performed as planned. Postoperative electrocardiogram and cardiac enzymes were unremarkable. The patient was transferred to high dependency unit for observation and cardiology review.

Case 2

This 26yrs old male, weighing 74kg, with ureteric stones, was scheduled for ureteroscopy. During routine preoperative visit, he was found healthy and denied any co-morbidity. His blood investigations were unremarkable. Patient accepted spinal anesthesia technique and consent was obtained. Patient was advised to fast as per guidelines and received oral midazolam 7.5mg as premedication.

On arrival to operation theatre patient was adequately sedated (Ramsay sedation score 2). Initial readings were 130/85mmHg for blood pressure, 70/min for heart rate and 99% for oxygen saturation on room air. Intravenous access was achieved using 18G intravenous cannula. Fluid preloading was done with 15ml/kg lactated Ringers. Under strict aseptic precautions with patient in the sitting position, spinal anesthesia was performed through L3-4 interspace using 25G Whitacre needle. We used 12.5mg of hyperbaric bupivacaine plus fentanyl 20mcg for subarachnoid injection. Vital signs were continuously monitored. Block level was assessed at regular intervals using pinprick and sensation for cold. At 15 min, the upper level of sensory block was T5 and patient was positioned in the lithotomy position. After 5 min post positioning, the complained of nausea. However his vital signs remained stable. While in conversation, he had abrupt bradycardia with heart rate down to 35/min. Immediately IV Atropine 0.5mg was administered and patient was repositioned in the supine position. Crystalloid rapid infusion was continued, but the patient suddenly became unconscious and developed asystole. Arrest code was activated and IV epinephrine 1ml (1:10,000) was given. He was revived after 3min of CPR and was fully awake with normal sinus rhythm. It was decided to continue with the planned surgical procedure. Post operative 12-lead electrocardiogram and cardiac enzymes were unremarkable. Cardiologist consultation was sought and patient was monitored in the high dependency unit.

Discussion

Bradycardia and cardiac arrest under spinal anesthesia is not an uncommon manifestation. It remained under reported. Ever since Caplan et al[2] reported 14 cases of cardiac arrest during spinal anesthesia in a American Society of Anesthesiologists

closed claim analysis, numerous case reports and reviews have been published[3-6].

The mechanism that triggers severe bradycardia and cardiac arrest under spinal anesthesia remains controversial and unclear. Over sedation, respiratory arrest, unintentional total spinal, myocardial infarction and local anesthetic toxicity were hypothesized as the causative factors[2-5]. However, contribution of intrinsic cardiac mechanisms and autonomic imbalance with the background of parasympathetic predominance may provide more convincing and physiological explanation for the occurrence of abrupt severe bradycardia and cardiac arrest under spinal anesthesia[7,8].

The protective cardiac reflexes triggered by hypovolemia resulting in bradycardia include, 1) right atrial stretch reflex 2) firing of low pressure barorecetpors in right atria and venacavae and 3) the paradoxical Bezold-Jarisch reflex, due to stimulation of left ventricular mechanoceptors[4,8,9]. Bradycardia represents one end of the spectrum with cardiac arrest at the other end and may also be associated with vagal symptoms including sweating, nausea and syncope. Thus onset of bradycardia may be well thought of as the warning sign of severe bradycardia or impending cardiac arrest.

Our patients were comfortable, hemodynamically stable and well oxygenated, except for the second patient who had nausea prior to bradycardia. No ischemic changes were noticed in the electrocardiogram. Causative factors like myocardial infraction, respiratory depression, local anesthetic toxicity, subdural injection and high level of spinal anesthesia were considered and excluded by the sequence of events and laboratory investigations. Thus we attributed autonomic imbalance with intrinsic cardiac reflexes as the primary trigger resulting in bradycardia and asystole in our patients.

Autonomic imbalance with background vagal dominance may intensify any tendency to bradycardia, that might otherwise been more benign, transient, or possibly unnoticed. There exist a number of risk factors (Table1) with variable impact on the occurrence of severe bradycardia and cardiac arrest under spinal anesthesia[8,10,11]. These factors may identify the vulnerable patients. However presence of two or more listed factors may place these patients at high risk for bradycardia and cardiac arrest under spinal anesthesia[8]. Due to inconsistent reporting, risk factor association with the occurrence of bradycardia and cardiac arrest under spinal anesthesia still remains uncertain and contradictory.

Table 1

Risk factors for bradycardia and cardiac arrest during spinal anesthesia

1. Age <50 years
2. Baseline heart rate <60/min
3. ASA physical status I and II
4. Use of beta blockers
5. Sensory level blockade above T6
6. Prolonged PR interval
7. Vagotonia

Hypovolemia with decreased preload may precipitate vagal symptoms and cardiac arrest in otherwise healthy patients[13]. Certain perioperative events are known to decrease preload or may cause vagal stimulation. Factors like surgical positioning, tissue retraction, bone cementing, reaming of long bones, membrane rupture and vasovagal syncope have been documented in the literature[1].

Our patients were young, healthy and with sensory block level T5/T6. There were no features suggestive of vagal predominance. Practically during routine anesthesia, it seemed unjustifiable to consider them as high risk for developing sudden and severe bradycardia under spinal anesthesia. Unexpected adverse events are known to occur under anesthesia, however being vigilant and use of a structured approach in the management of such an event still remains overemphasized.

Specific strategies to anticipate and prevent vagal predominance forms the mainstay in the management of severe bradycardia and cardiac arrest under spinal anesthesia are presented in Table2 . Appropriateness of spinal anesthesia in patients at risk must be evaluated carefully. Alternative anesthetic techniques should be considered whenever intraoperative massive blood loss or vasodilatation is anticipated. Adequate preloading and replacement of volume loss has been emphasized in number of studies[12-14].

Table 2

Management strategies for bradycardia and cardiac arrest during spinal anesthesia

Prevention: 1. Appropriate patient selection for spinal anesthesia when two or more risk factors are present (Table 1) 2. Maintaining adequate preload 3. Prompt replacement of fluid and blood loss. 4. Vigilant during patient positioning
Treatment of Bradycardia: 1. Mild to moderate bradycardia (HR 30-60/min)-stepwise escalation of therapy a. Inj Atropine 0.4-0.6mg, IV b. Inj Ephedrine 25-50mg, IV c. Inj Epinephrine 0.2-0.3mg, IV 2. Severe bradycardia or cardiac arrest a. Advanced Cardiac Life Support guidelines to be followed b. Early administration of epinephrine known to improve outcome
Management of associated factors: 1. Rapid fluid infusion 2. Patient repositioning 3. Avoid surgical manipulation

Whenever early vagolysis is required or vagal predominance continues, atropine and ephedrine must be administered. When the bradycardia is profound and unresponsive or a full cardiac arrest ensures, the early administration of epinephrine and effective cardiac compressions will be critical to maintain coronary perfusion and improve outcome. In addition, acute reduction in preload occurs during patient positioning, tourniquet release and acute blood loss. Thus rapid infusion of fluids and patient repositioning must be considered simultaneously. However, few questions still remain unanswered: 1) reliability and predictability of the stated risk factors 2) the extent of contribution of individual risk factors and 3) duration of post spinal anesthesia monitoring.

Conclusion

From literature review and our experience we conclude that bradycardia and cardiac arrest under spinal anesthesia is more common than once believed. However judicious patient selection, careful monitoring, early detection and prompt treatment may avert catastrophic outcome in these patients.

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EDUCATIONAL REPORT

WHERE ARE WE IN SIMULATION TRAINING? SIMMERK® TURKEY EXPERIENCES

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Simulation Training (ST) is a technique for practice and learning that can be applied to many different disciplines and trainees[1]. ST facilitates learning through immersion, reflection, feedback, and practice while minimizing the risks inherent in a similar real-life experience[2]. Simulators are used in various industries that include aviation, nuclear power plants, space aeronautics, the military, business, and healthcare[3].

However, Medical Simulation (MS) is still in its infancy. MS is quickly helping to train and educate medical product manufacturers, hospital personnel, nurses, physicians and residents. Furthermore, it is gradually becoming a standard part of professional training. MS is rapidly expanding as more centers are emerging around the world. These centers are bringing medical education to the next level by developing curricula that advances the technology to improve surgical skills and assess performance[4]. MS combines real life cases and studies with innovative and interactive procedures.

The simulation centers are also conducting research and providing evidence showing that MS is an effective learning tool. The Medical Device and Simulation Center (SIMMERK®) is the first MS center in Turkey. Since 2008, 2268 participants has completed medical simulation sessions at SIMMERK® in different fields of medicine such as anesthesiology, laparoscopic surgery, urology, pediatrics, radiology, and emergency medicine (Table 1). Several simulation systems are provided in SIMMERK® including high fidelity adult patient simulators (one in METI®HPS Adult and two in Leardal®SIMMAN), a high fidelity pediatric patient simulator in METI®HPS Pediatric, a high fidelity laparoscopy simulator in Surgical Science®LAPSIM, a high fidelity videoendoscopy simulator in Simbionix®GI Mentor, a high fidelity transurethral resection (TUR) simulator in Storz®TUR, a high fidelity ultrasound simulator in Schallware®, a high fidelity pulsatile organ perfuzor in Optimist®POP and a laparoscopic box trainer in I-Sim® LAP Trainer-1.

ST is superior to traditional medical teaching methods. Particularly, ST is safer, non-restrictive, repeatable, cost effective, creative, and efficient. ST provides both visual and oral education.

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Through ST, trainees can learn essential values such as positive teamwork behaviour, effective coordination, critical situation awareness, leadership comminication, crisis resource management, task management, precise decision making, effective hierarchy while they are given immediate feedback[5,6,7]. Establishing ST follows six steps as a method to enhance patient safety. These are professional skill, clinical performance, practice improvement, practice standards, patient outcome and patient safety[5].

SIMMERK is a new simulation center; however, it has made a great contribution for medical education in Turkey.

Table 1
2268 participants have attened ST in SIMMERK® between 2008 and 2012

	2008	2009	2010	2011	2012
	n = 114	n = 414	n = 605	n = 785	n = 350
ST for Anesthesiology	65	180	177	380	211
Laparoscopic ST		21	65	30	16
Radiologic ST		6	4	2	3
ST for Emercency Medicine and 112	49	202	353	316	83
Pediatric ST				45	32
ST for Urology		5	6	12	5

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