THE COMBINED EFFECT OF KETAMINE AND REMIFENTANIL INFUSIONS AS TOTAL INTRAVENOUS ANESTHESIA FOR SCOLIOSIS SURGERY IN CHILDREN

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Abstract

Background: This study was designed to assess the effect of combination of ketamine and remifentanil infusions as total intravenous anesthesia (TIVA) during scoliosis surgery in children.

Methods: Thirty two children, 8-14 yr of age, scheduled for posterior spinal fusion, were randomly allocated into two equal groups to receive either remifentanil infusion in a dose of 0.2 μg/kg/minutes or same dose of remifentanil infusion combined with ketamine infusion in a dose of 1 μg/kg/minutes after induction of general anesthesia. During surgery, hemodynamics, surgical bleeding, and electrophysiology monitors were recorded. After completion of surgery, recovery score, recovery time and rescue analgesia were assessed in post-anesthesia care unit (PACU) for 24 hours.

Results: The two groups were similar for age, weight, duration of surgery, and time to extubation. Intraoperative heart rate and arterial blood pressure were significantly decreased in remifentanil group when compated to remifentanil-ketamine group. The surgical bleeding and

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electrophysiological monitoring were not significantly affected by remifentanil-ketamine combination in second group. Recovery score and recovery time were not significantly increased in remifentanil-ketamine group. First pain scores recordings in arrival to (PACU) were significantly less in remifentanil-ketamine group than remifentanil group and the time passed to first patient controlled analgesia (PCA) demand dose was increased in remifentanil-ketamine group. The first 24 h morphine consumption was 38 ± 17 and 28 ± 10 mg (mean ± SD) in remifentanil and remifentanil-ketamine groups, respectively.

Conclusions: These data demonstrate that during posterior spinal fusion surgery in children, the combination of ketamine and remifentanil infusions as TIVA may provide hemodynamic stability, satisfactory surgical requirements with reliable electrophysiological monitoring and adequate post operative pain relief supplemented by PCA morphine.

Introduction

Anesthesia for correction of scoliosis in children is a challenge because of the frequent co-morbidities of these patients and the extensive nature of the procedure itself. Constrains put on the available anesthetic techniques, such as intraoperative spinal cord neurophysiological monitoring, is an additional factor.

The risk of spinal cord injury during scoliosis surgery could be due to direct cord contusion by the implant or an instrument, stretching or compression of the cord blood vessels, distraction cord injury and/or epidural hematoma. Ischemia is the most common injury, where the areas of the cord most vulnerable are the motor pathways supplied by anterior spinal artery[1]. Thus, early detection of ischemia by intraoperative spinal cord monitoring is a desired intervention which may prevent irreversible cord damage[2].

Typically a posterior approach is used which may involve extensive fusion of the spine, sometimes including the entire length of the thoracic and lumbar regions with the patient placed in the prone position. This group

of patients usually require multiple blood transfusions; occasionally one or more blood volumes are lost during the procedure[3]. Post operative pain is so severe that its management requires a multimodal approach[1].

Remifentanil hydrochloride, a new ultra-short-acting mu-opioid receptor agonist, is now currently used with propofol as total intravenous anesthesia (TIVA), it appears to provoke moderate to mild hypotension[4]. Also, an important concern with remifentanil infusion is the possibility of acute opioid tolerance or hyperalgesia that may increase postoperative pain[5].

Ketamine, a dissociative intravenous anesthetic, is not new. It was first used in humans in 1965. Over the years it has found many roles in pediatric practice, and remains the subject of interest in clinical investigations[6]. In recent years, investigations have led to a better understanding of its mechanism of action, its roles in analgesia and in sedation[7].

The aim of this study was to examine the hypothesis that a combination of ketamine-remifentanil and propofol infusions (TIVA) during scoliosis surgery in children, might provide more hemodynamic stability and decrease postoperative analgesic requirements.

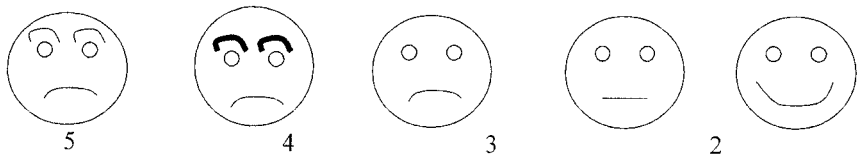
Patients and Methods

Approval of Hospital Human Ethics Committee was procured and an informed parental written consent was signed for each child. We studied 32 pediatric patients 13 (40%) males, 19 (60%) females (8-14 years old) with idiopathic scoliosis scheduled for posterior spinal fusion and instrumentation, in a prospective randomized manner. The 32 patient were randomly allocated into two equal groups to receive either remifentanil infusion 0.2 μg/kg/min (Group I) or remifentanil infusion 0.2 μg/kg/min combined with ketamine infusion 1 μg/kg/min (Group II), after induction of general anesthesia. All patients were planned to receive morphine patient-controlled analgesia (PCA) for postoperative analgesia. Exclusion criteria consisted of patients with neuromuscular disorders, severe cardiac dysfunction, need for postoperative mechanical ventilation, regular use of analgesics or opioids, a history of allergey to opioids or ketamine, inability

to understand PCA system, mental disorders, presence of severe hepatic or renal dysfunction.

The evening before surgery, patients were instructed how to use a five-point visual scale (sequence of faces – Fig. 1) on which number 1 represents no pain and 5 the worst imaginable pain, and how to use PCA machine.

Fig. 1
Sequence of faces visual analogue scale (8)



All patients were given midazolam 0.25 mg/kg orally 30 minutes before surgery. In the anesthesia waiting area, patients were prepared by a neurophysiologist for continuous intraoperative neurophysiological monitoring. Every patient had his baseline recordings and certain setups to get the best intraoperative responses as regard electroencephalogram (EEG), somatosensory evoked potentials (SSEP), and motor evoked potentials (MEP) respectively. MEP monitoring involved stimulating the motor cortex using transcranial electrical impulses and detecting the resulting signals from muscles as a compound muscle action potential (CMAPs).

TIVA technique was standardized throughout the study according to our hospital protocol for neurophysiology monitor. Volatile anesthetics, muscle relaxants and large boluses of depressive drugs were avoided to prevent false positive results.

On arrival to operating room, pulse oxymeter, ECG electrodes, and non invasive blood pressure cuff were attached to measure oxygen saturation (SpO_2), heart rate (beats/min) and mean arterial blood pressure (mmHg) respectively using an automatic device (Marquette solar 8000 anaesth, Drager, USA).

Under local anesthesia, size 20 gauge peripheral cannula was inserted for administration of anesthetics. After preoxygenation for 3 minutes by face mask with 100% oxygen, anesthesia was pre-induced with remifentanil 1 μg/kg in both groups followed by remifentanil infusion in a dose of 0.2 μg/kg/minutes in group (I), or followed by a combination of remifentanil infusion in a dose of 0.2 μg/kg/minutes and ketamine infusion in a dose of 1 μg/kg/minutes in group (II). Propofol 2 mg/kg IV bolus was given for induction in both groups followed by propofol infusion in a dose of 6 mg/kg/h, atracurium 0.6 mg/kg was given to facilitate orotracheal intubation, after which no muscle relaxants were given during surgery. The lungs were then ventilated to maintain a normocapnia with end-tidal carbon dioxide pressure around 35 mmHg using 50% oxygen in air. Bite blocker (oral airway) beside ETT was fixed in all patients as a tongue protector, because MEP monitoring results in sudden patient vigorous movements of muscle contractions. Another large size 16 gauge IV cannula was inserted in the other hand (transfusion hot line) and a radial arterial catheter size 22 gauge was inserted for continuous arterial pressure monitoring and frequent blood gase assessments. Core temperature via rectal probe was recorded throughout the surgical procedure.

Ringer's lactate was infused via IV fluid warmer at 10 ml/kg/h in addition to blood replacement as indicated. Foley's catheter connecting to a urine bag were inserted in all patients.

All patients were flipped to prone position where eyes, airway, and pressure points were checked, supported and protected. Continuous intravenous propofol and remifentanil (not ketamine) were adjusted in the two studied groups to maintain adequate anesthesia in a similar fashion.

Inadequate anesthesia was confirmed by the EEG traces given by the neurophysiology team and defined as heart rate exceeding preinduction values by 15% and/or systolic arterial blood pressure exceeding baseline values by 20%, without obvious presence of low volume status or low hematocrite for at least 1 minute.

In case abnormal neurophysiology traces were detected, all possible surgical and anesthetic causes were ruled out.

In both groups, propofol infusion was stopped on starting closure of the paravertebral muscles, while remifentanil and ketamine infusions were continued until the patient was turned to the supine position. After complete neuromuscular recovery was ensured by nerve stimulator and adequate spontaneous ventilation, the trachea was extubated in full awake state.

Post anesthesia recovery score[9] and immediate recovery time (anesthesia off to response of opening eyes on verbal command[10] were determined at 1-minute intervals from the time of discontinuation of remifentanil and ketamine infusions.

Table 1

Post-anesthesia (modified Alderet) recovery score[9]

Consciousness:	
Fully awake and oriented (name, place, date)	2
Arousable on calling	1
Not responding	0
Activity:	
Moves all four extremities voluntary or on command	2
Moves two extremities	1
Unable to move extremites	0
Respiration:	
Breathes deeply and coughs freely	2
Dyspnea, limited breathing or tachypnea	1
Apnea or on mechanical ventilation	0
Circulation:	
Blood pressure ± 20% pre-anesthetic level	2
Blood pressure ± 20-49% pre-anesthetic level	1
Blood pressure ± 50% pre-anesthetic level	0
Oxygen saturation:	
SpO_2 > 92% on room air	2
Supplemental O_2 is required to keep saturation > 90%	1
SpO_2 < 92% with O_2 supplementation	0
Maximum score:	10

In the PACU, oxygen was administered via a facemask to keep SpO_2 > 97%. The pain intensity was assessed by the patients using a five-point visual scale[8] (sequence of faces – Figure 1). Pain was controlled by titration of IV morphine boluses in doses of 0.01 mg/kg every 6 minutes administered by recovery nurses who were blinded to the treatment group until absence of any verbal or behavioral expression of pain and stopped if the respiratory rate decreased to less than 10 breath/minutes.

The PCA device (Baxter healthcare, corporation, Deerfield, IL60015, USA, Singapore made) was set to deliver morphine solution 0.5 ml (1 mg/ml) as an IV demand dose with a lockout interval of 6 minutes where neither continuous basal infusion nor top up boluses were allowed. This PCA regimen was started in PACU as soon as the patient pain score recorded 2 or less and then continued in the surgical ward.

Measurements

Heart rate (beats/min) and mean arterial pressure (mmHg) were recorded before induction and at 5-minutes intervals during surgery. Durations of anesthesia and surgery (minutes), volume of blood loss and urine output (milliliters), cases with interaoperative abnormal neurophysiology traces and those with false negative and false positive traces, were reported. Immediate recovery time and time to achieve recovery score more than 9 (minutes), were recorded.

Early pain perception was measured by the time (minutes) that passed between extubation and the first request of PCA demand dose. Primary outcome was the consumption of morphine given by IV titration and by PCA device during the first 4 h after extubation. Prolonged pain perception was measured by patients' total consumption of morphine (milligrams) over the 24 hours postoperatively.

Anesthetic-related complications, including nausea, vomiting, pruritus, dysphoria, hallucinations, diplopia, vision loss, shivering and respiratory depression, were recorded and managed accordingly.

Data were expressed as mean ± standard deviation and were analyzed using Student's and Chi-square tests at 0.05 level and significance.

Results

The two studied groups were comparable as regards age, weight, sex, duration of surgery and anesthesia (Table 2).

Table 2

Age, weight, sex, duration of surgery and anesthesia in Groups I & II

	Group I (n = 16)	Group II (n = 16)	P value
Age (years)	12.8 ± 6.07	13.1 ± 5.08	0.321
Weight (kg)	34.6 ± 9.68	39.7 ± 8.63	0.29
Sex (M: F)	6: 10	7: 9	0.41
Duration of surgery (min)	240.1 ± 3.3	235.4 ± 3.6	0.49
Duration of anesth. (min)	271.6 ± 5.3	266.7 ± 3.5	0.27

Data are mean ± SD.

M = male, F = female.

No differences in baseline values of hemodynamic variables were observed in both groups. The HR and MABP decreased significantly ($p < 0.05$) in remifentanil Group (I) than in ketamine-remifentanil group (II) (Fig. 2 and Fig. 3).

Fig. 2

Changes in heart rate (beat/min), in Groups I & II

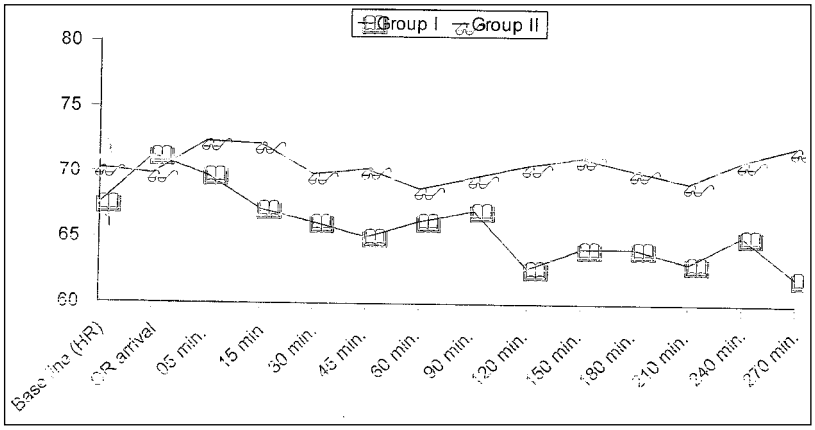
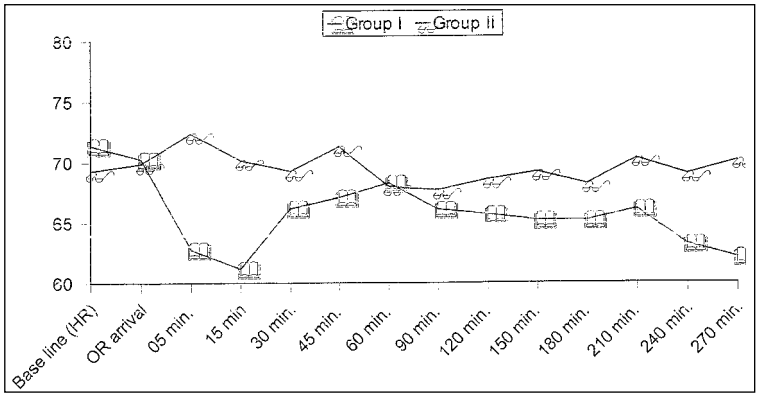


Fig. 3

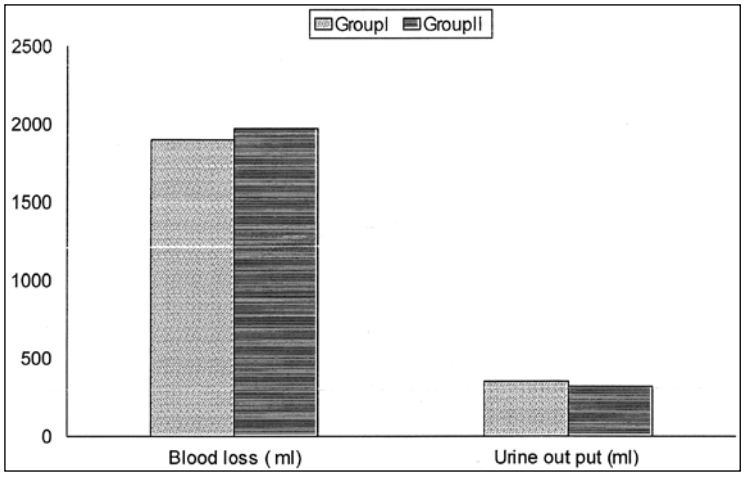
Changes in mean arterial blood pressure (mmHg), in Groups I & II



There was no significant differences between the two groups regarding both blood loss and urine flow. The mean values of blood loss were 1900 ± 5.6 ml in remifentanil group (I) and 1973 ± 8.1 ml in ketamine-remifentanil group (II). Mean urine volume was 350 ± 3.2 ml during a mean operative time of 271.6 ± 5.3 minutes in remifentanil group (I), and 318 ± 6.3 ml over 266.7 ± 3.5 minutes in the ketamine-remifentanil group (II) (Fig. 4).

Fig. 4

Intraoperative blood loss and urine out put, in Groups I & II



Under neurophysiological monitoring, both techniques produced reliable recordings of EEG, SSEP, and CMAPs. CMAPs traces were more enhanced in all patients of ketamine-remifentanil group (II). There were no false negative reports and there was only one persistent false positive report in the remifentanil group (I) who did not show postoperative neurologic deficit.

Regarding the immediate recovery time, time to achieve recovery score more than 9 and time passed to first PCA request in PACU, all were significantly increased ($p < 0.05$) in ketamine-remifentanil group (II) when compared to remifentanil group (I) (Table 3).

Table 3
Recovery times in both Groups I & II

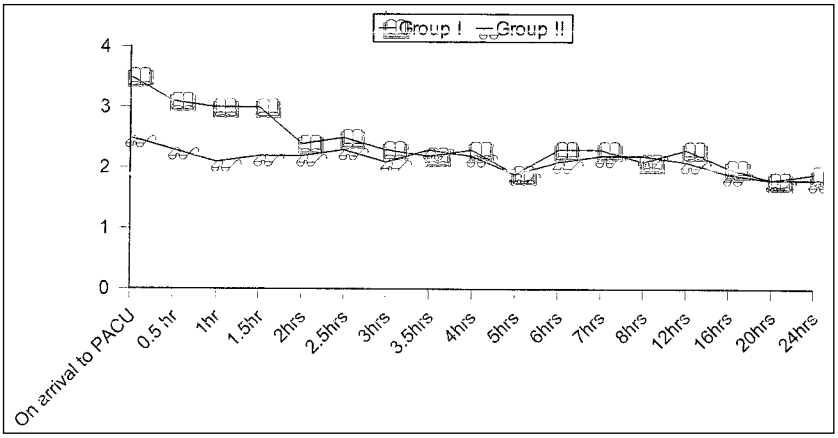
	Group I (n = 16)	Group II (n = 16)	P
Immediate recovery time (min)	3.7 ± 1.6	6.9 ± 3.1	0.0025*
Time to achieve recovery score > 9 (min)	6.2 ± 2.3	8.4 ± 5.2	0.027*
Time to first PCA dose request in PACU (min) (Early pain perception)	19.6 ± 3.3	23.2 ± 3.2	0.001*

Data are mean ± SD.

The pain scores during the first 6 hours were significantly lower ($p < 0.05$) in ketamine-remifentanil group (II) than in remifentanil group (I). Then after and until the end of the 24 hrs, the postoperative pain scores were similar in both groups. No significant difference was detected (Fig. 5). Accordingly, the total 24 hours postoperative morphine consumption, prolonged pain perception, as calculated by PRN boluses in PACU and PCA machine, showed that ketamine-remifentanil patients (Group II) were significantly (27%) less ($p < 0.05$) consumed morphine than remifentanil patients (Group I). The cumulative 24 h morphine consumption was 38 ± 17 mg and 28 ± 10 mg (mean ± SD) in remifentanil (Group I) and ketamine-remifentanil (Group II), respectively.

Fig. 5

Pain score on visual scale, Groups I & II



No patients in either group reported hallucinations or visual loss and no differences were noted in the incidence of pruritis and postoperative nausea and vomiting in the two groups.

Discussion

Anesthesia for scoliosis surgery has evolved over the last decade. New drugs and techniques allow intraoperative monitoring of motor pathways, permitting safer correction. The goals of monitoring are to warn the surgeon of impending ischemia to the spinal cord before permanent damage occurs and to help predict the neurological outcome of the patient.

The purpose of this study was to assess the effects of low constant dose of ketamine infusion when combined to the remifentanil-propofol total intravenous anesthesia (TIVA) during spinal surgery, in achieving the goals of motor pathway monitoring as well as hemodynaemic stability, satisfactory surgical conditions, recovery profile and postoperative analgesia. Hemodynamically, the HR, and MABP were significantly decreased in the remifentanil group (Group I) than in the ketamine-remifentanil group (Group II).

Previous studies have shown an unacceptable incidence of bradycardia associated with the use of remifentanil in the absence of a vagolytic drug[11].

However, opioid-induced bradycardia is generally accepted to be vagally mediated[12]. It also could be due to the impairment of baroreflex regulatory mechanisms caused by propofol infusion[13].

Several studies have demonstrated that remifentanil causes arterial hypotension and bradycardia with IV anesthetic agents[14] or general anesthetics[15]. In contrast, Glass et al. observed increased arterial blood pressure and heart rate after IV injection of remifentanil alone without any other agents on board, in unpremedicated healthy volunteers[16].

In the present study, the bradycardia and hypotention observed could be exaggerated in Group I patients either due to prone position, with or without blood loss, fluid shifts, and co-existing cardiac pathology[17]. Degoute et al found that remifentanil hydrochloride, which is currently known to have a hypotensive side-effect during a propofol total-intravenous anesthesia, was effective in inducing consistent and sustained controlled hypotension[18]. Sammons, AW et al. found that remifentanil produced profound hypotension as compared to fentanyl when used for day case microlaryngoscopy[19]. Kurdi, Okba et al. reported asystole during anesthetic induction with remifentanil and sevoflurane to a 78-yr-old man who was suffering from laryngeal cancer, and was scheduled for laryngeal endoscopy[20]. Also, Altermatt and Munoz reported asystole with propofol and remifentanil TIVA for a 52-yr-old obese woman admitted for elective cervical spine surgery[21].

In the ketamine-remifentanil Group II, the HR and MABP did not decrease below the preoperative values due to the catecholamine release of probably ketamine, commonly resulting in both tachycardia and hypertension[22], an action that attenuate remifentanil effects. We chose to use low constant dose of ketamine in the hope that a lower dose would lead to less tachycardia and hypertention and shorter duration of action, resulting in a lowered incidence of postoperative hallucinations and emergence delirium. In agreement with our results, Katz et al. found that alfentanil with ketamine resulted in significant obtundation of tachycardia and hypertension of ketamine after intubation, with little or no change in HR or ABP[23].

We found no significant difference between the two studied groups regarding blood loss and urine flow. The mean values of blood loss in both groups were 1900 ± 5.6 and 1973 ± 8.1 ml respectively. All patients required intraoperative packed RBCs to keep hemoglobin concentration above 9 grams/dl. On the other hand, both groups had adequate urine output where remifentanil group showed a mean urine volume 350 ± 3.2 ml during a mean operative time of 271.6 ± 5.3 minutes, while in ketamine-remifentanil group a mean urine volume was 318 ± 6.3 ml over 266.7 ± 3.5 minutes. This is possibly due to careful fluids and replacement therapy.

Continued reports of false negative SSEP monitor, made Winter (1997) to conclude that SSEP alone does not appear adequate as it monitors only the dorsal sensory pathway but no the most vulnerable anterior motor pathway[24]. Transcranial stimulation with recording of potentials from muscle depolarization results in CMAPs which monitor anterior motor pathway.

In the present study, our both techniques produced reliable recordings of EEG, SSEP, and CMAPs. By using adequate dose of remifentanil in Group I and adding ketamine in Group II both allowed marked reduction of propofol doses used which may not markedly depress SSEP and CMAPs. Remifentanil in a dose of 0.2 μg/kg/minutes may have a small hypnotic effect and has little depressive effects on both modalities except in large bolus doses[25]. It may be possible that the great advantage of adding ketamine in dose 1 μg/kg/minutes consists of enhancing the generation of CMAPs[26].

With regard to recovery from anesthesia, we found that after remifentanil-propofol technique, patients recovered quicker than those given the ketamine-remifentanil-propofol technique. This acceleration of recovery is not limited to the initial period of awakening from anesthesia; it also provided a higher recovery score (more than 9) allowing earlier neurological examination. These results are due to the short terminal plasma half-life of remifentanil which is 8-10 min and its context-sensitive time (i.e. biological half-life) which is 3-5 minutes[27]. In contrast with other opioids in the fentanyl family, the context-sensitive time of remifentanil is

independent of duration of infusion[7]. The presence of an ester side chain allows remifentanil to be rapidly broken down by non-specific esterases to nearly inactive metabolites, so recovery from intraoperative infusion can be rapid[28].

The time to first PCA dose request in PACU (Early pain perception), was significantly less in remifentanil Group I. This could be due to hyperalgesia of surgical injury and the development of opioid-induced tolerance related to remifentanil infusions. Both involve activation of N-methyl-D-asparate (NMDA) receptors in CNS, and subsequent biochemical processes resulting in centeral sensitization, increase spinal dynorphin activity and activation of intracellular protein kinase C[29]. Sharing of NMDA receptor activation by both processes suggests that ketamine, an NMDA receptor antagonist, in ketamine-remifentanil group may substantially enhance opiate-induced antinociception[30].

Frederic Adam[31] and his colleagues evaluated the effect of ketamine in a dose of 1.5 μg/kg/min for post operative pain relief and the total morphine consumption after total knee artheroplasty. They found that ketamine group required significantly less morphine than control group with early knee mobilization. Subramaniam K[32] and his colleagues investigated ketamine in 2280 patients of them 1412 received ketamine added to opioid analgesia. They concluded that addition of ketamine either IV bolus or continuous IV infusion, is more effective than morphine alone, while IV PCA of ketamine and morphine was not more effective than IVPCA morphine alone.

The quality of postoperative analgesia depends, in part, on the opioid infused during surgery. Different protocols have been studied after remifentanil infusion to reduce postoperative pain. After major surgeries, morphine 0.15 mg kg^{-1} given 30 min before the end of surgery, seems to provide acceptable pain relief. Despite this precaution, postoperative analgesic requirement often increased when patients receive relatively large intraoperative doses of remifentanil[33].

The results of the present study showed that continuous intraoperative ketamine-remifentanil combined infusions (Group II), when compared to continuous remifentanil infusion alone (Group I), the postoperative pain

scores and total morphine consumption were significantly decreased in the ketamine-remifentanil Group II. Ketamine may produce antinociception through interaction with spinal mu receptor, NMDA receptor antagonism, and activation of the descending pain inhibitory monoaminergic pathways[34], which is expressed by alpha2-adrenoceptors at the spinal level[35]. Although antinociception after the intrathecal administration of ketamine is reversed by naloxone in rats[34], analgesia produced in humans by systemic ketamine up to 300 μg/kg is not reversed[36], which suggests that the monoaminergic activation, rather than mu receptor agonist activity, may be involved in antinociception produced by analgesic doses of ketamine.

Despite the small ketamine dose used in our study, it produced significant decrease in postoperative pain scores and morphine consumption. The affinity of ketamine for NMDA receptors has been shown to be more than an order of magnitude higher than that for mu receptor[36] and several-fold higher than that for monoamine transporter sites or other non-NMDA receptors (i.e., acetylcholinesterase and the epsilon receptor)[37], which suggests that the smaller the dose, the more selective is the ketamine interaction with NMDA receptors. Other studies have shown that analgesia produced by the systemic coadministration of an opiate and an a2-adrenoceptor agonist (e.g., clonidine or meditonidine) is additive[38].

In agreement with our results, Stubhaug et al. showed in humans that 48-h continuous administration of small-dose ketamine, together with patient-controlled analgesia (PCA) with morphine, prolonged the time to the first use of PCA-morphine and reduced cumulative morphine[39]. Other studies have demonstrated a marked decrease in opiate consumption and/or pain intensity by systemic[40] or epidural[41] coadministration of ketamine and opiates. Guignard et al.[42] reported that adults receiving large dose remifentanil infusion for colorectal surgery, needed nearly double the amount of morphine and had higher pain scores in the first 24 hours after surgery as compared with patients administered small dose remifentanil infusion.

In contrast to our results, Schraag et al.[43] studied adult patients using target controlled infusions of alfentanil or remifentanil for post

operative self administered analgesia. They concluded that acute tolerance to alfentanil or remifentanil did not develope. Cortinez et al.[44] found no difference in morphine consumption or pain scores in patient randomized to receive remifentanil (0.23 μg/kg/min) or sevoflurane anesthesia for gynecological surgery.

Theoretically, coadministration of an opiate and ketamine reduces the doses of opiate and ketamine required for optimal pain relief below that required when used alone and thus may lower the incidence of side effects. Despite the larger dose of morphine consumption in remifentanil group, there was no significant difference in postoperative nausea, vomiting and pruritus between the two groups.

In summary, our results demonstrate that during posterior spinal fusion surgery in children, the combination of ketamine and remifentanil infusions as TIVA may provide more hemodynamic stability, satisfactory surgical requirements with reliable electrophysiological monitoring and adequate post operative pain relief.

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