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Remifentanil in combination with ketamine versus remifentanil in spinal fusion surgery – a double blind study

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Abstract. Aim: This study is aimed at conducting a program for two different anesthetic methods used during a spinal fusion surgery to ensure better intraoperative hemodynamic stability and post-operative pain control. Methods: A prospective, randomized, double blind study in patients scheduled for spinal fusion surgery, who were randomly allocated to two groups, G1 and G2, (n = 15 per group), class I – II ASA, was carried out. Both groups received pre-operatively midazolam, followed intra-operatively by propofol, sevoflurane, atracurium, and either remifentanil infusion 0.2 μg/kg/min (G1), or the same dose of remifentanil infusion and low doses of ketamine infusion 1 μg/ kg/min (G2) anesthetics, antidote medication and post operative morphine doses. HR, MAP, vital signs, surgical bleeding, urine output, duration of surgery and duration of anesthesia were recorded. In a 24 h recovery period in a post-anesthesia care unit (PACU) the recovery time, the first pain score and analgesic requirements were measured. Results: Intra-operative HR and arterial BP were significantly less ($p < 0.05$) in G1 as compared to G2. In the PACU the first pain scores were significantly less ($p < 0.05$) in G2 than in G1. The time for the first patient analgesia demand dose was greater in G2, as also morphine consumption which was greater in G1 than G2 ($p < 0.05$). Other results were the same. None of the patients had any adverse drug reaction. Conclusions: Adding low doses of ketamine hydrochloride could be a routine therapy to improve the hemodynamic stability and reduce the postoperative morphine consumption during spinal fusion surgery.

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Introduction

The intraoperative hemodynamic stability of a patient during surgery, the severity of their postoperative pain and the requirements for subsequent analgesic consumption, are all major challenges for the surgical team. Using different anesthetic strategies during surgery may positively influence subsequent analgesic requirements.

Remifentanil is a highly selective opioid analgesic, acting on mu opiate receptors. It is used with propofol to achieve a state of total intravenous anesthesia (TIVA) which also produces a more hypotensive effect as compared to other opioids [1]. It has an ultra short duration of action as compared with other mu receptor agonists. This short duration of action is exemplified by the finding that no residual effects are observed 5 – 10 minutes after stopping its administration. This property can be considered as a disadvantage of remifentanil in that the post-operative residual effect is minimal [2].

In the world literature concerning spinal fusion surgery little information exists as to how appropriate it is to use remifentanil in combination with low doses of ketamine for this type of surgery.

Ketamine hydrochloride is a nonbarbiturate intravenous anesthetic. Its anesthetic and analgesic effects are mediated primarily by a non-competitive antagonism at N-methyl-D-aspartic acid (NMDA) receptors. This drug has a preference for mu receptors, the stimulation of which is responsible for the analgesic effect of a low dose of ketamine, and this it is believed produces an opioid sparing effect during the postoperative use of analgesics.

In contrast to remifentanil, the blood pressure and the pulse rate are frequently elevated following the administration of ketamine alone. The elevation of blood pressure begins shortly after its administration, reaching a

Figure 1. Expresses the degree of pain according to facial expression. To use this scale, your doctor should explain that each face shows how a person in pain is feeling.

- Face 0 is very happy because he or she does not feel any pain.
- Face 1 feels a little pain.
- Face 2 feels a little more pain.
- Face 3 feels even more pain.
- Face 4 feels a lot of pain.
- Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad.

We considered the degree of pain as, no pain (face one) and pain (face 1, 2, 3, 4, 5).

maximum within a few minutes and usually returns to pre-anesthetic values within 15 minutes after cessation of its administration [3].

Postoperative pain is one of the most common therapeutic problems in hospitals [2] and many surveys have shown a high prevalence of significant pain after surgery [4]. A full understanding of the pharmacology and the mechanism of drug action can help to devise different anesthetic strategies which can be used both intra- and postoperatively.

It was intended to examine the hypothesis of using remifentanil and propofol infusions for TIVA with or without ketamine by determining if ketamine's use would alter the consumption of post-operative morphine.

Patients and methods

The Human Investigation section of the Institutional Review Board of the Arab Center Hospital, Amman, Jordan, read, considered and subsequently approved the ethics of this investigation and so gave their formal permission for this study to be carried out.

A prospective, randomized, study undertaken between Jan 2007 to Jan 2009 was carried out by the same surgical and anesthetic teams in one hospital in Amman.

All patients were informed about the details of the procedures and written consent was obtained for each patient. Patients who were studied were scheduled for posterior lumbar and thoracic spinal fusion surgery. In total 30 adult patients were allocated randomly to two equal groups, Group 1 (G1), 3 males and 12 females, and Group 2 (G2), 7 males and 8 females. The age range and weight of the patients in G1 were 49 – 58 years and 68 ± 12 kg respectively, while in G2 patients these were 53 – 59 years, and 66 ± 13 kg.

In this study a number of 'activities' were performed on both G1 and G2 patients.

The authors had a pivotal educational role in the different stages of the surgery and for patients before their operation, so as to allay their fears and apprehensions and to minimize the consequences of this very painful surgical experience.

The patients were tested pre-operatively to check their well-being and health conditions.

Furthermore, a scheme had been designed which ensured that plans were in place to ensure that all patients received morphine as a postoperative analgesic. To ensure that the patients received adequate analgesia post surgery, on the evening before their operation they were instructed how to use the visual face rating scale. This enabled patients when asked to point to various facial expressions ranging from a smiling face (no pain) to an extremely unhappy one that expresses the worst possible pain. [5] (Figure 1)

An active "follow up" was carried out for each patient, by conducting a post operative questionnaire, determining for both groups of patients their satisfaction about the care they had received.

Finally, during the entire study, steps were taken so that any occurrences of drug allergic responses and adverse effects could be recorded.

Chart review for medication selection

All drugs and drug doses used were accurately measured and fully documented in the patients' medical charts at the time of their administration.

Anesthesia

All patients were given midazolam 0.25 mg/kg orally 30 minutes before surgery as a

Table 1. The medications given for G1 and G2 patients during spinal fusion surgery.

Stages of medication admission	Groups of medications	Medication given	G1	G2
I- pre-operative	Sedative	Midazolam G1, G2		
II- Intra-operatively	Anesthetics:			
	i.v.	Propofol		
		Ketamine	–	
	Inhalers	Sevoflurane		
	Analgesics	Remifentanil		
	Muscle relaxants	Atracurium		
	Antidote	Neostigmine		
		Atropine,		
III- Postoperative	Analgesics	Morphine		

Key: = used, - : not used.

premedication. On arrival at the operating theater, the following drugs were given intraoperatively: Propofol 2 mg/kg IV bolus was given for induction in both groups followed by propofol infusion at a dose of 6 mg/kg/h and atracurium 0.6 mg/kg to facilitate orotracheal intubation just at the induction. Sevoflurane (1 – 1.5% v/v) in a carrier gas of a 1:1 nitrous oxide: with oxygen mixture was used for all patients. Anesthesia was pre-induced using remifentanil 1 μg/kg in both groups followed by remifentanil infusion at a dose of 0.2 μg/kg/minute, and a placebo infusion of normal saline 0.9% in G1 given at the same volume and rate as for the ketamine infusion (see below). In G2, a combination of remifentanil infusion at a dose of 0.2 μg/kg/minute plus a recemic ketamine infusion (Tekam Al-Hikma, Jordan) at a dose of 1 μg/kg/minute administered using two different cannulas (Table 1).

The lungs were ventilated to maintain a normocapnia with end-tidal carbon dioxide pressure around 35 mmHg using 50% oxygen in air. Continuous arterial pressure monitoring and frequent blood gas assessments were carried out on all the patients.

Patients received intravenously infused crystalloid in Ringer's lactate at a rate of 10 ml/kg/h. Blood loss was continuously collected and measured using "gauze and bottle suction technique" where the lost blood is continuously collected and which has been described elsewhere [1]. Briefly, the blood was very carefully collected, measured, its volume recorded and an equivalent volume of packed red blood cells was transfused when the blood loss exceeded 500 ml. In addition a Foley's catheter connected to a urine bag was inserted in all patients.

At the end of the operation all drugs were stopped, both groups received antidotes namely – neostigmine (2.5 mg/IV) and atropine (1 mg/IV) which were administered together in a single bolus dose from one syringe followed by 100% oxygen (Table 1).

Post operative analgesic administration

The severity of postoperative pain was assessed during the first 24 hours after the surgery by means of the visual face rating scale and was controlled by IV morphine. The morphine infusion pump was set to deliver a morphine solution of 1 mg/ ml at a rate of 3 – 5 mg/h in the PACU.

Quantitative Measurements made during the operation

To ensure the data was collected independently from the clinical pharmacist who organized the study or from any health professional members who were aware of the protocol, all the data was collected by pharmacy students, who had received very specific tuition but who were blind and not aware of the contents of the solutions which were at all times under the supervision of highly trained research technicians and nurses.

Heart rate (beats/min) and the mean arterial pressure (MAP) (mmHg) were recorded at 5-minute intervals during surgery where the dose of the infused drugs was adjusted to keep the MAP around 60 mmHg. The durations of anesthesia, the total time of the surgery (min), the volume of blood loss (ml), urine output (ml) and the immediate recovery time (min) were recorded. The early pain perception was measured by the time (min) that passed between extubation and the first request for a dose of analgesic. Total consump-

Table 2. Clinical measurements made during spinal fusion surgery for G1 and G2.

	G1	G2
Heart Rate (beats per minute)	67 ± 4	70 ± 1*
MAP (mmHg)	60 ± 2	66 ± 5*
Total blood loss (ml)	1800 ± 50.6	1833 ± 80.1 n.s.
Total urine out put (ml)	350 ± 3	337 ± 6 n.s.
Duration of surgery (min)	242.1 ± 3.3	238.4 ± 3.6 n.s.
Duration of anesthesia (min)	273.6 ± 5.3	266.7 ± 3.5 n.s.

*Signifies $p < 0.05$, n.s. = not significant, data are expressed as the mean ± 2SD.

Table 3. The differences in pain score between G1 and G2.

Number of patients with:	G1	G2	No.	Statistic
No pain	2	10	G1 + G2 12	
With pain	13	5	G1 + G2 18	$p < 0.05$

tion of morphine (mg) over the first 24 hours postoperatively was calculated. Finally, anesthetic-related complications, including nausea, vomiting, pruritus, dysphoria, vision loss, shivering and respiratory depression were recorded and managed accordingly.

Data analysis

Data were expressed as mean ± 2SD and were analyzed using the ^{2}-test and the Student's t-test. A p value < 0.05 was considered significant.

Results

Pre-surgical drug history

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

The analysis showed that there were no significant differences between the numbers of males and females in their respective groups and also for comparisons made between G1 and G2 for their ages, and body weight. In the absence of any significant differences being found they were subsequently considered as one group despite their apparent gender and age differences.

After the pre-operative tests, patients were found to be free of any major systemic disease such as coronary heart disease or hypertension and they were fit to be operated upon according to the criteria used by the anesthesiologists involved in this study.

Intra operative and Post surgical analysis

The HR was 67 ± 4 beats per minute for G1 and 70 ± 1 beats per min for G2, while MAP was 60 ± 2 mmHg for G1 and 66 ± 5 mmHg for G2, These results are significantly lower ($p < 0.05$) in G1 than in G2 (Table 2). However there were no significant differences between the two groups regarding blood loss which was 1800 ± 50.6 ml for G1, and 1833 ± 80.1 ml for G2. Also there were no differences in the urine flow which was 350 ± 3 ml for G1 and 337 ± 6 ml for G2. The mean operative time was 242.1 ± 3.3 min for G1 and 238.4 ± 3.6 min for G2, and duration of anesthesia was 273.6 ± 5.3 min for G1 and 266.7 ± 3.5 min for G2 (Table 2). Neither of which were significantly different.

The immediate recovery time was 3.3 ± 2.6 min for G1 and 7.1 ± 2.8 min for G2, and the time which went past to the first patient's analgesia request in PACU was 19.5 ± 3.2 min for G1, and 22.9 ± 3.5 min for G2; these results were significantly greater ($p < 0.05$) in G2 as compared to G1 (Table 3).

In G1, two patients had no pain, while 13 patients complained of different degrees of pain. In contrast, 10 patients from G2 had no pain, while just 5 of them complained of different degrees of pain (Table 3).

For G1, the dose needed for patients to ask for morphine was 60 ± 10 mg, as compared to G2 patients who had a mean dose of 45 ± 5 mg. This result was significant different ($p < 0.05$) during the first 24 hours after surgery as compared to G1 (Table 4).

Potential for drug allergic responses and adverse effects

No patients in either group reported dysphoria or hallucination, shivering and respiratory or visual loss but no differences were

Table 4. Post surgical analysis for G1 and G2.

	Group 1 (n = 15)	Group 2 (n = 15)
Immediate recovery time (min)	3.3 ± 2.6	7.1 ± 2.8*
Time to first patient analgesia dose request in PACU (min)	19.5 ± 3.2	22.9 ± 3.5*
Needed dose of morphine (mg)	60 ± 10	45 ± 5*

*Signifies $p < 0.05$, data are mean ± SD.

noted in the incidence of pruritis and postoperative nausea and vomiting in the two groups.

Discussion

Hemodynamically, the HR and MAP were significantly lower in G1 than in G 2. Several studies which have been previously reported agree with the findings in this paper as remifentanil has been shown to cause arterial hypotension and bradycardia with IV anesthetic agents or general anesthetics [1, 6, 7].

In G 2, a low dose of ketamine was chosen because this lower dose would lead to less tachycardia and hypertension and a shorter duration of action, potentially resulting in a lowered incidence of ketamine side effects such as, postoperative hallucinations and emergence delirium. The finding that the HR and MAP did not decrease below the normal values may be explained by previous reports where catecholamine release by ketamine has been reported to commonly cause both tachycardia and hypertension. [8, 9]

However, no significant difference was discovered between the two groups regarding blood loss and urine flow. The same blood loss suggests the degree of trauma and subsequent vascular "leakage" experienced during the operative procedure was similar in both groups. The finding that both groups had adequate urine output is possibly due to the very careful fluid replacement therapy carried out during the surgical procedure.

As regards the recovery from anesthesia, it was found that patients in G1 recovered quicker than those given the ketamine-remifentanil-propofol technique in G2. These results are perhaps due to the short terminal plasma half-life, 3 – 5 minutes, of remifentanil [10]. The presence of an ester side chain allows remifentanil to be rapidly broken down by non-specific esterases to inactive metabolites, so that recovery from an intraoperative infusion can be rapid [11]. In contrast, in G2, the long elimination half life of ketamine (2.3 ± 0.5 hours), delays the patients' recovery [12].

The time to the first request for patient controlled analgesia in PACU was significantly less in G I. This could be due to hyperalgesia induced by surgical injury and the development of opioid-induced tolerance related to remifentanil infusions. Both involve activation of N-methyl-D-asparate (NMDA) receptors in the CNS, and subsequent biochemical processes resulting in central sensitization, increase spinal dynorphin activity and activation of intracellular protein kinase [13]. Sharing of NMDA receptor activation by both processes suggests that ketamine, an NMDA receptor antagonist, in the ketamine-remifentanil group may substantially enhance opiate-induced antinociception [14].

Frederic Adame and colleagues [15] 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. Their results confirmed that ketamine is a useful analgesic adjuvant in perioperative multimodal analgesia with a positive impact on early knee mobilization. They also confirmed that their patients required significantly less morphine than the control group.

Continuous intraoperative ketamine-remifentanil combined infusions (G2), when compared to continuous remifentanil infusion alone (G1), resulted in the postoperative pain scores and total morphine consumption being less in G2. Ketamine may produce antinociception through interaction with spinal mu receptors, NMDA receptor antagonism and activation of the descending pain inhibitory monoaminergic pathways (16), which is expressed by 2-adrenoceptors at the spinal level [17]. Analgesia produced in humans by systemic ketamine up to 0.3 mg/kg is not reversed [18], which suggests that the analgesic effect of ketamine is mediated by a non-opioid mechanism, possibly involving Phencyclohexyl piperidine receptor-mediated blockade of the NMDA-receptor-operated ion channels.

Even though a smaller ketamine dose was used in this study, it produced a significant decrease in postoperative pain scores and mor-

phine consumption. The affinity of ketamine for NMDA receptors has been shown to be more than an order of magnitude higher than that for mu receptors [19] and several-fold higher than that for monoamine transporter sites or other non-NMDA receptors (i.e., acetylcholinesterase and the epsilon receptor) [20], which suggests that the smaller the dose, the more selective is the ketamine interaction with NMDA receptor. A further development might be to use the observations of Ossipov and his colleagues who have shown that analgesia produced by the systemic coadministration of an opiate and 2-adrenoceptor agonist, for example clonidine or meditonidine, are synergistic [21] which may reduce opiate use even further.

Our results agree with those of Stubhaug et al. who showed that a low-dose IV infusion of ketamine during and after surgery reduces mechanical punctuate hyperalgesia surrounding a surgical incision. This indicates that the blockade of NMDA receptors prevents the central sensitization caused by nociceptive input during and after surgery [22]. Other studies have demonstrated that ketamine in combination with morphine provides superior postsurgical pain relief at a lower dosage and with fewer side effects than morphine alone [23].

Conclusion

These results demonstrate that the combination of low dose ketamine and remifentanil infusions as TIVA may provide better hemodynamic stability, so satisfying a major surgical requirement. Additionally it enables a reliable and adequate post operative pain relief to be achieved, reducing the postoperative consumption of morphine.

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