The influence of anaesthetic drug selection for scoliosis surgery on the management of intraoperative haemodynamic stability and postoperative pain – pharmaceutical care programme

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ABSTRACT

Aim: The aim of this study was to conduct a pharmaceutical care programme for two different anaesthetic methods used during scoliosis surgery, to investigate which method ensured better intraoperative haemodynamic stability and postoperative pain control.

Methods: A clinical pharmacist actively participated in a prospective randomised double blind study for 40 patients who had a physical status class I-II ASA, scheduled for scoliosis surgery, who were randomly allocated into two groups, 20 in each group. Both groups received midazolam preoperatively, propofol, sevuflorane, atracurium, and either remifentanil infusion 0.2 μg/kg/min for (Group 1 = G1), or the same dose of remifentanil infusion and low dose ketamine infusion 1 μg/kg/min (Group 2 = G2), antidote medications and postoperative morphine. Patients were subject to a pharmaceutical care programme. Heart rate HR, MAP, vital signs, surgical bleeding, urine output, time to accomplish the wake up test, duration of surgery and duration of anesthesia were recorded. In postanesthesia care unit (PACU) for 24 hours, the recovery time, the first pain score and analgesic requirements were assessed. All drugs used were documented in medical charts for statistical analysis.

Results: Intraoperative heart rate and arterial blood pressure were significantly less ($p < 0.05$) in G1 as compared with G2. In the (PACU) the first pain score recordings were significantly less ($p < 0.05$) in G2 than G1. The time which passed until the first patient analgesia demand dose was greater in G2 and morphine consumption was greater in G1 than G2 ($p < 0.05$). The rest of the results were not significantly different between the two groups. None of the patients had any allergic or adverse drug reaction to any of the medications.

Conclusions: Adding a low dose ketamine hydrochloride infusion during scoliosis surgery could be applied as a routine therapy to improve the haemodynamic stability during the surgery and reduce the postoperative morphine consumption. A pharmaceutical care programme tested in this study gave a high score for patient satisfaction.

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Introduction

Intraoperative haemodynamic stability of patients during scoliosis surgery, the severity of the postoperative pain and the requirements for subsequent analgesic consumption, are major challenges for both the anesthetist and the clinical pharmacist, who has to advise on the best anaesthetic/analgesic drugs which are to be used.

Using different anaesthetic strategies during surgery may positively influence all the above challenging areas of this type of surgery.

Remifentanil is a highly selective opioid analgesic, acting on mu opiate receptors. It is used with propofol as total intravenous anesthesia (TIVA) and it also produces a more hypotensive effect as compared with 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 point can be taken as a disadvantage of remifentanil in that the postoperative residual effect is minimal.[2]

Ketamine hydrochloride is a nonbarbiturate intravenous anaesthetic. Its anaesthetic and analgesic effects are mediated primarily by non-competitive antagonism at the N-methyl-D-aspartic acid (NMDA) receptors. It has a preference for mu receptors, which is responsible for the analgesic effect of low-dose ketamine, with an opioid-sparing effect for postoperative analgesia.

In contrast to remifentanil, the and rate are frequently elevated following the administrations of ketamine alone. The elevation of begins shortly after injection, reaches a maximum within a few minutes and usually returns to pre-anaesthetic values within 15 minutes after injection.[3]

In the world literature concerning scoliosis surgery little information exists on the appropriate use of remifentanil in combination to low dose ketamine for this type of surgery.

Postoperative pain is one of the most common therapeutic problems after operations for scoliosis.[4] Many surveys have

shown a high prevalence of significant pain after surgery.[5] The clinical pharmacist utilising a full understanding of the pharmacology and the drug mechanism of action will help to formulate different anaesthetic methods which can be used both intraoperatively and postoperatively.

This study was conducted to apply the concept of a clinical pharmacist providing drug utilisation information during scoliosis surgery. Although the final decision for drug usage during anaesthesia is the choice of the anaesthetist, we believe that the pharmacist can play some role in drug usage decision-making. Central to this concept was to examine the hypothesis of adding ketamine to propofol/remifentanil TIVA during scoliosis surgery. Using remifentanil and propofol infusions for TIVA, as a secondary endpoint we examined the effect of Ketamine on postoperative analgesic requirements.

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 randomised study was carried out by the same surgical and anaesthetic teams in one hospital during the period January 2007 to January 2009..

All patients were informed of the details of the procedures and their written consent was obtained for each patient. All the patients who presented for this study were undergoing scoliosis surgery for the first time with a curvature of the spine greater than 40°. We studied 40 adult patients allocated randomly into two equal groups, Group 1 (G1) and Group 2 (G2) (Table I).

Pharmaceutical care programme

In this study a clinical pharmacist performed many activities on G1 and G2 patients.

All medications consumption was monitored for two weeks prior to the surgery specifically for those drugs which are known to have an effect on blood clotting.

Pharmacists also checked the storage instructions and expiry date for all drugs before they were used and they provided the patients with simple information about the disease and drug therapy pre-, intra- and postoperatively during their hospital stay.

The clinical pharmacist had a pivotal educational role in different stages of the surgery, especially during the wake up test[6] and before the patients' operation, so as to allay patients' fears and apprehensions and to attempt to minimise the consequences of this stressful surgical experience.

The duration of onset and reversal of the motor blocks were monitored in order to avoid possible damage to the spinal cord. Furthermore, the clinical pharmacists again had a significant role as they had set up a scheme which ensured that plans were in place to ensure that all patients received morphine as a postoperative analgesic. To ensure the patients received adequate analgesia following their operation, on the evening before surgery, they were instructed how to use the visual faces rating scale. During this instruction, patients were 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.[7]

The pharmacist applied active follow up for patient treatment compliance, and they conducted a postoperative questionnaire indicating the rate of patient satisfaction about the care received, for both groups of patients.

Finally the potential for drug allergic responses and adverse effects were recorded.

Chart review for medication selection

All drugs and drug doses used were counted and documented in medical charts to ensure that accurate observations were recorded.

Anaesthesia

All patients were given oral midazolam 0.25 mg/kg 30 minutes before surgery as a premedication. On arrival at the operating theatre, the following drugs were given intraoperatively: 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 just at the induction; sevoflurane (1–1.5% v/v) was given in a carrier gas of a 1:1 nitrous oxide: oxygen mixture and a bolus dose of 1 μg/kg of remifentanyl was given at induction for both groups followed by remifentanil infusion in a dose of 0.2 μg/kg/minutes in G1, 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 G2 administered in two different cannulas (Table II).

The lungs were ventilated to maintain a normocapnia with end-tidal carbon dioxide pressure around 35 mmHg using 50% oxygen/50% nitrous oxide. Continuous arterial pressure monitoring and frequent blood gas assessments provided appropriate data for all patients.

Patients received Ringer's Lactate intravenously at a rate of 10 ml/kg/hr. Blood loss was continuously collected and measured using a gauze and bottle suction technique which has

Table I: The gender, age, body weight, baseline heart rate and mean arterial pressure in the patients (n = 40) used in this study

	Group 1 (n = 20)	Group 2 (n = 20)	
Male/female	8–12	7–13	
Age (years)	19–23	20–24	NS
Body weight (kg)	54±13	5±15	NS
Baseline heart rate value (beats per minute)	80±2	83±4	NS
Baseline MAP value (mmHg)	90±3	93±2	NS

NS: Not Significant

Table II: The medications given to G1 and G2 patients during scoliosis surgery

Stages of medication admission	Groups of medications	Medication given	G1	G2
I – Preoperative	Sedative	Midazolam G1, G2	√	√
II – Intraoperatively	Anaesthetics; IV	Propofol Ketamine	√ -	√ √
	Inhalation	Sevoflurane	√	√
	Analgesic	Remifentanil	√	√
	Muscle relaxant	Atracurium	√	√
	Antidotes	Neostigmine Atropine	√ √	√ √
III – Postoperative	Analgesics	Morphine	√	√

√ : Used
– : Not used

been described elsewhere.[8] Briefly, the blood was very carefully collected, measured, its volume recorded and an equivalent volume of packed red blood cells was replaced. A transfusion for replacement started when the blood loss had exceeded 500 ml. In addition, a Foley's catheter, connected to a urine bag was inserted in all patients.

Wake-up test
The wake-up test was measured using the procedure described by Barash et al in 2006.[6] Essentially, the duration of the onset and regression time of motor blockade are assessed in this wake-up test by asking the patient to move their fingers and their toes. It is a precautionary test done to assess any possible damage to the spinal cord caused by the surgical technique and placement of the correction devices.

In order to carry out the wake-up test all the drugs were stopped, antidotes were given including: neostigmine (2.5 mg/IV) and atropine (1 mg/iv) which were administered together in a single bolus dose from one syringe (Table II).

When the wake-up test was completed, which was when the patient responded to the first verbal commands, they were then re-anaesthetised with the same induction drugs in doses identical to those used originally.

During the operation, for the purposes of maintenance, the patients in Group 1 and 2 received their respective drugs. At the end of the operation both groups received doses of neostigmine, atropine as described above along with 100% oxygen. Approximately 15 min before the end of the surgery, a 1–2 mcg/kg dose of Fentanyl IV was given.[9] A neurological assessment was done after the patient woke up but before being transferred to the recovery room, in order to ensure that no spinal injury had occurred.

Postoperative analgesic administration
The severity of postoperative pain was assessed during the first day after surgery by means of a visual faces rating scale and pain was controlled by IV morphine. The morphine infusion pump was set to deliver morphine solution (1 mg/ml) at the rate of 3–5 mg/hr in the PACU.

Quantitative measurements made during the operation
To ensure the data was collected independently from the clinical pharmacist who organised the study, all the data was collected by very carefully prepared pharmacy students who were blinded and so not aware to the contents of the solutions, and who acted in this role under the supervision of highly trained research technicians and nurses.

Heart rate (beats/min), mean arterial pressure (MAP) (mmHg) was recorded at 5-minute intervals during surgery where the dose of the infused drugs was adjusted to keep the mean blood pressure around 60 mmHg. The duration of anaesthesia and the total time of the surgery (min), the volume of blood loss (ml) and urine output (ml) were recorded. The time to achieve the wake-up test and the immediate recovery time were recorded. The early pain perception was measured by the time (min) that passed between extubation and the first request for an analgesia dose. Total consumption of morphine (mg) over the first 24 hours postoperatively was measured. Finally, potential anaesthetic-related complications, including nausea, vomiting, pruritus, dysphoria, vision loss, shivering and respiratory depression, were, if found, recorded and managed accordingly.

Data analysis
Data were expressed as mean ± 2SD and were analysed using Student's t test. A $p < 0.05$ level was considered significant.

Results

Pre-surgical drug history
The two groups studied were comparable as regards age, weight, and sex.

Preliminary analysis showed that there were no significant differences between male and female in their respective groups for any of the parameters measured and so they were subsequently considered as one group despite their gender and age differences, perhaps indicating the success of the initial randomisation process (Table I).

Intraoperative and postsurgical analysis
The HR and MAP was significantly lower ($p < 0.05$) in G1 than

Table III: Clinical measurements (mean ± 2SD) made during scoliosis surgery for G1 and G2 groups of patients

	G1	G2	
Heart rate (beats per minute)	67 ± 4	70 ± 2*	
MAP (mmHg)	60 ± 3	70 ± 5*	
Time needed for wake up test (min)	13 ± 1.3	14 ± 1.2	NS
Total blood loss (ml)	1800 ± 50.6	1833 ± 80.1	NS
Total urine output (ml)	350 ± 3	338 ± 6	NS
Duration of surgery (min)	240.1 ± 3.3	238.4 ± 3.6	NS
Duration of anaesthesia (min)	271.6 ± 5.3	266.7 ± 3.5	NS

* Signifies $p < 0.05$
NS: Not Significant

Table IV: Postsurgical analysis for patients (n = 40) for their immediate recovery time, time to first request for analgesia and total morphine consumption in G1 and G2. All values mean ± 2SD.

	G1 (n = 20)	G2 (n = 20)
Immediate recovery time (min)	3.3 ± 2.6	7.1 ± 2.9 *
Time to first patient analgesia dose request in PACU (min)	19.5 ± 3.2	22.9 ± 3.6*
Total 24 hr morphine consumption (mg)	60 ± 10	45 ± 5*

* Signifies $p < 0.05$

in G2 (Table III). However, there were no significant differences between the two groups regarding blood loss, urine flow, wake-up test, mean operative time and duration of anaesthesia (Table III).

Concerning the immediate recovery time and the time which passed until the first patient analgesia request in the PACU, the recorded values were significantly different. A value of $p < 0.05$ was found when G2 was compared to G1 (Table IV).

G2 patients also consumed significantly (25%) less morphine than G1 patients, which, on analysis, was found to have a value of $p < 0.05$ (Table IV).

Potential for drug allergic responses and adverse effects
No patients in either group reported dysphoria, shivering and respiratory or visual loss and no differences were noted in the incidence of pruritis, postoperative nausea and vomiting in the two groups.

Discussion
We have applied a full pharmaceutical care programme in this study, and, as in all the previous studies in which a similar pharmaceutical care programme was applied, have shown a high positive impact on the patients, drug use and total results in the different surgical and medical fields. [10]

Our results showed high patient satisfaction with the pharmaceutical care programme, similar to one which has been recorded for that of heart failure.[11]

The finding that haemodynamically the HR and MAP were significantly lower in G1 than in G2 concurs with several other studies which showed that remifentanil causes arterial hypotension and bradycardia with IV anaesthetic agents or general anaesthetics.[1,12,13]

In G2, we chose to use a low constant dose of ketamine as the lower dose would lead to less tachycardia and hypertension and shorter duration of action, resulting in a lowered incidence of ketamine side-effects such as postoperative hallucinations and emergence delirium. In agreement with our results, the HR and MAP did not decrease below the normal values, possibly to the catecholamine release by ketamine, which commonly results in both tachycardia and hypertension,[14] an action that attenuates remifentanil's effects.

We found no significant difference between the two studied groups with regard to blood loss and urine flow. On the other hand, both groups had adequate urine output and this is possibly due to very careful fluid replacement therapy which was carried out in the surgical procedure.

With regard to recovery from anaesthesia, we found that patients in G1 recovered quicker than those given the ketamine-remifentanil-propofol technique in G2. These results are due to the short terminal plasma half-life of remifentanil which is 3–5 minutes.[15] In contrast with other opioids in the fentanyl family, the context-sensitive half-time of remifentanil infusion is independent of duration of infusion. 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,[16] while it is well known that there is a big difference between ketamine elimination half-life and remifentanil.[17]

The time to first patient controlled analgesia dose request in PACU (early pain perception), was significantly less in G1. This could be due to hyperalgesia of surgical injury and the development of opioid-induced tolerance related to remifentanil infusions. Both involve activation of NMDA receptors in CNS, and subsequent biochemical processes resulting in central sensitisation, increased spinal dynorphin activity and activation of intracellular protein kinase.[18] 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.[19]

Frederic Adam[20] evaluated the effect of ketamine in a dose of 1.5 _g/kg/min for postoperative pain relief and the total morphine consumption after total knee artheroplasty. Their results confirm that ketamine is a useful analgesic adjuvant in perioperative multimodal analgesia with a positive impact on early knee mobilisation. In this study 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, the postoperative pain scores and total morphine consumption were significantly less in G2. How can this be explained?

Ketamine may produce antinociception through interaction with the spinal mu receptor, NMDA receptor antagonism, and activation of the descending pain inhibitory monoaminergic pathways,[21] which is expressed by alpha2-adrenoceptors at the spinal level.[22] Analgesia produced in humans by systemic ketamine up to 0.3 mg/kg is not reversed,[23] which suggests that the analgesic effect of ketamine is mediated by a non-opioid mechanism, possibly involving PCP-receptor-mediated blockade of the NMDA-receptor-operated ion channel.

Even though a small ketamine dose was used in this study, it produced a 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[24] and several-fold higher than that for monoamine transporter sites or other non-NMDA receptors (i.e. acetylcholinesterase and the epsilon receptor),[25] which suggests that the smaller the dose, the more selective is the ketamine interaction with NMDA receptors. his colleagues have shown that analgesia produced by the systemic coadministration of an opiate and an α2-adrenoceptor agonist (e.g. clonidine or medetomidine) are synergistic.[26]

In agreement with our results, Stubhaug et al showed that low-dose IV infusion of ketamine during and after surgery reduces mechanical punctuate hyperalgesia surrounding the surgical incision. This indicates that blockade of NMDA receptors prevents the central sensitisation caused by nociceptive input during and after surgery.[27] Other studies have demonstrated that ketamine, in combination with morphine, provides superior postsurgical pain relief at lower dosage and with fewer side-effects than morphine alone.[28]

In summary, our results demonstrate that the clinical pharmacist can have many positive roles during presurgery, during posterior spinal fusion surgery and in the management of postoperative pain. Furthermore, the combination of ketamine and remifentanil infusions as TIVA may provide more haemodynamic stability, satisfactory surgical requirements with reliable and adequate postoperative pain relief.

Collaborative clinical pharmacy practice can have an effective role in improving the general patient satisfaction of patients undergoing scoliosis surgery.

Finally, adding low dose ketamine hydrochloride infusion during scoliosis surgery can be applied as a routine therapy to improve the haemodynamic stability during the surgery and reduce the postoperative morphine consumption. **SAJAA**

References:

1. Malcolm-Smith NA, MacMaster MJ. The use of induced hypotension to control bleeding during posterior fusion for scoliosis. J Bone Joint Surg Br 1983;65:255–8.
2. McQuay H, Moore A, Justins D. Treating acute pain in hospital. Br Med J 1997;314:1531–1535.
3. Barash PG, Cullen BF, Stoelting RK. Handbook of Clinical Anesthesia. 5th ed. New York: Lippincott Williams & Wilkins; 2006. 167–85.
4. McQuay H, Moore A, Justins D. Treating acute pain in hospital. Br Med J 1997;314:1531–1535.
5. Antonio V, Cristina A, Josep M, et al. Management of postoperative pain in abdominal surgery in Spain. A multicentre drug utilisation study. Br J Clin Pharmacol 1999 June;47(6):667–673.
6. Barash PG, Cullen BF, Stoelting RK. Handbook of Clinical Anesthesia. 5th ed. New York: Lippincott Williams & Wilkins; 2006. 659–76.
7. Morgan GE, Mikhail M, Murray M. Clinical anesthesiology 4th ed. Lange medical books/Mc Graw-Hill; 2006. 359–410.
8. Malcolm-Smith NA, MacMaster MJ. The use of induced hypotension to control bleeding during posterior fusion for scoliosis. J Bone Joint Surg Br 1983;65:255–8.
9. Samra SK, Dy EA, Welch KB, Lovely LK, Graziano GP. Remifentanil and fentanyl-based anesthesia for intraoperative monitoring of somatosensory evoked potentials. Anesth Analg 2001;92:1510-5.
10. González-Martin G, Joo I, Sánchez I. Evaluation of the impact of a pharmaceutical care program in children with asthma. Patient Educ Couns. 2003 Jan;49(1):13–8.
11. López Cabezas C, Falces Salvador C, Cubí Quadrada D, et al. Randomized clinical trial of a postdischarge pharmaceutical care program vs. regular follow-up in patients with heart failure. FARM HOSP. 2006 Vol. 30. No 6, pp. 328–342.
12. Hogue CW Jr, Bowdle TA, O'Leary C, et al. A multi-center evaluation of total intravenous anesthesia with remifentanil and propofol for elective inpatient surgery. Anesth Analg 1996; 83:279.
13. Schüttler J, Albrecht S, Breivik H, et al. A comparison of remifentanil and alfentanil in patients undergoing major abdominal surgery. Anaesthesia 1997;52:307.
14. White PF. Comparative evaluation of intravenous agents for rapid sequence induction-thiopental, ketamine and midazolam. Anesthesiology 1982;57:279.
15. Glass PSA, Hardman D, Kamiyama Y, et al. Preliminary pharmacokinetics and pharmacodynamics of an ultra short acting opioid: remifentanil. Anesth Analg 1993;77:1031.
16. Thompson JP, Rowbotham DJ. Remifentanil – an opioid for the 21st century. Br J Anaesth 1996;76:341.
17. Uvarov BS, Vorob'ev AA, Uriupov OIu, Katkov VF, Katkova EB. Effect of antioxidants and nootropic agents on the duration of ketamine general anesthesia and on the course of the postanesthesia period. Anesteziol Reanimatol 1987 Sep–Oct;(5):3–6.
18. Mao J. Opioid-induced abnormal pain sensitivity: implication in clinical opioid therapy. Pain 2000;100213.
19. Mao J, price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. Pain 1995;62:259.
20. Adam F, Chauvin M , Du Manoir B, et al. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee artheroplasty. Anaesth Analg 2005;100:475.
21. Pekoe GM, Smith DJ. The involvement of opiate and monoaminergic neuronal systems in the analgesic effects of ketamine. Pain 1982;12:57.
22. Howe JR, Wang J-Y, Yaksh TL. Selective antagonism of the antinociceptive effect of intrathecally applied alpha adrenergic agonists by intrathecal prazocin and intrathecal yohimbine. J Pharmacol Exp Ther 1983;224:552.
23. Maurset A, Skoglund LA, Hustveit O, et al. Comparison of ketamine and pethidine in experimental and postoperative pain. Pain. 1989;36:37.
24. Smith DJ, Azzaro AJ, Saldivar SB, et al. Property of the optical isomers and metabolites of ketamine on the high affinity transport and catabolism of monoamines. Neuropharmacology 1981;20:391.
25. Ossipov MH, Harris S, Lloyd P, et al. An isobolographic analysis of the antinociceptive effect of systemically and intrathecally administered combinations of clonidine and opiates. J Pharmacol Exp Ther 1990;255:1107.
26. Stubhaug A, Breivik H, Eide PK, et al. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997;41:1124.
27. Javery KB, Ussery TW, Steger HG, et al. Comparison of morphine and morphine with ketamine for postoperative analgesia. Can J Anaesth 1996;43:212.
28. Chia YY, Liu K, Liu YC, et al. Adding ketamine in a multimodal patient-controlled epidural regimen reduces postoperative pain and analgesic concentration. Anesth Analg 1998;86:1245.