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ORIGINAL ARTICLE

A randomized, controlled trial of a clinical pharmacist intervention in microdiscectomy surgery – Low dose intravenous ketamine as an adjunct to standard therapy

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Abstract *Aim:* The hypothesis that postoperative pain would be reduced by using 1 μg/kg/min of ketamine, both intra- and post-operatively, for lumbar microdiscectomy surgery was assessed by measuring morphine consumption. Patient side effects were reported.

Methods: Forty-five patients undergoing microdiscectomy surgery were randomized under double-blind conditions into three groups: Group1 (G1) received normal saline, Group 2 (G2) ketamine (1 μg/kg/min) intra-operatively and Group 3 (G3) ketamine (1 μg/kg/min) both intra- and post-operatively. Morphine consumption, pain scores, nausea and vomiting, CNS disorders were recorded for 24 h post surgery. This study was conducted by applying the concept of a clinical pharmacist intervention.

Results: The time for the first analgesia demand dose was significantly shorter ($P < 0.05$) in G117 ± 1.7 min than for G2 and G3. In G3 morphine consumption 6, 12, and 24 h after surgery was 3 ± 2.26, 9.2 ± 2.11 and 26.9 ± 2.71 mg. Total morphine consumption was significantly lower for G3 than for G1 or G2 ($P < 0.05$). The visual analog scale score (VAS) values were significantly lower in G3 ($P < 0.05$) than for the other groups during the first 24 h. The rate of nausea and vomiting was significantly higher in G1 vs G3 ($P < 0.05$). No difference in drug induced CNS disturbances was observed among the groups.

Conclusions: Using 1 μg/kg/min of ketamine hydrochloride intra- and post-operatively for microdiscectomy surgery could be an adjunct therapy to reduce postoperative morphine consumption minimizing its side effects.

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Collaborative clinical pharmacy practice on the basis of pharmacology had an effective role in improving the general outcome of microdiscectomy surgery.

1. Introduction

Patients undergoing lumbar microdiscectomy experience severe pain in the postoperative period, which may increase the incidence of postoperative morbidity and complications (Fountas et al., 1999).

Postoperative pain, nausea and vomiting are the most common therapeutic problems in hospitals (McQuay et al., 1997; Kovac, 2000) and many surveys have shown high prevalence of significant pain and nausea–vomiting after surgery (Antonio et al., 1999; Bell et al., 2005).

Ketamine hydrochloride is an intravenous anesthetic. Its anesthetic and analgesic effects are mediated primarily by a non-competitive antagonism at N-methyl-D-aspartic acid (NMDA) receptors (Hadi et al., 2009). Low dose ketamine has a direct analgesic effect and also induces a postoperative morphine-sparing effect in some forms of surgery (Himmelseher and Durieux, 2005).

Low dose ketamine (1 μg/kg/min) was previously tested intra-operatively in scoliosis and spinal fusion surgery (Hadi et al., 2009, 2010) and peri-operatively in major abdominal surgery (Zakine et al., 2008; Guillou et al., 2003) to decrease post-operative intravenous morphine consumption (Rebel et al., 2011; Ribezzi et al., 2010; Xiao et al., 2011). Systemic opioids can be associated with significant nausea–vomiting side effects (Kovac, 2000; Nortcliffe et al., 2003), and lowering the morphine dose leads to a lower incidence of nausea–vomiting (Zakine et al., 2008).

In the world literature, up to our best knowledge; clinical pharmacist has positive interventional role in the hospital, and in the community pharmacy in controlling chronic diseases as; blood pressure, blood cholesterol level, blood sugar level, and asthma (Roughead et al., 2005; Machado and et al., 2008).

On the other hand little information exists about the clinical pharmacist intervention in the surgery room, PC Gordon (2004) has advised that the SA Society of anesthesiologists should be involved with the pharmacist for different improvements.

In this study, an investigational primary end-point was the time for the first request of analgesia. We intended to examine the hypothesis that postoperative pain would be reduced by using this very small-dose of ketamine (1 μg/kg/min) intra- and post-operatively to an intra-operative remifentanil-based anesthesia regimen for lumbar microdiscectomy surgery. Furthermore, the secondary end-points were the cumulative morphine consumption 6, 12 and 24 h after surgery, severity of postoperative pain using the (VAS), the existence or not of nausea–vomiting, and the transient psychotic side effects induced by ketamine.

Furthermore, due to the positive impacts of the clinical pharmacist in different medical areas, we conducted a novel idea, by carrying out the clinical pharmacist intervention to different anesthetic strategies during microdiscectomy surgery.

2. Methods

All patients were treated by the same surgical anesthetic and nursing teams and all were scheduled for lumbar microdiscectomy surgery using the same operative procedures.

The human investigation section of the institutional review board of the hospital read, considered and subsequently approved the ethics of this investigation and so gave their formal permission for this study to be carried out. All patients were informed about the details of the procedures and written consent was obtained from each patient.

2.1. Patient selection

Forty-five patients scheduled for lumber microdiscectomy surgery were prospectively randomized under double-blind conditions to one of three groups of 15 patients: Group (G1) received normal saline; Group 2 (G2) received intra-operative ketamine (1 μg/kg/min) and Group 3 (G3) received intra-operatively and post-operatively ketamine (1 μg/kg/min) for the first 24 h after surgery.

Inclusion criterion was that the patient was adult who had a level of education which enabled him to understand the use of the patient-controlled analgesia technique. Those patients who had used bed rest and had physical therapy sessions by licensed physical therapists to relieve their lower back pain at least 48 h prior to surgery were included in the trial.

Exclusion criteria were that patients with severe back pain who were receiving chronic narcotic analgesic treatment were excluded, as were patients with major systemic diseases.

Details of patient gender, age, and body weight for the three groups are shown in Table 1.

2.2. Clinical pharmacists involvement with the study

Together on the basis of the clinical pharmacology knowledge and the experience of the anesthesiologist, we applied the idea of using the multi character of keamine in microdiscectomy surgery.

In our study a clinical pharmacist performed many activities for the patients pre-operatively, during, and after a different surgery. They had a pivotal educational role in different stages of the surgery and before the operation to allay patients' fears and apprehensions and to minimize the consequences of this very painful surgical experience, they tested the patients pre-operatively to check their wellbeing and health condition, and they monitored medication consumption for two weeks prior to the surgery specifically for those drugs which are known to have an effect on blood clotting.

The storage instructions and expiry date of all drugs were checked; they provided the patients with simple information about the disease and drug therapy pre-, intra- and post-operatively during their hospital stay.

To ensure that patients received adequate morphine as a postoperative analgesic whenever it was required following

Table 1 Gender, age, body weight in the three groups of patients studied.

Variable	Group 1 ($n = 15$)	Group 2 ($n = 15$)	Group 3 ($n = 15$)
Gender[a]	8–7	7–8	6–9
Age (years)	51 ± 2.47	55 ± 2.47	55 ± 2.60
Body weight (kg)	71 ± 2.60	69 ± 2.60	70 ± 2.30

[a] Gender is displayed as a ratio of male to female. Values are presented as the mean ± standard deviation or number. There were no significant differences between three groups.

their operation, on the evening before surgery, patients were instructed how to use the 100 visual analog scale score (VAS).

The pharmacists had set up a scheme which ensured that comprehensive plans were always in place to ensure that all patients received morphine as a postoperative analgesic whenever it was required.

They recorded all the details of the potential drug allergic responses and major side effects if exist. They played an investigational role both in the primary and the secondary endpoints.

2.3. Anesthesia

All patients were given midazolam 0.25 mg/kg orally, 30 min before surgery as a premedication. On arrival at the operating theater, the following drugs were given: propofol 2 mg/kg as an IV bolus for induction in all the three groups followed by atracurium 0.6 mg/kg to facilitate orotracheal intubation. Sevoflurane (1–1.5% v/v) in a carrier gas mixture of 1:1 nitorus oxide/oxygen was used for all patients.

Anesthesia was pre-induced using remifentanil 1 μg/kg for the three groups followed by a remifentanil infusion at a dose of 0.2 μg/kg/min. A placebo infusion of 0.9% normal saline in G1 was given at the same volume and flow rate as for the ketamine infusion, which was given for G2 and G3 combined with the remifentanil infusion (0.2 μg/kg/min) [Tekam Al-Hikma, Jordan] at an infusion rate of 1 μg/kg/min administered using two different cannulas. All drugs were stopped at the end of the operation except for G3 where the ketamine was continued to be administered at 1 μg/kg/min for 24 h.

2.4. Post-operative analgesic administration

The severity of postoperative pain was assessed during the first 24 h after surgery by means of the visual analog scale score (VAS), identifying 0 as no pain and 100 the worst imaginable pain. When the (VAS) score was $\geqslant 40$, IV morphine was given until the (VAS) score was $\leqslant 40$ for all three groups. The morphine infusion pump was set to deliver the morphine solution (1 mg/ ml) at a rate of 3 mg per demand in the PACU for all three groups. Group 3 received an additional infusion of ketamine 1 μg/kg/min for 24 h, whereas the other two groups (G1, G2) simply received the placebo – 0.9% normal saline.

2.5. Quantitative measurements made during the operation

Collecting the data was carried out independently from the clinical pharmacist who organized the study or from physicians who were cognizant of the protocol. The anesthesiologist technicians assist the anesthesia team in patient monitoring, where they collected all the data blindly.

The duration of surgery (min), the time taken from intubation to extubation were recorded for each patient and expressed as the duration of the operation.

Early pain perception was measured by the time (min) that passed between extubation and the first request for a dose of analgesic. The total consumption of morphine (mg) and numeric rating scale were monitored at 6, 12 and 24 h postoperatively.

Anesthetic-related complications such as dysphoria or hallucination were recorded when present. Nausea and vomiting were recorded by using a three response scoring system: none, mild nausea, severe nausea and vomiting. The complications were managed according to each individual case.

2.6. Data analysis

On completion of the 'field work', coded data were examined by using the Statistical Package for Social Sciences (SPSS/PC+) program, version 19. All data entries were double checked to ensure accurate data entries.

The sample size estimation was based on a power calculation showing that 15 patients per group were necessary to achieve 80% power for detecting a 20% difference in the different variables between Group 1 with Groups 2 and 3 with $\alpha = 0.05$. Data are presented as the mean ± standard deviation or as numbers. Differences among group means were compared using one-way analysis of variance and post hoc comparisons at various points in time using Bonferroni's type I error rate correction for multiple tests of significance. Gender and complication rates were analyzed by Pearson's Chi-square test. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Group characteristics and pre-surgical medical and drug history

The three groups of patients studied were found to be comparable as regards sex, age, weight, and the duration of the surgery (Table 1). Comparisons of the data found that there were no significant differences ($P > 0.05$) between any of the parameters measured across the groups. There were no significant differences between the number of males and females in their respective groups and also for comparisons made between G1, G2 and G3 for their ages, and body weight. In the absence of any significant differences being found between the groups they were subsequently considered as comparable groups despite their apparent gender and age differences (Table 1).

After the pre-operative tests, patients were found to be free of any major systemic disease such as coronary heart disease

and/or hypertension and they were considered fit to be operated upon according to the usual criteria used by the anesthesiologists involved in this study.

The drug history of each patient taken by the pharmacists did not show any major differences between individuals in the three groups and so all were considered suitable for the trial.

3.2. Analysis of the duration of the surgical procedure

The duration of the surgery was not significantly different between the patients in the three groups ($P > 0.05$) (Table 1).

3.3. Time for the first request for analgesia in the PACU

The time to the first patient's analgesia request in PACU was 17 ± 1.7 min for G1, 23.60 ± 1.80 min for G2 and 23.9 ± 1.83 min for G3. The results of the statistical comparisons show that there was a significant difference between the results of G1 and G2 ($P > 0.05$), and between the results of G1 and G3 ($P > 0.05$), while there was no significant difference between G2 and G3 (Table 2).

3.4. Dosage of morphine requested at 6, 12 and 24 h after surgery

All the comparisons made established that the three groups were significantly different from each other for morphine dose 6, 12, and 24 h after the surgery, the cumulative morphine dose was significantly the lowest for G3 ($P < 0.05$), while the doses required for those patients not treated with a continuous infusion of ketamine were significantly greater than when it was present. These results are shown in Table 3.

3.5. Results from the (VAS) of patients' perception of pain

The visual analog scale score (VAS) results for the perception of pain were measured at 6, 12, and 24 h after surgery and are shown in Table 4. All the comparisons made established that the three groups were significantly different from each other; where G3 was significantly the lowest and G1 was the highest ($P < 0.05$).

3.6. Drug side effects

No transient psychotic events e.g. hallucinations were reported for any of the groups including the ketamine group at any of the time points measured. Nausea and vomiting were the main drug induced side effects observed over the first 24 h post-operative period (Table 5). All the comparisons made established that the three groups were significantly different from each other; where G3 patients had the lowest side effect verses G2 and G1, where G1 had the highest score ($P < 0.05$).

Table 3 The cumulative requested doses of morphine for the 6, 12 and 24 h post-operative period.

Group (mg)	Group 1 ($n = 15$)	Group 2 ($n = 15$)	Group 3 ($n = 15$)
6 h dose	9 ± 2.30	6.8 ± 2.65[a]	3 ± 2.26[a,b]
12 h dose	21 ± 2.65	16.2 ± 2.73[a]	9.2 ± 2.11[a,b]
24 h dose	60 ± 2.60	45.3 ± 3.26[a]	26.9 ± 2.71[a,b]

Notes: Data are presented as the mean ± standard deviation.
[a] $P < 0.05$ versus Group 1.
[b] $P < 0.05$ versus Group 2.

Table 4 VAS score assessments after 6, 12, and 24 h.

Group	Group1 ($n = 15$)	Group 2 ($n = 15$)	Group 3 ($n = 15$)
VAS 6	44.00 ± 5.071	36.0 ± 5.0[a]	27.3 ± 4.5[a,b]
VAS 12	58.00 ± 6.761	50.7 ± 4.5[a]	40.0 ± 3.8[a,b]
VAS 24	56.00 ± 5.071	44.7 ± 5.2[a]	35.3 ± 5.2[a,b]

Notes: Data are presented as the mean ± standard deviation.
[a] $P < 0.05$ versus Group 1.
[b] $P < 0.05$ versus Group 2.

4. Discussion

We have examined the use of low dose ketamine in both intra- and post-operative lumbar microdiscectomy surgery because it is well known that patients undergoing this type of surgery experience severe pain in the postoperative period (Mastronardi et al., 2002).

Fountas et al. (1999) have examined different methods for postoperative pain after lumbar microdiscectomy surgery but have not used a low dose of ketamine, such as 1 μg/kg/min as used in this study, as a possible method for such control.

The dual effect of ketamine of being a good analgesic at sub-anesthetic doses and a mechanism of action mediated primarily by a non-competitive antagonism at N-methyl-D-aspartic acid (NMDA) receptors Hadi et al. (2009) make this drug a somewhat unusual analgesic. However this unusual analgesic action is well documented as is its ability at low doses to induce a morphine-sparing effect, which can be a very useful effect to utilize post-operatively (Himmelseher and Durieux, 2005), and for this reason we have chosen low dose ketamine in this study. Furthermore, the low dose of ketamine would lead to less tachycardia, hypertension and a shorter duration of action, which potentially would result in a lower incidence of ketamine side effects such as postoperative hallucinations and emergence delirium (Schmid et al., 1999).

Low dose ketamine (1 μg/ kg/min) was previously tested intra-operatively in back surgeries including scoliosis and spinal fusion surgery as a randomized placebo-controlled two groups

Table 2 Duration of surgery (min), and the time (min) for the first request for analgesia in the PACU.

	Group 1 ($n = 15$)	Group 2 ($n = 15$)	Group 3 ($n = 15$)
Duration of surgery (min)	61 ± 2.80	60 ± 2.90	61 ± 1.1 NS
Time for first patient analgesia request in PACU (min)	17 ± 1.7	23.60 ± 1.80[a]	23.9 ± 1.83 [a]

Notes: NS: not significant, data are expressed as the mean ± SD.
[a] $P < 0.05$ versus Group 1.

Table 5 Nausea and vomiting over the first 24 h post-operative period.

Nausea and vomiting Status	Group 1 ($n = 15$)	Group 2 ($n = 15$)	Group 3 ($n = 15$)	Statistic
No	7	10	14	$P < 0.05$
Yes	8	5	1	$P < 0.05$

Values are presented as numbers.

study (Hadi et al., 2009, 2010). In this study we randomly tested controlled group G1, with G2 patients who used ketamine intra-operatively, and G3 who used ketamine intra and post-operatively in laminectomy surgery.

In this study the time needed to the first request of analgesia in PACU was significantly less ($P < 0.05$) in the groups who received ketamine, either intra-operatively or both intra and post-operatively (G2, G3), rather than those who did not receive ketamine (G1). These results were similar to those reported by Hadi et al. (2010), who tested ketamine intra-operatively during spinal fusion surgery. However the present study showed that adding ketamine either intra-operatively or both intra and post-operatively did not show a significant difference for the time to the first request of analgesia. Both groups (G2, G3) receiving the same dose of ketamine until the end of operation and due to the half life of the drug would still have pharmacologically active concentrations in the blood stream for some time afterwards thus giving them some analgesic and morphine -sparing effects.

It is interesting to note that continuous intra-operative ketamine-remifentanil combined infusions (G2) and (G3), when compared with continuous remifentanil infusion alone (G1), resulted in less postoperative pain scores and total morphine consumption in G2 and G3. These results were similar to Hadi et al. (2010). On the other hand, intra and post-operative ketamine–morphine infusions (G3), when compared with continuous morphine infusion alone (G2), resulted in lower postoperative pain scores and total morphine consumption in G3. Similar results were previously reported by Zakine et al. (2008), who carried out an investigation by using the same method of drug administration in another type of surgery.

We used the visual analog scale score (VAS) for the assessment of pain as Kundra et al. (1997) evaluated this method, and recommended using it. Consequently this technique of recording pain scores for this type of surgery proved to be useful and discriminatory. Two other studies have demonstrated that ketamine in combination with morphine provides superior postsurgical pain relief at a lower morphine dose, with a lower (VAS) score, and fewer side effects than morphine alone (Javery et al., 1996; Chia et al., 1998). These results were similar to ours as our results showed that lowering morphine consumption is associated with reducing its side effects such as nausea and vomiting, and the use of the low dose (1 μg/kg/min) of ketamine was not associated with any transient psychotic effects. These results were also confirmed in a previously reported study (Snijdelaar et al., 2004; Webb et al., 2007).

This is not the first study in which ketamine has been used at a low concentration post surgery as Frederic Adame and his colleagues (Adam et al., 2005) evaluated the effect of low dose ketamine on post-operative pain relief and the total morphine consumption after total knee artheroplasty. Their results confirmed that low dose ketamine was a useful analgesic adjuvant in perioperative multimodal analgesia with a positive impact on early knee mobilization. Their patients required significantly less morphine than the control group. These results were similar to ours. In a further meta-analysis study by Bell et al. (2005) it was observed that in the first 24 h after surgery, ketamine reduced postoperative nausea and vomiting which could have been due to a morphine-sparing effect. The problem with this study is that it could not be translated into any specific administration regimen with ketamine and so the present study establishes a safe and effective concentration to use. The present study, by establishing a statistically significant difference between the three groups (G1, G2, and G3) for morphine induced nausea and vomiting side effects clearly showed the effectiveness of ketamine to counter such effects.

In this study we have examined different parameters concerning adding low dose ketamine intra and post-operatively, other studies have tested further positive impacts of ketamine, on narcotic tolerance patients (Urban et al., 2008), the achievements of haemodynamic stability (Hadi et al., 2010) and its prevention of post-operative hyperalgesia effect (Gu et al., 2009), all these parameters give ketamine a superior impact over other analgesics.

4.1. Clinical pharmacists involvement with the study

All previous studies have shown high positive impact of clinical pharmacists on the patients in the different fields (Damso et al., 2003).

In this study we have applied uniquely a full pharmaceutical care program in different surgeries, where up to our best knowledge; this is a new field for the clinical pharmacist.

The pharmacist was trained to follow all the renowned procedure of the surgery together with the physicians (Kuwajerwala et al., 2008; http://www.surgeryencyclopedia.com/Pa-St/Postoperative-Care.html#b, 2012; Subishpalaian et al., 2006; Morgan et al., 2006; Classen et al., 1997; Taitel et al., 2012; Barone et al., 2003).

We have applied the major duties of the clinical pharmacist, starting pre-operatively by: physical preparation (Kuwajerwala et al., 2008).

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.

Patients are often fearful or anxious about having surgery. We have applied the psychological preparation (Kuwajerwala et al., 2008; http://www.surgeryencyclopedia.com/Pa-St/Post-operative-Care.html#b, 2012; Subishpalaian et al., 2006) to allay patients' fears and apprehensions and to attempt to minimize the consequences of this very stressful surgical experience.

Postoperative pain care was fulfilled in the evening, before the operation, patients were instructed how to use the 0–100

visual analog scale score (VAS) for microdiscectomy (Morgan et al., 2006).

We set up a scheme to fulfill the rest of the clinical pharmacists' duties (Classen et al., 1997; Taitel et al., 2012), which ensured that plans were in place for all medications used, to avoid errors and for the documentation.

As other previous studies did post-operatively (Barone et al., 2003); our patients were moved to the PACU to continue receiving high care, and they were observed intensively for the first 24 h.

Clinical pharmacist took a training course on the detail of anesthesia care before starting the investigational research.

In this study we have applied a pharmaceutical care intervention in the three groups equally, as it was previously advised by PC Gordon (2004), who advised that the SA Society of anesthesiologists should be involved with the pharmacist for different improvements (Gordon, 2004).

Further comparison studies should be done in the future between control group and interventional group of pharmacy care to score the satisfaction deferent between groups.

5. Conclusion

Adding a low dose of ketamine hydrochloride both intra- and post-operatively could be an adjunct therapy to maintain postoperative analgesic control while reducing postoperative morphine consumption reduces nausea and vomiting side effects in the traditional lumbar microdiscectomy surgery without experiencing ketamine's side effects such as transient psychotic effect.

Collaborative clinical pharmacy practice on the basis of pharmacology had an effective role in improving the general outcome of microdiscectomy surgery, clinical pharmacists can have many positive roles pre-surgery, during the surgery and in the management of postoperative pain.

We advise the clinical pharmacists to take a new role in the surgery room.

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