Analgesic Effects of Ketamine Infusion on Postoperative Pain after Fusion and Instrumentation of The Lumbar Spine: a Prospective Randomized Clinical Trial

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Background: Intractable pain occurs as a result of extensive damage to soft tissue, bones and muscles after fusion of lumbar spondylolisthesis. Although different drugs and protocols have been suggested for postoperative pain management, the best method of treatment has not been proposed yet. Therefore, this study tried to compare the efficacy of ketamine infusion and routine opioid administration on postoperative pain.

Methods: A double-blind prospective randomized clinical trial was performed on 45 patients candidate for fusion of lumbar spondylolisthesis. Patients were divided into two groups of A (treatment) and B (control). In group A, pain was controlled by intravenous infusion of ketamine. Morphine was also administrated when the patients scored their pain above 4 on a visual analogue scale (VAS). In group B, intravenous infusions of morphine were performed every 6 hours. VAS and whole dosage of morphine were compared between two groups every 6 hours.

Results: Morphine and ketamine were both effective on pain control. Mean values of pain intensity at the first to fourth time points were 2.1, 1.8, 1.6, and 1.7 in group A and 3.9, 3.4, 3.5, and 3.5 in group B, respectively (p < 0.01 for all periods). However, ketamine was more efficient in pain reduction during the first 24 hours (p < 0.001).

Conclusion: Ketamine could be a good alternative analgesic after fusion of lumbar spondylolisthesis. However, the probable side effects should also be considered. Ketamine infusion is more effective than morphine on postoperative pain control. In addition, tolerance to drug application is not a challenging problem at least during 24 hours after operation.

Key words: Ketamine, Lumbar spine surgery, Postoperative pain.

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1. INTRODUCTION

Pain control after spine surgery in patients who had undergone spinal fusion and instrumentation is a major problem. Due to the intractable pain that occur by extensive damage to soft tissue, bones and muscles, pain tolerance is sometimes impossible and patients pass tormenting hours early after operations (1). Postoperative pain may also affect other aspects of treatment such as restriction of ventilation or limbs motility. Reports of these complications including deep vein thrombosis (DVT) (2, 3), muscle atrophy (4, 5), and bed sore (6) had been published.

Although different types of analgesics and protocols for postoperative pain control had been offered, pitfalls of effective pain management remain constant for many patients. Ketamine is an N-methyl-D-aspartate receptor antagonist which has been suggested among different analgesics for postoperative pain control. Despite being an anesthetic drug inducing a state called dissociative anesthesia, at lower doses, ketamine can be used as an analgesic agent (7). Opioid is the most popular drug used during the first 24 postoperative hours while the patients are NPO (nil per os). However, the application of opioid is very challenging since some patients do not consent such a method. Some others, on the other hand, are addicted and resistant to the usual dose of opioid (8). Therefore, ketamine would be a more appropriate option based on its effects on different receptors. It has been shown to be useful in the reduction of acute postoperative pain. It has been used as an analgesic in a variety of surgical interventions with variable routes of administration including oral, intramuscular, intrathecal, subcutaneous, intravenous and topical routes (9). Many clinical trials have reported ketamine as a good analgesic agent in many fields of medicine such as orthopedics, gynecology, oncology, and pediatrics.
(7, 9, 10). In the present study, the analgesic efficacy and safety of low-dose intravenous ketamine infusion for pain management in patients with spondylolisthesis who had undergone lumbar spinal fusion and instrumentation were evaluated. Although different routes for administration of ketamine exist, we preferred the intravenous route since it could provide better control over side effects due to the low half-life of intravenous ketamine (10).

2. METHODS

A double-blind prospective randomized clinical trial study was planned on patients suffering lumbar spondylolisthesis who had undergone surgery. After obtaining approval from the Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran, 45 ASA (American Society of Anesthesiologists) I or II patients aged 20-70 years old were recruited in the study. Patients were all referred by a surgical clinic in Alzahra University Hospital, in Isfahan during 2011. Written informed consents were obtained from all study participants. Then, the patients were randomly allocated to one of the analgesic drug groups based on simple randomization process. Uniform random number algorithm was used to produce random numbers in the interval from 0.0 to 1.0. Neither the participants, nor the investigators responsible for following the participants, collecting data, and assessing the outcomes were aware of the intervention assignments.

Patients with any neurological, psychological or cardiovascular problems were excluded. Individuals were also excluded if any problems, such as duodenal ulcers or nerve root damage, occurred during the operation. The same surgical technique was conducted for all patients. The procedure consisted of fixation by pedicular screws, rod placement, and autogenous iliac bone graft harvesting. After transferring patients to the recovery room or ward, neurological examination was performed and analgesic drugs were administrated. In the control group (Group B), routine analgesic protocol of the department (a slow intravenous infusion of 5 mg morphine sulfate for adults) was applied as patients requested for analgesics (maximum every 4 hours). For the intervention group (Group A), ketamine hydrochloride (manufactured by Rotexmedica Company) 0.5 mg/kg/h was continuously infused intravenously by an automatic infusion pump. We used continuous heart and blood pressure monitoring for all patients receiving ketamine in group B. Every 6 hours, a physician, who was not associated with the surgeons, used a questionnaire to evaluate all patients in terms of pain severity, and any side effects of the drugs such as delirium, confusion, salivation and hypotension. Pain severity was assessed by a pain visual analogue scale (VAS) ranging between zero and ten (0 = no pain at all; 10 = the most severe pain the patient might have suffered from). For ethical considerations, supplementary morphine sulfate 5 mg was used subcutaneously if patients scored their pain more than 4. At the end of the study, the supplementary doses were analyzed for each patient.

2.1. Statistical analysis

The results for all studied variables are presented as mean ± standard error (SE). The main statistical method used for analyzing data was repeated measures analysis of variance (ANOVA). Mauchly’s sphericity test was conducted to assess sphericity as a perquisite assumption. Huynh-Feldt correction was applied when this assumption was not satisfied. Within group comparisons at each follow-up time point were made using repeated contrasts. On the other hand, between groups comparisons were conducted using two independent samples t-test adjusted for multiple testing. All analyses were performed in SPSS (16) (version 16, SPSS Inc., Chicago, IL).

3. RESULTS

In this study, 45 ASA I or II patients aged 20-70 years old (24-70 years in group A and 30-68 years in group B) were selected. All patients were referred from surgical clinic of Alzahra University Hospital, Isfahan, Iran.

Overall, 29 (64.4%) female and 16 (33.6%) male patients were studied. Group A contained 22 patients (12 (54.5%) females and 10 (46.5%) males) and group B included 23 patients (18 (78.3%) females and 5 (21.7%) males). In group B, 4 patients experienced drug abortion, 3 suffered from severe uncontrollable nausea and vomiting. One case of systolic hypertension (systolic blood pressure > 180 mmHg) was also observed. In addition, due to mild hallucination, drug dose was decreased to 3 mg/kg for 2 patients. A 70-year-old female in group B, experienced DVT without any previous medical risk factor. The distribution of surgical levels in both groups is presented in Table-1.

Repeated measures ANOVA revealed a significant reduction in measured pain (p < 0.001) among both groups over the follow-up period (Table 2). The test also showed the significant effects of treatment (F = 138.06; p < 0.001) on the recorded pain based on VAS. In addition, the level of pain was consistently higher in the control group compared to the treatment group (Figure 1). Statistically significant group effects on pain were identified at all time points except for the beginning of the study (Table 2, see t-test results). Within groups pain comparisons for successive time points using repeated contrasts showed significant differences between time 1 and time 0 (p < 0.01), and between time 2 and time 1 (p < 0.05) in group A. Similarly in group B, significant pain differences were observed between time 1 and time 0 (p < 0.05) and marginally between time 2 and time 1 (p < 0.1). There was a statistically significant correlation between treatment and time (p < 0.001).

The results of repeated measures ANOVA showed statistically significant differences between the groups in terms of opioid use (F = 141.00; p < 0.001) at all time points (Table 2, see t-values for opioid). In fact, the overall amount of opioid use was significantly lower in the ketamine group compared to the control group.
 opioid use in was higher in the control group than the treatment group (Figure 2). Time had significant effects in the treatment group (p = 0.007) while in the control group the effects were only marginally significant (p < 0.1). A statistically significant difference in opioid use was found between time 1 and time 3 in the treatment group (p < 0.001). In the control group however, the differences between any two successive did not reach the statistical significance level. Furthermore, mean ± SE of total opioid use in the treatment and control groups were 3.68 ± 0.92 and 18.41 ± 0.83, respectively (p < 0.001).

Mean values of pain intensity (measured every six hours by a VAS) were 2.1, 1.8, 1.6, and 1.7 for group A and 3.9, 3.4, 3.5, and 3.5 for group B. The values were significantly different as all intervals (p < 0.01). However, ketamine reached was more efficient in pain control during the first 24 hours (p < 0.001). We considered the request for supplementary morphine as an indicator of insufficient pain control. At the four studied intervals, mean doses of morphine were 1.0, 1.3, 1.3 and 0.0 for group A and 5.2, 4.5, 4.7 and 3.8 for group B. The differences between the two groups were completely significant (p < 0.01).

**Table 2.** Results of within and between groups comparisons for the study variables ¥ p < 0.1; † p < 0.05; ‡ p < 0.01 for within groups comparisons based on repeated contrasts Group A= Treatment group; Group B = Control group ¥ The presented t-values show the results of between groups comparisons.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Period 0</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
<th>Period 4</th>
<th>Treatment</th>
<th>Time</th>
<th>Time * Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>A</td>
<td>5.263 ± 0.252</td>
<td>2.158 ± 0.12‡</td>
<td>1.895 ± 0.13‡</td>
<td>1.684 ± 0.13</td>
<td>1.737 ± 0.10</td>
<td>F = 138.06 p &lt; 0.001</td>
<td>F = 154.13 p &lt; 0.001</td>
<td>F = 14.27 p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>5.455 ± 0.171 t = -0.64 p = 0.52</td>
<td>3.909 ± 0.146† t = -0.22 p = 0.01</td>
<td>3.455 ± 0.11† t = -0.28 p = 0.01</td>
<td>3.500 ± 0.13 t = -0.92 p = 0.01</td>
<td>3.545 ± 0.11 t = -12.03 p &lt; 0.01</td>
<td>F = 43.75 p &lt; 0.001</td>
<td>F = 4.27 p &lt; 0.007</td>
<td>F = 0.603 p = 0.61</td>
</tr>
<tr>
<td>Opioid</td>
<td>A</td>
<td>-</td>
<td>1.053 ± 0.48</td>
<td>1.316 ± 0.52</td>
<td>1.316 ± 0.52</td>
<td>0 ± 0‡</td>
<td>F = 161 p &lt; 0.001</td>
<td>F = 4.27 p &lt; 0.007</td>
<td>F = 0.603 p = 0.61</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>-</td>
<td>5.27 ± 0.40 t = -6.73 p &lt; 0.01</td>
<td>4.55 ± 0.31 t = -5.33 p &lt; 0.01</td>
<td>4.77 ± 0.23 t = -6.10 p &lt; 0.01</td>
<td>3.86 ± 0.46 t = -8.45 p &lt; 0.01</td>
<td>F = 2.79 p = 0.065</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 1.** Mean and 95% confidence interval (CI) of pain in the two studied groups at baseline and during the follow up period [Blue: group A (treatment), Green: group B (control)]

**FIGURE 2.** Mean and 95% confidence interval (CI) of opioid use in the two studied groups during the follow-up period [Blue: group A (treatment), Green: group B (control)]

### 4. DISCUSSION

Pain after surgery is one of the most important reasons causing surgeons and patients to hesitate about the time of surgical intervention. Pain could also affect the early post-surgical results (8, 11, 12). Pain management is thus vital in the final satisfaction of patients and surgeons.

Extensive surgical manipulations to soft tissue, bones and muscles, during operations cause intractable pain that is not easy to tolerate (6, 7). Different protocols and drugs administration routes for pain control exist in neurosurgical departments. Such drugs include opioid, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics and anesthetics drugs. As an analgesic, ketamine has been used with more or less satisfactory results and has recently gained growing attention in pain management (8, 10). A considerable number of trials and analyses have studied the efficacy of ketamine and reported strong evidence supporting its short-term advantages for neuropathic pain (7, 10, 12, 14).

Ketamine is an antagonist receptor of N-methyl-D-aspartate that has been used for many years. It is typically used in anesthesiology but in lower doses it can also be used for analgesia (15). In addition, ketamine has different receptors compared to opioid and thus can be effective even for opioid addicts. The side effects of the drug such as hallucination (16), hypertension, nausea and vomiting have been discussed (11, 17). Ketamine can be administered through different routes such as subcutaneous, intravenous, intramuscular, intrarectal, and intrathecal routes or even locally. However, controversy exists about the
best choice for pain in each patient.\textsuperscript{2,14} Although its usage as an analgesic agent in many fields like orthopedics, gynecology, oncology, pediatrics, and neurology has been reported, we could not find an analysis of the benefits of ketamine on post spinal surgery in the literature.

As mentioned above, ketamine can be used through different routes. However, no preferable route has been suggested for spine surgery. Therefore, we selected intravenous application since it was more convenient and more controllable. Short half-life of the drug, which is 2.5-3 hours by this route, is one of the powerful properties. It provides the opportunity to maintain or reduce the dosage of drug in case of side effects. In our study, 2 patients in group A experienced hallucination that was eliminated during one hour after decreasing the dose.

According to our study, pain levels in both groups were the same at the beginning of the study. Both morphine and ketamine were effective in pain control. Mean values of pain intensity showed that ketamine reached was more efficient in pain control during the first 24 hours. We considered the request for supplementary morphine as an indicator of insufficient pain control. At the four studied intervals, the differences of mean doses of morphine between the two groups were completely significant. Although tolerance had been reported to be a main problem in some studies,\textsuperscript{7,14} we did not see any tolerance to ketamine in patients (Figure 2). The request for supplementary morphine during the final 6 hours (i.e. 18-24 hours after surgery) was lower in group A which indicates the beneficial analgesic effects of ketamine without tolerance to the drug.

As previously noted, ketamine might have some side effects (7, 10, 11, 12, 13, 14, 15, 16). During ketamine infusion in the present study, three patients suffered from intractable nausea and vomiting. We were thus forced to suspend the drug. In one case, ketamine was aborted due to systolic hypertension (systolic blood pressure > 180 mmHg). DVT has also been reported as a complication after operation (4). We observed a case of DVT in group B (control) during the first 24 hours after operation. Although the two groups were not significantly different in terms of DVT occurrence, such finding could highlight the benefits of ketamine administration. It seems that future studies with larger sample sizes are necessary to evaluate this correlation.

Finally, we found ketamine infusion more effective than morphine on postoperative pain control. Moreover, tolerance to drug application was not a challenging problem at least during 24 hours after operation. Therefore, we suggest ketamine as a good alternative analgesic after lumbar spinal fusion and instrumentation. However, the probable side effects should be considered.

**Conflict of interest: none declared.**

**REFERENCES**


