Opioid-Sparing Effect of Preemptive Bolus Low-Dose Ketamine for Moderate Sedation in Opioid Abusers Undergoing Extracorporeal Shock Wave Lithotripsy: A Randomized Clinical Trial

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BACKGROUND: Ketamine has been used as part of a multimodal analgesia regime in opioid abusers undergoing general anesthesia. We studied the opioid-sparing effect of a very low-dose bolus of ketamine as part of moderate sedation for opioid abuse patients undergoing extracorporeal shock wave lithotripsy.

METHODS: In this randomized, placebo-controlled clinical trial, 190 opioid abusers were enrolled. They were stratified into 2 blocks based on their daily opioid consumption. Both blocks were then randomized to receive 0.1 mg/kg IV ketamine (group K) or placebo (group P). Lithotripsy was performed under moderate sedation with intermittent bolus doses of remifentanil (0.2 µg/kg) to alleviate pain. The total remifentanil dose (primary outcome) and respiratory adverse events (secondary outcome) were compared in the 2 groups.

RESULTS: Remifentanil administration in the group with low-opioid consumers was 1.6 ± 0.4 µg/kg (group P) compared with 1.0 ± 0.2 µg/kg in group K (confidence interval [CI] difference 95%, 0.4–0.7; P < 0.001). Patients who had high-opioid consumption received 2.0 ± 0.5 µg/kg (group P) vs 1.5 ± 0.3 µg/kg (group K) remifentanil (CI difference 95%, 0.40–0.75; P < 0.001). Ready to discharge time was statistically longer in high-consumption opioid abusers who received placebo compared with group K (55 ± 13 minutes vs 44 ± 8 minutes, CI difference 95%, 6–15; P < 0.001). The incidences of bradypnea, apnea, nausea, vomiting, and hemodynamic changes were not statistically different between the ketamine and placebo groups.

CONCLUSION: Preemptive low-dose ketamine (0.1 mg/kg) as a bolus has opioid-sparing effects in opioid abusers undergoing moderate sedation. (Anesth Analg 2013;116:75–80)

Ketamine as an N-methyl-d-aspartate receptor antagonist has analgesic effects in acute and chronic pain. Ketamine enhances the inhibitory control of pain perception via descending pathways, boosts the peripheral antinociceptive effect of opioids, prevents opioid tolerance, and enhances analgesia via other mechanisms.1–6 A growing body of evidence supports ketamine use as an adjuvant therapy in postoperative analgesia.7–9 However, there are still controversies.10–12

Postoperative analgesia in opioid abusers requires cautious administration of multimodal therapy to minimize adverse events.13 The success of opioid-sparing effects of intraoperative ketamine has been studied in opioid abusers.14–15 Nevertheless, the effectiveness of bolus low-dose ketamine in moderate sedation has not been elaborated in previous studies especially with very low doses such as 0.1 mg/kg.

We hypothesized that a single preemptive IV low-dose ketamine bolus would have a remifentanil-sparing effect (primary outcome) in opioid abusers undergoing moderate sedation for extracorporeal shock wave lithotripsy (ESWL). The incidence of bradypnea, apnea, nausea, vomiting, hemodynamic changes, and ready to discharge time were also evaluated as secondary outcomes.

METHODS

General Description

After obtaining IRB approval and written informed consent, 190 opioid abuse candidates for ESWL were enrolled in this prospective, double-blind, placebo-controlled, randomized clinical trial. This study was conducted in a university-affiliated hospital (Labbafinejad Hospital, Shahid Beheshti University of Medical Sciences) over a 1-year period (September 2009 through October 2010).

Patient Requirements

Male and female patients, ASA physical status I and II, aged 18 to 60 years, with a renal stone in the kidney or upper one-third of the ureter, who were nonpregnant, not allergic to ketamine, midazolam, or remifentanil, with no risk of difficult airway management, or history of cognitive or memory disorders, and no previous abuse of tranquilizer, crack cocaine, alcohol, or IV drugs were included. An opioid abuser was defined as a patient taking daily oral opioid (either only opium or methadone) for at least the...
previous 6 weeks. Patients were asked to take their daily opioid as routine with 100 mL water, despite fasting for the procedure.

**Blocking and Randomization**

Patients were stratified into 2 blocks according to their opioid intake. High-opioid intake was defined as daily opioid abuse of >2 g/d or 50 mg/d methadone whereas those with lower requirement than this value were defined as the low-opioid requirement group. This was based on a pilot study by our group. In the pilot study, we recruited 20 subjects receiving oral methadone maintenance therapy (MMT) for detoxification. We found that the median consumption was 50 mg/d at steady-state conditions (interquartile range, 40–58 mg/d). These patients initiated MMT and quit taking any other opioids (confirmed by urinalysis 1 week later) and gradually adjusted the dose of methadone until they had no craving for their previous opioid use nor symptoms of overdose/withdrawal. They remained on the same dose of methadone for 2 weeks (steady-state condition) and the methadone dose was gradually reduced (detoxification started). In the same pilot study, median oral opium usage (mean consumption in 2 weeks before MMT initiation) was 2 g/d (interquartile range, 1.5–3 g/d). In each block, subjects were randomized to receive ketamine (group K) or placebo (group P; Fig. 1).

**Study Protocol**

Patients were placed on the ESWL table (Dornier Compact Delta II lithotripsy) and standard monitoring, including electrocardiogram, noninvasive arterial blood pressure, heart rate (HR), pulse oximetry, and end-expiratory carbon dioxide ($P_{\text{etCO}_2}$), were applied. A facemask was positioned to deliver 6 to 8 L/min oxygen with a sampling catheter attached to measure $P_{\text{etCO}_2}$ and respiratory rate (RR). After obtaining baseline values (systolic, diastolic, and mean arterial blood pressure, HR, RR, pulse oximetry, $P_{\text{etCO}_2}$), patients were trained to evaluate their baseline level of pain (defined as “a feeling of physical hurt”) using an 11-point verbal rating scale (VRS; with 0 = none and 10 = most severe). After obtaining baseline measurements, an IV catheter was placed and normal saline was infused at a rate

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**Figure 1.** Flow diagram showing the selection, blocking, and randomization of patients.

#### Flow Diagram

- **Eligible patients (n = 190)**
- **Stratified (n = 190)**
  - **High-opioid requirement group** (n = 86)
    - Randomized to receive ketamine or placebo
      - Allocated to **ketamine group**
        - n = 43
        - All patients completed trial
          - Completed trial (n = 43)
      - Allocated to **placebo group**
        - n = 43
        - One patient required rescue morphine therapy for intractable pain
          - Completed trial (n = 42)
  - **Low-opioid requirement group** (n = 104)
    - Randomized to receive ketamine or placebo
      - Allocated to **ketamine group**
        - n = 52
        - Three patients required rescue morphine therapy
          - Two patients quit the trial
            - One patient required antihypertensive therapy
          - Completed trial (n = 46)
      - Allocated to **placebo group**
        - n = 52
        - Four patients required rescue morphine therapy
          - Two patients quit the trial
          - Completed trial (n = 46)

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*: Patients with an oral opiate requirement more than or equal to 2 gr/day of opium or 50 mg/day of methadone.

**: Patients with an oral opiate requirement less than 2 gr/day of opium or 50 mg/day of methadone.
of 10 mL/kg/h. Midazolam (0.03 mg/kg) was then injected to reduce the anxiety of the participants.

Subjects in group K received a bolus dose of 0.1 mg/kg IV ketamine (Rotexmedica, Trittau, Germany) diluted in 10 mL distilled water before the procedure (prepared by an anesthesiologist), whereas subjects in group P received the same volume of placebo. The anesthesiologist administering the drug and the patient receiving the medication were blinded to the content of the syringe. During the procedure, VRS was assessed every 5 minutes; in addition, patients were asked to notify the anesthesia provider of any sensation of pain >3 on a VRS. Any episode of pain with a VRS score >3 was treated with a bolus of IV remifentanil (0.2 µg/kg; Ultiva, GlaxoSmithKline, UK) as long as it was >2 minutes from the last injection.

Primary outcome was defined as the total remifentanil administration during the procedure for both groups. Secondary outcomes included apnea (no air movement with no respiratory effort lasting >10 seconds), bradypnea (RR < 10), nausea and vomiting, hemodynamic changes (±30% changes in the mean arterial blood pressure or HR lasting >1 minute), and ready to discharge time (time between entering recovery room until achieving the home-discharge criteria). Discharge criteria were as follows: fully awake, walking with no dizziness, having no pain, or hemodynamic change. Secondary outcomes were evaluated every 5 minutes until the patient was discharged.

Exclusion Criteria
Patients with procedures lasting >1 hour (from the initiation of sedation until the cessation of lithotripsy) and those requiring extra medications (e.g., morphine for intractable pain, IV antihypertensive drugs, or vasopressors) were excluded from the study; however, they were reported.

Statistical and Power Analysis
In a pilot study (conducted by the authors) in which high- and low-opioid abusers received placebo, remifentanil administration was 1.65 ± 2 µg/kg for ESWL. Information from the study by Loftus et al.18 indicates that the total intraoperative morphine requirements in those who received ketamine was 5 ± 7 mg, whereas it was 11 ± 21 mg in their placebo group; this shows a 50% reduction in opioid requirement when ketamine was added. Therefore, we assumed that total remifentanil dose should also be halved by ketamine administration. Based on these findings and assuming that the SD was the same between the 2 populations and using a power of 80% with α = 5%, we required 90 patients in each group. Considering the likelihood of dropouts, we enrolled 190 opioid abusers in this study.

Data were analyzed to assess distribution based on Lilliefors test, histogram plot, skewness, kurtosis, and mean–median difference. Data were treated as normal whenever the histogram appeared normal and one of the above-mentioned tests (e.g., Lilliefors) had a P > 0.05. Independent t test (when appropriate, Student t test with unequal variance, based on a method described by Zhou et al.19) was applied to compare means for continuous variables. Mann-Whitney–Wilcoxon tests were applied for ordinal variable (e.g., VRS). Fisher exact test was applied for frequencies. Spearman correlation was used for skewed variables (e.g., ready to discharge time). Significance was accepted at the 5% level (P < 0.05).

RESULTS
One hundred ninety opioid abuse candidates for ESWL were included in this study; 177 participants completed the trial (13 dropouts; Fig. 1). Of 190 opioid abusers, 86 patients were high-consumption opioid users, whereas 104 were low-consumption opioid users. Fifty-two patients in the high-consumption opioid group (60%) were taking oral opium and the rest (40%) were taking methadone. In the low-consumption opioid group, 69 patients (66%) used opium and the rest used methadone. Median oral opium and methadone usage in low-consumption opioid subjects were 1 g/d and 35 mg/d, respectively (interquartile range, 0.5–1.4 g/d and 10–56 mg/d, respectively), whereas it was 4 g/d and 80 mg/d, respectively (interquartile range, 2.6–8 g/d and 65–120 mg/d, respectively) in high-consumption opioid subjects.

Patients’ characteristics are depicted in Table 1. Weight, age, and gender were not statistically different between ketamine and placebo groups (both in high- and low-consumption opioid abusers).

Outcomes are shown in Table 2. Total remifentanil administration (primary outcome) and VRS were statistically higher in group P compared with group K (both in high- and low-consumption opioid abusers). Remifentanil administration in low-opioid consumers was 1.6 ± 0.4 µg/kg (in group P) vs 1.0 ± 0.2 µg/kg in group K (confidence interval [Cl]adj difference 95%, 0.4–0.7; P < 0.001). Patients with high-opioid consumption received 2.0 ± 0.5 µg/kg (group P) vs 1.5 ± 0.3 µg/kg (group K) remifentanil (Cladj difference 95%, 0.40–0.75; P < 0.001).

Ready to discharge times were longer in those who received placebo in the high-consumption opioid users compared with group K (55 ± 13 minutes vs 44 ± 8 minutes; Cladj difference 95%, 6–15; P < 0.001). Spearman correlation coefficient between “ready to discharge times” and “total remifentanil requirements” was 0.3 (95% Cl, 0.19–0.45; P < 0.001), which is depicted (also showing subgroups) in Figure. 2. The incidence of bradypnea, apnea, nausea, hemodynamic change, and vomiting was not statistically different between groups.

DISCUSSION
Preemptive intraoperative low-dose ketamine has generally been shown to have intra- and postoperative analgesic effects in opioid-naive patients.17–21 However, a few studies have contradicted these findings.3–12

<table>
<thead>
<tr>
<th>Table 1. Patients’ Characteristics in Each Group and Subgroup</th>
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<tr>
<td><strong>Low-consumption opioid user, n = 92</strong></td>
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Figures are presented as mean ± SD or number of patients.
Group P = placebo group; Group K = ketamine group.
We demonstrated in this study that a preemptive very low bolus dose of ketamine (0.1 mg/kg) has an opioid-sparing effect in opioid abuse (both in high- and low-consumption opioid) candidates for ESWL. This study confirms findings advocating ketamine (N-methyl-D-aspartate antagonist) as an effective adjuvant in perioperative analgesia in patients who are opioid abusers.\textsuperscript{13–15}

Ketamine as an analgesic adjuvant has been used in opioid abusers in several studies. In these patients, ketamine had marked analgesic effects.\textsuperscript{13–15} Previous studies have focused on the effect of intraoperative infusions of ketamine on the intra- and postoperative reduction of opium consumption in opioid abusers undergoing general anesthesia. We evaluated the opioid-sparing effect of preemptive single-shot low-dose ketamine for patients who underwent moderate sedation.

In a pilot study conducted before this research, we examined 2 different bolus doses of ketamine (0.3 mg/kg and 0.1 mg/kg) from a wide range examined in previous literature.\textsuperscript{9} There were more patients who became uncooperative and agitated with the high dose of 0.3 mg/kg ketamine than the lower dose. Therefore, we used 0.1 mg/kg ketamine for the current study.

A VRS was used for pain assessment. Anesthesiologist or a trained nurse was always with the patient throughout the procedure and recovery until his or her discharge. Because a VRS score >3 was used for analgesia administration, very few patients had higher scores.

ESWL is usually performed under moderate sedation. Various protocols have been proposed.\textsuperscript{22–26} Rego et al.\textsuperscript{26} demonstrated that intermittent boluses of remifentanil were more effective in reducing pain in ESWL compared with its infusion. Therefore, we administered intermittent boluses of remifentanil for pain relief.

Intra- and postoperative pain management in opioid abusers requires meticulous titration of opioid analgesia to prevent adverse effects.\textsuperscript{27} Therefore, multimodal therapy including nonsteroidal anti-inflammatory drugs, ketamine, acetaminophen, and anticonvulsants were administered to minimize potential complications related to opium consumption.\textsuperscript{13,15}

The amount of opioid consumption, its duration, and patient characteristics will affect the dose response to opioid analgesics.\textsuperscript{15,28,29} Contrary to previous studies, opioid abusers in our study usually consumed oral opium.\textsuperscript{30} Although high- and low-dose opioid use has not been extensively studied and there are controversies on its definition,\textsuperscript{31–33} our pilot study provided data that allowed us to separate high- from low-dose consumption.

The data were analyzed to evaluate the effect of high- or low-opioid consumption on the primary and secondary
outcomes. Remifentanil administration (primary outcome) was higher in the placebo group compared with those who received ketamine in both subgroups. As described by Angst and Clark, we assume that ketamine affects upregulated antinociceptive pathways (in both high- and low-consumption opioid abusers); therefore, these pathways may be sensitive to even low doses of ketamine.

Several studies have focused on the effect of low-dose ketamine on acute and chronic pain management. However, the dosage, type of surgery and anesthesia, time of injection, type of postoperative analgesia (e.g., epidural analgesia), and patients’ characteristics vary in different studies with different results. A review of the literature shows that low-dose ketamine has been administered (mostly in opioid-naive patients) in a range between 0.1 mg/kg and 1 mg/kg as an initial loading dose that could be followed (or applied as a single injection) with an infusion (in some studies with no loading dose) ranging from 42 µg/kg/h to 83 µg/kg/h.

For opioid-dependent patients, Loftus et al. administered 0.5 mg/kg IV ketamine as an initial loading dose followed by an infusion of 10 µg/kg/min during surgery that resulted in an opioid-sparing effect. In another study by Subramaniam et al. of patients with a history of preoperative narcotic intake who were given very low-dose ketamine infusion (2 µg/kg/min) during and after spinal surgery and postoperatively, epidural analgesia did not show further pain relief from the ketamine.

One of the limitations in this study was how opioid abuse was defined. Our investigation is similar to Loftus et al.’s study in which patients with a history of daily opioid use for at least 6 weeks were enrolled. Loftus et al. considered these patients opioid-dependent; however, we believe dependency requires documentation of withdrawal symptoms. Therefore, we applied the term opioid abuser instead.

Patients in this study did not use opioids for a medical purpose. Oral opium is a street drug that is unreliable when measuring the exact amount of effective drug released. To attenuate this confounding factor, we stratified patients according to their daily opioid consumption based on our pilot study. Moreover, in this study we included subjects who were only consuming oral opium or methadone (not both at the same time). Those who misused other opioids or took the drug via other routes were not studied. Although those with a history of tranquilizer, crack cocaine, alcohol, or IV drugs abuse were not included, subjects who took nonsteroidal anti-inflammatory drugs were not excluded.

Future multicenter studies should concentrate on enrolling 1 type of opioid abuser, duration of opioid abuse, concomitant drug usage, patients’ characteristics, and ethnicity. Further randomized clinical trials are required to determine the most appropriate dose of ketamine for moderate sedation in opioid abusers, considering the duration and type of opioid abuse.

In conclusion, we demonstrated that a preemptive bolus dose of ketamine (0.1 mg/kg) has opioid-sparing effects in opioid abusers undergoing moderate sedation.

DISCLOSURES
Name: Babak Gharaei, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the article and final review.

Attestation: Babak Gharaei has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Alireza Jafari, MD.
Contribution: This author helped conduct the study and analyze the data.
Attestation: Alireza Jafari has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Attestation: Alireza Salimi has seen the original study data and approved the final manuscript.

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REFERENCES
27. Davis JJ, Swenson JD, Hall RH, Dillon JD, Johnson KB, Egan TD, Pace NL, Niui SY. Preemptive “fentanyl challenge” as a tool to estimate postoperative opioid dosing in chronic opioid-consuming patients. Anesth Analg 2005;101:389–95
34. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology 2006;104:570–87