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ORIGINAL ARTICLE

Assessment of Ketamine Effect as Adjuvant to Morphine in Post- Operative Pain Reduction in Donor Kidney Transplanted

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Abstract

Background: Morphine is a strong analgesic agent being used in acute pain but adverse effects may lead to its discontinuation before sufficient pain relief is obtained. Ketamine is an anti-nociceptive drug which blocks N-Methyl-D-Aspartate receptors and can modulate acute pain. In this study, ketamine effect as an adjuvant with morphine for post-operative pain management is evaluated.

Method: In a double blind randomized clinical trial, 50 kidney donors undergoing nephrectomy and receiving morphine as analgesics were enrolled. Patients were divided into two groups receiving ketamine (ketamine group) and saline serum (placebo group). Post-operative pain was assessed by measuring cumulative morphine consumption and visual analog scale pain scores were assessed in 48 hours duration after surgery.

Results: Pain intensity and cumulative morphine consumption were lower and sedation score was higher in the ketamine group. Both groups were similar regarding the side effects.

Conclusion: Regarding post-operative analgesia management, ketamine administration improved pain intensity and when its administration was continued for 48 hours post-operatively, there was a significant decrease in morphine consumption.

Keywords: Ketamine; Morphine; Pain; Analgesia; Post-operation

Introduction

Pain control after surgery is an important issue in pain management. Morphine is a strong analgesic agent used routinely in acute pains. Repeated morphine administration or continual infusion usually provides rapid and effective analgesia after surgery. However, adverse effects sometimes occur and may require discontinuation of morphine before sufficient pain relief is obtained.[1] The combination of non-opioid analgesics with morphine provides a morphine-sparing effect and decreases toxicity. This concept is the basis of multimodal analgesia.[2]

Ketamine is an anti-nociceptive drug which blocks N-Methyl-D-Aspartate (NMDA) receptors. The role of the NMDA receptor in modulating acute pain and the subsequent central sensitization has been demonstrated.[3-5] In addition to that of morphine, the effect of NMDA antagonist like ketamine on pain control, solely or in combination with other drugs has been shown in animal models.[6-11] Although clinical studies have provided evidence for the potentiating effect of ketamine on morphine analgesic effects,[12-24] some studies could not find an association between morphine and ketamine in pain relief.[25-29]

Post-nephrectomy pain is very severe because of large subcostal incision and interaction with breathing.[30] On the other hand, post-operation pain in living donor kidney transplantation is a disincentive factor.

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Pain control in these patients is critical and requires significant and effective intervention. Thus larger doses of opioids are needed for analgesia in the first few days after surgery.[31]

The aim of the current clinical trial was to determine the effects of ketamine on post-operation opioid consumption, pain intensity and the side-effects when used simultaneously with morphine during the first 48 hrs after nephrectomy in donor kidney transplantation.

Materials and Methods

The research proposal was approved in two research and medical ethics committees in Baqiyatallah University of Medical Sciences. The study was a double blind randomized clinical trial. Sixty subjects who were candidate for nephrectomy as donors were selected in Baqiyatallah Hospital. The hospital is one of the greatest general hospitals in Tehran affiliated to Baqiyatallah University of Medical Sciences. All subjects were donors of renal transplantation admitted to the hospital from May 2007 to December 2008. During the day before surgery, an anesthesiologist visited the patients and included the ones with the American Society of Anesthesiologists (ASA) class I criteria. Informed consent was obtained from each patient, and the patients were instructed before surgery on the use of the Visual Analogue Scale (VAS), and Pain Faces Scale (PFS). They were randomly divided into two parallel groups. Randomization was assigned to patients of the two groups according to random numbers table.

All patients had the same anesthesia protocol. They received 0.1 mg/kg of morphine as premedication. Anesthesia was induced by thiopental (5-7 mg/kg) and atracurium (0.5 mg/kg) afterwards. Maintenance of anesthesia was done with isoflurane (proportionate to the patients' hemodynamic status), N2O (50%) and O2 (50%).

All operations were done in lateral decobitus position and flank incision was performed for all the patients. At the end of the surgery, the patients' neuromuscular relaxation was reversed pharmacologically and they were extubated in the operating room. The patients were taken to the recovery room for immediate postoperative follow-up.

When patients entered the recovery room and achieved an acceptable level of consciousness, VAS was measured. In the ketamine group, ketamine was administered separately with an initial bolus of 0.5 mg/kg followed by infusion of 2 μg/kg/min during the first 24 hours and 1 μg/kg/min in the following 24 hours. In the placebo group, ketamine was replaced by saline serum as placebo and administered under the same conditions. In both groups, if the patients requested analgesia, 2 mg of morphine was administered by nurses without any limitations as the loading dose followed by 1 mg every 5 minutes until the VAS became less than 4.

All the patients were monitored in the wards in an intensive care unit setting. In both groups; morphine consumption, pain intensity, the sedative effect and the side effects were evaluated 0, 1, 2, 3, 4, 8, 12, 24, 48 hours after operation. The side effects included nausea, vomiting, itching, headache, hallucinations, and nightmares. Pain intensity was assessed in rest and during cough, using two ways; the first was the use of a 100-mm VAS an anchored by "no pain" at one end and by "worst possible pain" at the opposite end. The second one was the Pain Faces Scale (PFS) consisting of six schematic face pictures among which the patients selected the most similar pictures to themselves. For evaluation of the sedative effect, we used Ramsey Sedative Score (RSS). It is an objective evaluation ranging 0-6, which was done by the anesthesiologist.

The analyses were performed, using the SPSS software for Windows, Version 15 (SPSS Inc., Chicago, IL, USA). The data are presented as proportion and mean±SD. The dependent and independent variables were the treatment group and pain intensity (VAS, PFS), amount of morphine consumption, and RSS, respectively. T-test was used for comparison between the two groups. The repeated measurement of ANOVA model was utilized to determine the changes of pain intensity and morphine consumption during the study. For ordinal variables like RSS, we used Mann-Whitney test for the independent comparison and Freidman test was conducted for the measurement during 48 h. Differences with $p<0.05$ were considered statistically significant.

Results

Sixty patients fulfilled the study criteria for randomization, but five in the ketamine group and five in the Placebo group dropped out of the study. Table 1 shows the demographic and surgical characteristics of the patients. The data were similar between the two study groups. Itching, headache, hallucination, and

Table 1: Patients demographic and surgical characteristics in two study groups

Variable	Ketamine group	Placbo group	*P* value
Sex (M/F)	24/1	20/5	0.189*
Age (mean±SD)	27.3±5.5	27.9±3.9	0.656**
Weight (mean±SD)	68.8±8.1	70.3±10	0.57**
History of previous surgery	10/15	12/13	0.776**
Operation duration	106±7	106.8±10	0.745**

* Fisher's exact test; **Two sample t test

nightmares were not detected in either group, but there were 3 (12%) cases in each group with nausea and vomiting. There was only one case of short-term hallucination (less than 3 hours) in ketamine group which appeared as a feeling of a unilateral face inflammation. Both groups were comparable with respect to pain intensity after surgery before any analgesic administration (86±12.6 in the ketamine group vs. 83.6±14.4 in the placebo group; t=0.628, p=0.533).

The cumulative morphine consumption reduced significantly in the ketamine group (3.0±2.0 mg in ketamine, in contrast to 17.8±9.2 mg morphine in the placebo group; t=7.817, p<0.001). There was a ~83% reduction in the total amount of morphine administration in the ketamine group during the 48 hrs of study. Ketamine administration reduced the morphine dose and declined pain intensity significantly (Table 2). Moreover, the repeated measured ANOVA showed that pain intensity in rest and with cough (VAS) during the 48 hours follow-up period was consistently and significantly (p<0.001) lower for the ketamine group compared with that in their placebo counterparts (Figure1).

This was the case despite the larger amounts of morphine administered to the placebo group. Figure 1 shows the significant pain intensity reduction between the two study groups. In contrast to pain reduction, sedation score was higher in the ketamine group. The patients with ketamine administration had a higher rank in RSS significantly, while this increased rank continued until 12 hours after surgery. The two groups were, of course, comparable in 24 and 48 hours follow up in this regard (Figure 2).

Discussion

The main finding of this double blind randomized trial was that the adjunction of small doses of ketamine with morphine resulted in a significant reduction in pain intensity associated with a reduction in cumulative morphine consumption in post nephrectomy. Many studies showed that ketamine interacts

Table 2: The comparison of pain intensity (VAS) mean between ketamine and placebo groups

	Group	No.	Mean	SD	t	*P* value
VAS before analgesia	placebo	25	83.6	14.4	0.628	0.533
	ketamine	25	86	12.6		
vas1	placebo	25	81.6	16.5	4.984	*P*<0.001
	ketamine	25	53.2	23.2		
vas2	placebo	25	80	14.7	7.01	*P*<0.001
	ketamine	25	49.2	16.3		
vas3	placebo	25	80.4	12.4	8.948	*P*<0.001
	ketamine	25	44.4	15.8		
vas4	placebo	25	80	12.6	8.256	*P*<0.001
	ketamine	25	45.6	16.6		
vas8	placebo	25	78.8	13.9	8.1	*P*<0.001
	ketamine	25	45.6	15		
vas12	placebo	25	73.2	16	5.936	*P*<0.001
	ketamine	25	43.6	19.1		
vas24	placebo	25	65.6	13.6	8.413	*P*<0.001
	ketamine	25	32.8	14		
vas48	placebo	25	46	9.6	7.477	*P*<0.001
	ketamine	25	24.8	10.4		

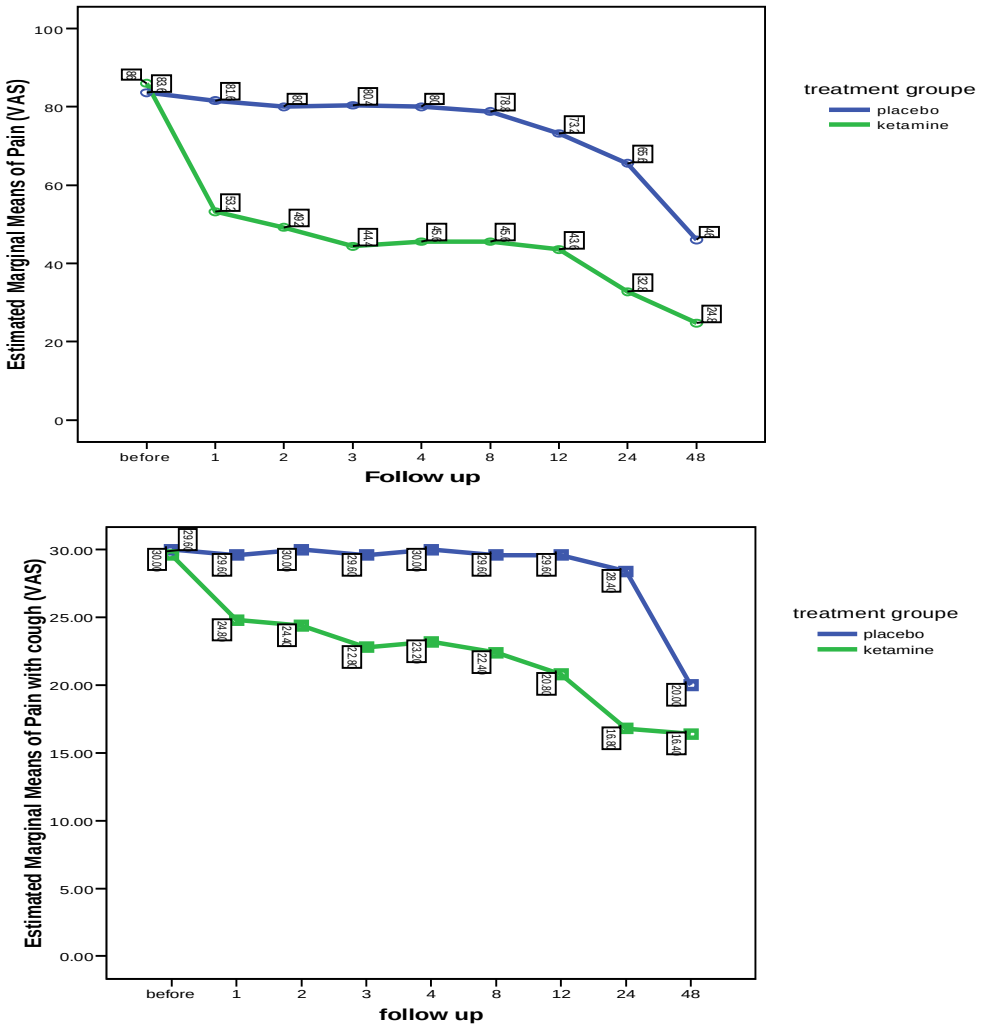

Fig. 1: Pain intensity during 48 hours follow-up in two study groups

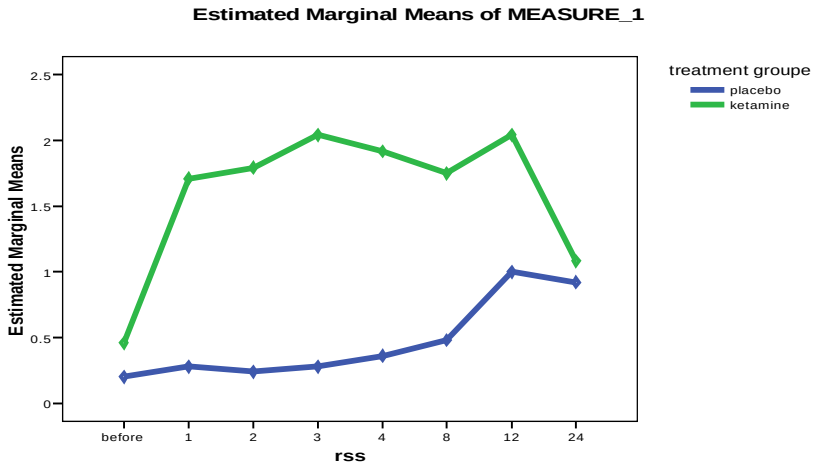

Fig. 2: The Ramsey sedative score during 48 hours follow up in two study groups

with opiate receptors, and it has been suggested that ketamine-induced analgesia is mediated through opiate receptors.[32-34] Release of peptide from the spinal cord during surgery evokes NMDA receptors' activity and neuronal excitation. This activation leads to hyperalgesia and wind-up.[35] Therefore, it seems logical to encourage the ketamine use (NMDA Antagonist) as an adjuvant therapy with morphine for post-operative analgesia.

Our findings were similar to those of some studies with the same design. Nesher *et al.* (2008) and Michelet *et al.* (2007) examined the aforementioned hypothesis in thoracotomy. They declared 50% reduction in pain and 25% reduction in morphine consumption in the ketamine group.[36,37] The same results have been published by Kollender *et al.* in bone and soft tissues surgery,[38] Snijdelaar *et al.* in prostatectomy,[24] and Taura *et al.* in liver resection.[21] Weinbroum used a single dose 250 µg/kg ketamine adjunct with morphine for post-operation pain release. After 120 min, the pain intensity was 2.5 folds, approximately lesser in ketamine injection.[22] Adriaenssens *et al.* found that VAS score decreased significantly during 48 hrs. However, this was similar in both groups. Cumulative morphine consumption at 48 hrs was lower in the ketamine group than that in the placebo one (28 vs. 54 mg).[18] Guillou *et al.* (2003) got the same results like Adriaenssons'.[23] Ketamine used through epidura with a combination of morphine had the same effect as that used intravenously (IV).[15-17,39,40] Many studies used ketamine preemptively to manage post-operation pain. They found that it was effective but it should be administered over 75 µg/kg.[41,42] However, other studies which have used preemptive ketamine are not conclusive.[27,43-46]

Bilgin *et al.* conducted a triple group randomized trial. The patients in group 1 received ketamine (0.5 mg/kg IV) bolus before the induction of anesthesia; The patients in group 2 received 0.5 mg/kg of ketamine (IV bolus) before the induction of anesthesia, followed by ketamine infusion (600 µg/kg/h), which was stopped at wound closure; the patients in group 3 received normal saline (IV bolus) before the induction of anesthesia followed by saline infusion and then 0.5 mg/kg ketamine (IV bolus) immediately after wound closure. The results of this study showed that there was a significant difference between groups 1 and 2 and groups 1 and 3 regarding pain intensity (VAS).[47] Perhaps, these differences were due to pain intensity experienced before the operation.[18]

Nevertheless, some studies could not support the post-operative analgesic effect of ketamine with a combination of morphine. Edwards *et al.* did not find any difference either in pain intensity or in lung function and morphine consumption. They conducted their study on the elderly (>65 yrs) patients.[25] In two separate studies on females who underwent abdominal hysterectomy, neither pain intensity nor morphine consumption was different in the ketamine and control groups.[28,29] Becke *et al.* explained that intra-operative low-dose ketamine had no effect on morphine consumption during the first 72 hrs after urologic surgery. They believed that the difference in pain intensity reflected additional sedation and anti-nociceptive effects of ketamine rather than a true 'prevention' of pain,[43] but we believe that they used ketamine during operation but not after it. In addition, neither post-tonsillectomy nor appendectomy pain was reduced in children by adding ketamine to morphine.[48-51]

Overall, it seems that ketamine is an appropriate adjuvant therapy with morphine in post-operative period. Ketamine decreases the tolerance to morphine and declines morphine consumption. Conflicting results existing among studies refer to the following factors: 1) time of injection (pre, intra or post- operative), 2) kind of injection (IV, subcutaneous, epidural …), 3) duration of administration (0 to 72 h), 4) Ketamine dose, 5) age of patients and 6) kind of operation.

There were some limitations in our study. The sedation was only assessed but mental and physical status should also be evaluated. We did not have any intravenous patient control analgesia (IV-PCA) devices and could not prepare them. At the end, a systematic review and meta-analysis is necessary to evaluate the ketamine effect as adjuvant with morphine for analgesia.

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