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Effect of Adding Ketamine to Pethidine on Postoperative Pain in Patients undergoing Major Abdominal Operations: A Double Blind Randomized Controlled Trial

[1]A. Nourozi, [1]H. Talebi, [2]S. Fateh, [1]A. Mohammadzadeh, [3]P. Eghtesadi-Araghi,
[4]Z. Ahmadi, [4]A. Savarabadi and [4]A. Mohebbi
[1]Department of Anesthesiology, Arak University of Medical Sciences, Arak, Iran
[2]Department of Surgery, Arak University of Medical Sciences, Arak, Iran
[3]Parsteb Pajouheshyar Medical Sciences Research Institute, Tehran, Iran
[4]Department of Medicine, Arak University of Medical Sciences, Arak, Iran

Abstract: To determine the effect of adding ketamine to pethidine in reducing post-operative pain in patients undergoing major abdominal operations, in a double blind randomized controlled trial, 100 patients aged 15-60 years who were candidate for elective major abdominal surgery allocated into two groups of pethidine + ketamine group (5 mg pethidine and 0.25 mg kg^{-1} ketamine) or pethidine and placebo group (10 mg pethidine and NS) according to the regimen prescribed in postanesthesia care unit. Severity of pain (using visual analogue scale), prescribed dose of pethidine and side effects were recorded until 24 h after operation. Regarding post-operative pain, pethidine + ketamine group showed significant lower scores in all the times except 0 min, 2, 6 and 16 h. Nausea was significantly less frequent amongst pethidine + placebo group at times of 0, 15, 30 and 45 min ($p<0.05$). Comparison of two groups did not show significant differences in prescribed pethedine dose in 0, 9, 12, 16, 20 and 24 h ($p>0.05$). Yet, the mean dose of administered pethidine as rescue analgesic was significant lower in pethidine + ketamine group compared to pethidine + placebo group (112±31.5 mg vs. 133.5±24.5 mg, $p<0.001$). In conclusion, our results showed that co-administration of ketamine and pethidine in postanesthesia care unit will improve postoperative pain and reduce narcotic consumption. It may, however, increase rate of postoperative nausea in the first hour after operation.

Key words: Ketamine, pethidine, postoperative, pain, analgesia, nausea

INTRODUCTION

Major abdominal surgeries are accompany with severe postoperative pain which necessitate prescription of high doses of analgesics for pain relief (Reeves *et al*., 2001). Although, opioids widely use for this purpose, they are associated with adverse effects such as nausea and emesis, tolerance, pruritis, urinary retention and respiratory depression (Baig *et al*., 2006; Weinbroum, 2003). Thus, introducing adjunct drugs to be able to reduce the required dose of opioids would have great clinical relevance (Baig *et al*., 2006).

On the other hand, it has been shown that ketamine is a potent analgesic and diminish postoperative pain and can be used alone or as an adjunct drug (Dich-Nielsen *et al*., 1992). However, like opioids, ketamine may accompany with some adverse effects such as sedation, pruritus, or adverse psychological reactions (Himmelseher and Durieux, 2005). These adverse effects are dose dependent and lowering dose of ketamine will reduce these side effects (Himmelseher and Durieux, 2005). Although, there are several evidences regarding adding ketamine to morphine for management of postoperative pain (Himmelseher and Durieux, 2005; Schmid *et al*., 1999; Subramamiam *et al*., 2004), to our knowledge, there is no study to compare the effects of combination of low dose ketamine and pethidine for reducing postoperative pain. Efficacy of 1 mg kg^{-1} (Dich-Nielsen *et al*., 1992) and 0.3 mg kg^{-1} (Maurset *et al*., 1989) in alleviating postoprtaive pain compared to pethidine have been reported. Consequently, in the present study, we aim to study the effects of combination of pethidine and lower dose ketamine on postoperative pain.

MATERIALS AND METHODS

This study conducted at Valiasr Hospital of Arak University of Medical Sciences (Arak, Iran), from September 2003 to September 2004. Ethical committee of

Corresponding Author: Payam Eghtesadi-Araghi, No. 30, Apartment No. 5, 1st Golzar St., Ashrafi Esfahani Blvd., Ponak Sq., Tehran-1476783476, Iran Tel/Fax: ++98 (21) 44 45 48 14

human research of the university approved the study. Also written informed consent was obtained from each patient before entering the study. Hundred patients aged 15-60 years who were candidates for elective major abdominal operations were enrolled into the study. Exclusion criteria included patient refusal for participating in the study, chronic pain, chronic opioid consumption, drug or alcohol abuse and contraindication for ketamine or pethidine. Thus, patients with history of cardiovascular disease, allergy to study drugs, hypertension, pheochromocytoma, psychological disorders, loss of consciousness, seizure or renal diseases were excluded. Moreover, we did not enter obese cases (body mass index >25 kg m^{-2}), urgent surgical procedures.

Patient with these characteristics allocated into two groups of pethidine + ketamine and pethidine + placebo by using a table of random numbers.

Method of anesthesia: On arrival in the operation room, an intravenous line was set up and patients were premedicated with 2.5 μg kg^{-1} Fentanyl (Aborayhan Co., Tehran, Iran) and 0.03 mg kg^{-1} midazolam (Tehran Kimia Co., Tehran, Iran) intravenously before induction of anesthesia. After 3 min of pre-oxygenation with oxygen 100%, general anesthesia was induced with incremental doses of sodium thiopentone (Sandoz, France) up to 5 mg kg^{-1} until disappearance of the ciliary reflex under standard monitoring. To facilitate laryngoscopy and endotracheal intubation, 0.5 mg kg^{-1} Atracuronium (Aborayhan Co., Tehran, Iran) was used. Three minutes later, laryngoscopy using Macintosh blade size 3 and intubation using intratracheal tube (size 7.5-8) were performed by an anesthesiologist. After that, anesthesia was maintained with 1-1.5 MAC (inspiratory saturation) of Halothane in O_2 and N_2O (50% mixture). Atracuronium 0.2 mg kg^{-1} was used for maintenance of neuromuscular blockade. Fentanyl 3 μg kg^{-1} was given before skin incision, with additional doses as required. The patients were ventilated mechanically with tidal volume of 10-15 mg kg^{-1} and a respiratory rate of 12 min^{-1}.

At the end of surgery, after antagonizing the remaining effects of neuromuscular blockage with neostigmine (0.04 mg kg^{-1}) and atropine (0.15 mg kg^{-1}), patients were transported to the Post Anesthesia Care Unit (PACU) and next to the ward for the remainder of the study period after achieving criteria of discharge from PACU. Intravenous administration of study drugs was done in the postanesthesia care unit immediately after awakening the patient when he/she was conscious. Prescribed regimen was 5 mg pethidine (Cehkad Daru Co., Tehran, Iran) and 0.25 mg kg^{-1} ketamine (Rotexmedica, Trittau, Germany) in pethidine + ketamine group and pethidine (10 mg) and NS in pethidine + placebo group. Study drugs were in identical syringes with similar appearances that only the supervisor (AN) was aware of their contents.

After transferring the patient to the surgery ward, a rescue dose of analgesic (25 mg of pethidine, IM) was injected upon each request of the patient for analgesics.

A questionnaire was utilized for demographic data. The severity of pain was evaluated on a 10 cm Visual Analogue Scale (VAS) (from 0, which means no pain sensation, to 10 as the most intense pain the patient has ever experienced). It was measured every 15 min during the first postoperative hour. Then it was measured every 1 h during the first 12 h and every 4 h between 12-24 h. Furthermore, complications (including nausea, vomiting, light headedness, hallucination) and the total dose and frequency of rescue analgesic adminstrations were evaluated for each patient following completion of surgery by a single independent investigator blinded to subject group assignment.

Sample size calculation and statistical analysis: Sample size and power were estimated by determining the number of patients required to show at least 16.5 mg (near 10%) difference between mean pethidine requirements as rescue analgesic during the first post-operative 24 h. It was determined that 48 patients in each arm (96 total) would be required to show a statistically significant difference between the two arms using an α of 0.05 and power of 80%. We enrolled two extra patients in each arm in the event that a patient dropped out of the study.

Statistical analysis was performed utilizing SPSS software version 13 (SPSS Inc., Chicago, Illinois, USA). All quantitative data have been presented as Mean±SD in this study. Chi square test was used to analyze categorical data while independent t-test was utilized for analysis of quantitative data. The $p<0.05$ was considered statistically significant.

RESULTS

In each group 50 patients were assessed. There were no significant differences regarding age and sex of the patients between two groups (Table 1). Laparotomy was the most frequent operation (48%), followed by hysterectomy (21%), cholecystectomy (21%) and splenectomy (10%).

Table 1: Comparison of age and sex between two groups

Variable	Pethidine + ketamine	Pethidine + placebo	p-value
Age (year)	43.18±13.24	39.3±14.76	0.16†
Sex (male)	18(36%)	18(36%)	0.99*

†Independent samples t-test; *Chi square test

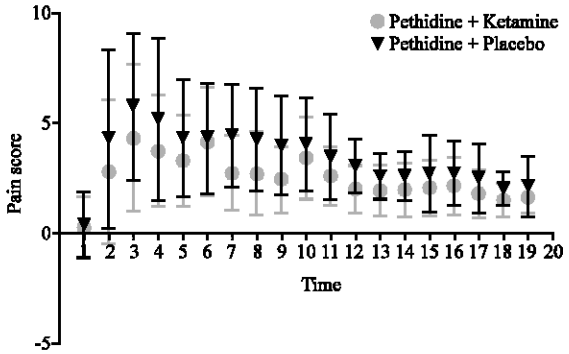

Fig. 1: Severity of postoperative pain in two groups in different time intervals. 1: 0 min, 2: 15 min, 3: 30 min, 4: 45 min, 5: 1 h, 6: 2 h, 7: 3 h, 8: 4 h, 9: 5 h, 10: 6 h, 11: 7 h, 12: 8 h, 13: 9 h,14: 10 h, 15: 11 h, 16: 12 h,17: 16 h,18: 20 h, 19: 24 h

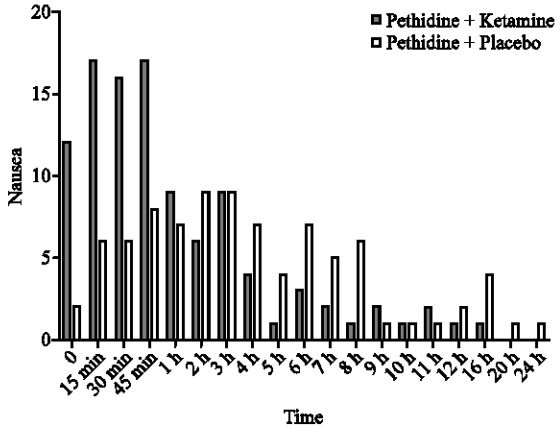

Fig. 2: Frequency of nausea in two groups in different time intervals after surgery

Regarding post-operative pain, scores in all measurements were significant lower in pethidine + ketamine group, except for 0 min, 2, 6 and 16 h (Fig. 1). Nausea was seen less frequently in pethidine + placebo group at the times of 0, 15, 30 and 45 min which was statistically significant ($p<0.05$) (Fig. 2). Other complications did not occur.

Comparison of two groups regarding prescribed pethidine dose as post-operative rescue analgesic revealed that its dose were significant lower in pethidine + ketamine group, in all measurements except for doses in 0, 9 h, 12 h, 16 h, 20 h and 24 h ($p>0.05$) (Fig. 3). The mean dose of administered pethidine as rescue analgesic was 112±31.5 mg in pethidine + ketamine vs. 133.5±24.5 mg in pethidine + placebo group which showed a significant difference ($p<0.001$).

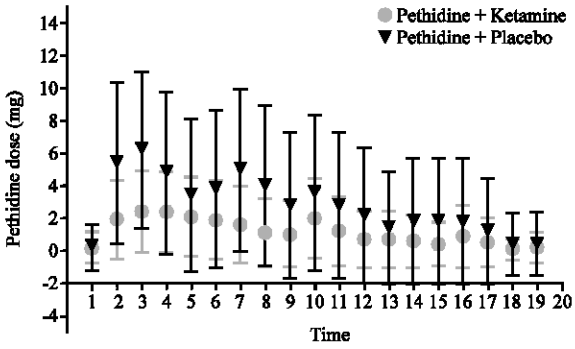

Fig. 3: Prescribed pethidine dose as postoperative rescue analgesic in two groups in different time intervals. 1: 0 min, 2: 15 min, 3: 30 min, 4: 45 min, 5: 1 h, 6: 2 h, 7: 3 h, 8: 4 h, 9: 5 h, 10: 6 h, 11: 7 h, 12: 8 h, 13: 9 h,14: 10 h, 15: 11 h,16: 12 h,17: 16 h, 18: 20 h, 19: 24 h

DISCUSSION

Present results revealed that mean pain scores were lower in pethidine + ketamine group in all postoperative measurements; however, it was not statistically significant at the beginning of the study (at 2, 6 h) and 16 h after surgery. It is in concordance with the majority of previous studies which showed that low dose ketamine is a potent analgesic (Guillou *et al*., 2003; Javery *et al*., 1996; Lester *et al*., 2010; Rakic *et al*., 2009; Tang *et al*., 2010; Zempsky *et al*., 2010). In a similar study, Javery *et al*. (1996) compared the effect of combination of morphine and ketamine with morphine alone on postoperative pain. They found superiority of combination compared to morphine alone. However, a study by Edwards *et al*. (1993) failed to show beneficial effect of adding ketamine to continuous infusion of morphine on postoperative analgesia following abdominal surgery in elderly patients. Two mechanisms for pain relief effect of ketamine have been suggested. Ketamine inhibits sensitization nociceptive pathways (Himmelseher and Durieux, 2005). Moreover, ketamine prevents activation of pronociceptive systems by opioids and tolerance to opioids (Himmelseher and Durieux, 2005).

The role of ketamine as a postoperative opioid sparing agent has been confirmed in some studies (Adriaenssens *et al*., 1999; Schmid *et al*., 1999; Suzuki *et al*., 1999). Adriaenssens *et al*. (1999) evaluated the effect of adding ketamine to the intravenous morphine patient-controlled analgesia following laparotomy. Although, they did not find significant differences between two groups regarding postoperative pain, consumption of morphine was significantly lower in

ketamine group. Also our results showed that after 12 h, there is no difference regarding consumption of pethidine between two groups.

Three ranges have been described for ketamine: anesthetic dose (1-3 mg kg^{-1}), analgesic dose (100-500 μg kg^{-1}) and very small doses of ketamine which have not prominent analgesic effect but in combination with opioids and act as opiate sparing agents (Schmid *et al*., 1999; Suzuki *et al*., 1999). We prescribed analgesic dose of ketamine in our study (0.25 mg kg^{-1}). Advantage of combination of ketamine with opioids is reduction of doses of both ketamine and opioid which prevents dose related adverse effects of these drugs (Baig *et al*., 2006; Himmelseher and Durieux, 2005; Michelet *et al*., 2007; Weinbroum, 2003).

The most important side effect of ketamine is cognitive impairment (Himmelseher and Durieux, 2005; Suzuki *et al*., 1999). In the present study, although, we did not see any cognitive impairment in patients received ketamine, nausea was observed more frequently amongst patients in ketamine group. It is in contrast with previous reports which showed lower frequency of nausea and vomiting in ketamine and opioid group compare to opioid alone (Adriaenssens *et al*., 1999; Aveline *et al*., 2006; Javery *et al*., 1996). However, it has been shown that ketamine when administered in healthy subject, incidence of nausea and vomiting would increase (Krystal *et al*., 1998; Sethna *et al*., 1998). We also did not see any other complications among studied subjects.

In conclusion, present results showed that administration of ketamine and pethidine will improve postoperative pain and reduce narcotic consumption. However, it may increase rate of postoperative nausea at the first postoperative hour.

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