Original Article

Is preemptive analgesic effect of ketamine dose dependent? Effect of increasing dose on post septorhinoplasty pain

Mansoor Aqil[1], Aziz-ul-Haq[2], Amjad Rasheed[3], Altaf Hussain[4], Mueenullah Khan[5], Abdulhamid Al-Saeed[6]

ABSTRACT

Objective: To find out the effect of increasing the dose of preemptive ketamine on ketoprofen requirement in first 24 hours after surgery.

Methodology: 120 patients, scheduled for elective septorhinoplasty were randomly divided in to four groups. At the time of induction of general anesthesia one test drug was given. Group1 received placebo, group 2, 3 and 4 received I.V ketamine, 0.5 mg kg^{-1}, 1.0 mg kg^{-1} and 1.5 mg kg^{-1} respectively. The total postoperative consumption of ketoprofen and pethidine as rescue analgesia in 24 hours was recorded. The incidence of common side effects was recorded.

Results: There was no difference in ketoprofen requirement between group 1 & 2(P=0.108).Patients in group 1 & 2 required more ketoprofen than patients in group 3 and 4 (P=0.00). Group 4 patients required significantly less ketoprofen compared to group 3 patients (P=0.01). Time to first request analgesia was longer in the groups 2, 3 and 4 compared to group 1 (P=0.00). Time to discharge from PACU was found to be longer in patients where ketamine was used (P=0.018). No patient in any group required pethidine as rescue analgesia. There was no significant difference in the common side effects among the groups.

Conclusion: Ketamine in the doses of 0.5 mg kg^{-1} failed to produce reduction in ketoprofen requirement. However, the dose of 1.0 mg kg^{-1} and 1.5 mg kg^{-1} resulted in reduction in post operative ketoprofen requirement and prolonged the time to first request analgesia without any increase in side effects.

KEY WORDS: Ketamine, Preemptive analgesia, Post operative pain.

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1. Mansoor Aqil, FCPS,
2. Aziz-ul-Haq, FCPS,
3. Dr. Amjad Rasheed, FCPS,
4. Altaf Hussain, FCPS,
5. Mueenullah Khan, FCPS,
6. Abdulhamid Al-Saeed, FFARCSI,

1-6: Department of Anesthesiology, King Saud University Hospitals, Riyadh, Saudi Arabia.

Correspondence:

Dr. Mansoor Aqil,
Associate Professor,
Department of Anaesthesiology (41),
King Khalid University Hospital, King Saud University,
P.O Box 7805, Riyadh 11472, Saudi Arabia.
E-mail: mansooraqil@yahoo.com

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INTRODUCTION

In septorhinoplasty, control of post operative pain is challenging as most of the surgeons pack the nostrils resulting in blocked nose. Narcotic analgesics are commonly used for postoperative analgesia and their main side effect is respiratory depression. Use of narcotic analgesics may be life threatening in such patients due to the combination of respiratory depression and blocked nose. Respiratory depression can be avoided by the use of non steroidal analgesics (NSAIDS) but they are effective for mild to moderate pain. Pre emptive analgesia reduces post operative analgesic requirement and is initiated before the start of surgical trauma, in order to reduce sensitization of central nervous system.[1,2]

Ketamine is an intravenous (I.V) anesthetic agent with marked analgesic activity without any respiratory depression. It has been trialed widely as preemptive analgesic with variable success.[3-6] The reasons for inconsistency in the result may be due to difference in the dosage, time of injection, site of surgery, delivery as a single dose or infusion throughout the procedure and duration of surgery.[7,8] In most of the studies done so far, the pre emptive dose of the ketamine used is 0.5 mg kg^{-1} or less. However, it has also been studied in the dose of 1.0 mg kg^{-1} in patients undergoing laparoscopic surgery.[9] We did not find any study in which it has been trialed in the dose higher than 1.0 mg kg^{-1}. The aim of this study is to find out the effect of increasing the dose of preemptive ketamine on ketoprofen or pethidine requirement in the post operative period in patients undergoing septorhinoplasty.

METHODOLOGY

After taking permission from institutional review board and written informed consent, 120 patients of ASA physical status I and II, age between 18-35 years, scheduled for elective septorhinoplasty were included in the study. Patients having any contraindication to general anesthesia or ketamine, unable to give informed consent, hypertension, hyperthyroidism, ischemic heart disease, diabetes mellitus, bronchial asthma, morbid obesity (body mass index >30 kg/m^2), increased intracranial or intraocular pressure, arterial aneurysms, psychiatric illness, alcohol abuse or on regular oral analgesic medication and porphyria were excluded from study. During the preoperative anesthetic evaluation, the patients were explained about visual analog scale (VAS 0-10).All the patients received oral Lorazepam tablet in the dose of 2 mg about 1-2 hours before surgery. The patients were randomly allocated into four groups using computer-generated random numbers. Group l (placebo) received I.V normal saline, Group 2, 3 and 4 received ketamine I.V in the dose of 0.5, 1.0 and 1.5 mg kg^{-1} respectively. All syringes containing the study drugs were diluted to a total volume of 5 ml and marked by one of the anesthesiologist who was independent of the study.

In the operating room, all the four groups received glycopyrrolate I.V in the dose of 0.2 mg. Anesthesia was induced with I.V propofol 2mg kg^{-1}, fentanyl 2 microgram (mcg) kg^{-1} and one of the study drug was given I.V. Orotracheal intubation was facilitated with RAE (Portex) endotracheal tube following muscle relaxation attained by cisatracurium 0.2 mg kg^{-1}. Anesthesia was maintained with sevoflurane need tidal concentration 3% in 50% oxygen-nitrous oxide (N_2O) mixture. All the patients received 8mg dexamethasone I.V before the start of surgery. Cisatracurium 0.02 mg kg^{-1} was repeated on appearance of two twitches on train of four (TOF) stimulation of ulnar nerve. I.V fentanyl bolus of 0.5 mcg kg^{-1} was repeated if heart rate (HR) or arterial blood pressure (BP) increased by 20% of baseline values. ECG, SPO_2, $ETCO_2$, $FiO_2$and end tidal concentration of anesthetics (sevoflurane and N_2O) were continuously monitored. Non-invasive B.P was regularly recorded at 5 minutes intervals throughout the procedure. The final fentanyl dose was given approximately 20 minutes before the end of surgery. All the surgical procedures were done by the same surgeon who was unaware of the patients' group. At the end of surgery, inhalational anesthetics were terminated. Residual neuromuscular block was antagonized with 2.5 mg neostigmine and 1mg atropine. Trachea was extubated after establishment of adequate breathing.

The total intraoperative fentanyl used was recorded. Anesthesia time (defined from the start of induction to the time when trachea was extubated) and operation time (the duration from skin incision to final dressing) were also recorded. In the postanesthesia care unit (PACU), the intensity of pain was rated on patient's complain using a 10cm VAS, in which 0 = no pain and 10 = worst possible pain. Assessment of VAS scores and vital signs were done on arrival in the PACU and repeated every 15 min thereafter until discharge. In the ward the VAS scores was done every six hours for first 24 hours. The anesthesiologist recoding anesthesia time, operation time and assessing VAS was blinded to the patients' group. Post operative analgesia was administered in the form of intramuscular (I.M) ketoprofen 1.5 mg kg^{-1} when VAS was 4 or more on the scale and not repeated within six hours. Injection pethidine I.M was given as rescue analgesia in the dose of 0.5 mg kg^{-1} if patient complained of pain (VAS > 4) after 30 minutes of receiving ketoprofen. The total postoperative consumption of ketoprofen and pethidine in first 24 hours was recorded.

Side effects such as sedation, nausea, vomiting, respiratory depression, hallucination, sedation, drowsiness, respiratory distress, bronchospasm, excessive secretions, skin eruptions, agitation and hemodynamic abnormality were recorded.

RESULTS

There was no significant difference among the four groups regarding demographic data, anesthesia time,

Table-I: Demographic characteristics, anesthesia and operation time for the four groups.

	Group 1 (n=30)	*Group 2 (n=30)*	*Group 3 (n=30)*	*Group 4 (n=30)*	*P value*
Age (years)	22.3 ± 3.89	23 ± 4.43	22.8 ± 4.71	22.9 ± 4.55	0.930
Weight (kilograms)	72 ± 9.23	74.3 ± 11.91	72.9 ± 8.88	73.7 ± 9.56	0.825
Sex (F: M)	18:12	16:14	17:13	18:12	0.788
Anesthesia time (min)	113 ± 11.15	110 ± 13.04	114 ± 12.35	116 ± 10.97	0.271
Operation time (min)	89 ± 17.92	93± 12.51	91± 12.87	90 ± 15.16	0.753

Data are expressed as mean ± SD. Different groups are compared with ANOVA.

operation time (Table-I) and total fentanyl used during operation (Table-II). Total ketoprofen consumption in first 24 hours was similar in group 1 and 2 (P=0.108).There was significantly more consumption of ketoprofen in 24 hours in groups 1 patients in comparison to those in group 3 (P=0.00) and group 4 (P=0.001); and it was also higher in group 2 patients (P=0.001) compared to groups 3 and 4. Group 4 patients required significantly less ketoprofen compared to group 3 (P= 0.01). Time to first request analgesia was longer in patients in group 2, 3 and 4 (P=0.00) compared to those in group 1 and it was also longer in group 3 and 4 patients (P=0.001) compared to group 2. Time to discharge from PACU was found to be longer in all the patient groups where ketamine was used (P=0.018) and with the increasing dose of ketamine it was prolonger further (P=0.00 and P= 001). No difference was found in complications like nausea, vomiting, sedation, bronchospasm, drowsiness, hallucinations, agitation, respiratory distress, respiratory depression, excessive secretions and skin eruption (Table-III).

Statistical analysis: All the data was analyzed by using SPSS 11.0 for Windows statistical package for social sciences. One way ANOVA was used to compare the continuous variables between different groups for multiple comparisons. Chi square test was used to compare categorical data. P value of < 0.05 was taken as significant. Post HOC test (Bonferoni) was used for multiple comparisons between the different groups. Data are expressed as mean±SD.

DISCUSSION

Ketamine is an I.V anesthetic and has marked analgesic effect even when used in small doses. The exact mechanism of its analgesic effect is not known.[10] The analgesic activity may be due to its effects on spinal μ opioid receptors and descending monoam-

Table-II: Comparison of analgesic dosage, time to request analgesia and time to discharge from PACU for all groups.

	Group 1(n=30)	*Group 2(n=30)*	*Group 3(n=30)*	*Group 4(n=30)*	*P value*
Total fentanyl used during operation (micrograms)	125 ± 24.07	120 ± 19.52	126 ± 23.76	118 ± 16.64	0.399
Total ketoprofen used (milligrams)	175 ± 50.0	165 ± 25.43	100 ± 42.04	50 ± 53.74	0.108*
					0.00 ◇
					0.00 Δ
					0.001◣
					0.01❖
Total pethidine used as rescue (milligrams)	0	0	0	0	
Time to first request analgesia (min)	17 ± 5.67	25± 6.85	38 ± 15.34	67 ± 19.54	0.00*
					0.00 ◇
					0.00 Δ
					0.00 ▼
					0.001◣
Time to discharge from PACU (min)	55±7.54	64±13.75	69±10.42	76±9.31	0.108*
					0.00 ◇
					0.00 Δ
					0.001◣

Data are expressed as mean ± SD. Different groups are compared with ANOVA.

*=Group 1versus group 2; ◇ =Group1 versus group 3; Δ=Group 1versus group 4

▼=Group 2versus group 3; ◣= Group 2 versus group 4; ❖=Group 3versus group 4

Table-III: Comparison of Complications in all four groups.

	Group 1(n=30)	*Group 2(n=30)*	*Group 3(n=30)*	*Group 4(n=30)*	*P-value*
Nausea	40 (12)	47 (14)	47 (14)	50 (15)	0.88774
Vomiting	13 (4)	10 (3)	10 (3)	13 (4)	0.95556
Respiratory depression	0	0	0	0	———-
Sedation	7 (2)	13 (4)	13 (4)	30 (9)	0.08243
Bronchospasm	3 (1)	7 (2)	7 (2)	7 (2)	0.9286
Drowsiness	3 (1)	10 (3)	13 (4)	20 (6)	0.24017
Hallucination	0	0	7 (2)	10 (3)	0.13079
Respiratory distress	0	0	0	7 (2)	0.10676
Excessive secretions	0	0	10 (3)	10 (3)	0.09722
Skin eruption	0	0	3 (1)	3 (1)	0.565401
Agitation	13 (1)	7 (2)	7 (2)	17 (5)	0.26943

Data is expressed as percentage (number of patients) and different groups compared by Chi Square test.

inergic systems in central nervous system which is expressed by alpha 2-adrenoceptors at the spinal level and inhibition of morphine metabolism.[11, 12] Other possible mechanism may be because of prevention of opioid-induced hyperalgesia, resulting in reduction of postoperative pain.[13] The objective of our study was to observe the effect of increasing dose of ketamine on postoperative analgesic requirement in first 24 hours.

Ketamine has been studied in the dose of 0.5 mg kg^{-1} or less as preemptive analgesic. In many studies it has been found to be effective in reducing post operative analgesic requirement.[14,15] Contrary to that, we did not find any preemptive analgesic effect with the ketamine in dose of 0.5 mg kg^{-1}. It is not surprising to have such results as many clinical trials deny preemptive analgesic effect of ketamine.[16,17] Similarly, a systematic review of randomized trials concluded that the role of ketamine, as a component of perioperative analgesia remains unclear.[8,18] The reasons of failure of ketamine to show lack of preemptive analgesic effect in most of the studies may be small dose or improper dosing schedule.[19, 20] Our study supports the idea that the dose of 0.5 mg $kg^{-1}$is small to produce preemptive analgesic effect in this type of surgery.

Our results show that preemptive I.V ketamine in the dose of 1mg kg^{-1} was effective in reducing total dose of ketoprofen required in first 24 hours compared to placebo or the dose of 0.5 mg kg^{-1}. Contrary to our results, ketamine was studied in the dose 1 mg kg^{-1} in the patients undergoing laparoscopic cholecystectomy and no pre-emptive analgesic effect was found.[9]The reason for this contradiction to our results may be due to the site of surgery as laparoscopic surgery is intra abdominal procedure requiring greater degree of dissection and tissue trauma.[7]

We found that preemptive ketamine in the dose of 1.5 mg kg^{-1}resulted in significant reduction in post operative ketoprofen requirement in first 24 hours compared to the placebo group or patients who received ketamine in the dose of 0.5 mg kg^{-1}. There is no report in the literature regarding the use of this dose as preemptive analgesic. Our results support the idea of preemptive analgesia to be dose dependent.[19]

Time to request analgesia was found to be significantly longer in all the groups receiving preemptive ketamine compared with placebo. With the increasing doses of ketamine, there was statistically significant increase in the time to first request for analgesia. Other investigators have also found that preemptive ketamine delayed the need for post operative analgesic.[15, 21]

Time to discharge from PACU was found to be longer in the patients where ketamine was used. Regarding the common side effects of ketamine like vomiting, agitation, skin eruption, hallucination, drowsiness or respiratory distress, excessive secretions, we did not find any statistically significant difference among all the four groups. The use of preemptive ketamine in the dose of 0.15 mg kg-1 has been found to be without any complication.[15, 22] Although we used higher doses of preemptive ketamine in our study, still we did not find any of the above mentioned side effects. The reason for lack of side effects in our study may be that all the patients were premedicated with lorazepam. Additionally, the duration of surgery was more than 100 minutes in all the groups and there was sufficient time for the drug to be metabolized.

CONCLUSION

Preemptive ketamine in the doses of 0.5mg kg^{-1}failed to produce reduction in ketoprofen

requirement. However, ketamine in the dose of 1.0 mg kg^{-1} and 1.5 mg kg^{-1} had pre-emptive analgesic effect in patients undergoing septorhinoplasty and reduced post operative ketoprofen requirement. The pre emptive analgesic effect of ketamine was highest in the dose of 1.5 mg kg^{-1}. Similarly, the time to request analgesia was also longest with the preemptive ketamine dose of 1.5 mg kg^{-1} compared with other doses of ketamine or placebo. Additionally, the time to discharge from PACU was also found to longer in all the patient groups where ketamine was used. Ketamine in the dose of 1-1.5 mg kg^{-1}as preemptive analgesic can be useful in reducing the requirement of NSAIDS or narcotic analgesics in the post operative period without any increase in the complication rate. Further studies are needed to find the effect and complications of preemptive ketamine in the dose of 1.5 mg kg^{-1} in surgical procedures with greater tissue trauma or intra peritoneal procedures.

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Authors Contribution:

* M Aqil conceived, designed the study, wrote and revised the manuscript.
* AU Haq & A Rasheed did data collection and helped in revising the manuscript.
* A Hussain & M Khan helped in data collection, literature search and statistical analysis of the data and in revising the manuscript.
* A Saeed reviewed and gave final approval.