Original Article

Analgesic Effects of Pre-induction Low-dose Ketamine on Post-tonsillectomy Patients

Muhammad Delwar Hussain[1], Md Torab Mallick[2], Mohammad Kamal Hossain[3]

Received: January 23, 2018 Accepted: April 15, 2018
doi: http://dx.doi.org/10.3329/jemc.v8i2.36729

Abstract

Background*: Post-operative pain management aims to decrease pain intensity with patient comfort and to improve post-operative outcome. Multimodal analgesia is currently recommended for effective post-operative pain control with lower total doses of analgesics and fewer side effects.* ***Objective****: To compare the analgesic effect of pre-induction low-dose ketamine against conventional general anaesthesia.* ***Materials and Methods****: This prospective comparative study was conducted over a period of 12 months at Combined Military Hospital, Dhaka. Two hundred and forty patients of either sex requiring tonsillectomy were divided into two groups: conventional general anaesthesia (control group) and general anaesthesia with low-dose ketamine (ketamine group). Non-invasive blood pressure, heart rate and SpO2 were recorded at regular intervals throughout the anaesthetic period. Post-operative analgesia was provided for both the groups using pethidine intramuscularly. Time to complete operation, pain intensity, time to request for first analgesia were noted and total opioid consumption and complications, if any occurred in 24 hours post-operatively, were also recorded and addressed accordingly.* ***Results****: The demographic data and mean operation time were similar in both the groups ($p>0.05$).Time to request for first analgesia was longer in low-dose ketamine group (mean ± SD 5.36±3.21 hours) than in control group (mean ± SD 2.49±1.53 hours) ($p<0.05$). Total dosage of pethidine consumption over 24 hours period was less in ketamine group with satisfactory pain relief (mean ± SD 98.73±2.60 mg) than in control group (mean ± SD 142.52±3.48 mg) ($p<0.05$). Post-operative complications were also less in ketamine group than control group ($p<0.05$).* ***Conclusion****: The result of this study suggests that pre-induction low-dose ketamine has pre-emptive analgesic effect and reduces overall post-operative opioid requirements.*

Key words*: Ketamine; Low-dose; Anaesthesia*

J Enam Med Col 2018; 8(2): 74−79

Introduction

Ketamine is a popular anaesthetic drug producing dissociative anaesthesia. It has intense analgesic properties which outlast its duration of anaesthesia and is present even in sub-anaesthetic doses. The term "low-dose" is used when ketamine is administered as bolus dose of <2 mg/kg intramuscularly and <1 mg/kg via intravenous (IV) or epidural route.[1] Post-operative pain is a form of acute pain caused by noxious stimuli typically associated with neuro-endocrine response that is proportional to pain intensity.[2] Pre-emptive analgesia is currently in practice for the management of post-operative pain. The analgesic property of ketamine is related to its action as a non-competitive NMDA receptor antagonist, these receptors present an excitatory function on pain transmission and these bindings seem to prevent or reverse the central sensitisation of every kind of pain, including post-operative pain.[3] Ketamine demonstrates a potent

1. *Classified Specialist, Department of Anaesthesia, Combined Military Hospital, Dhaka*
2. *Classified Specialist, Department of Anaesthesia, Combined Military Hospital, Dhaka*
3. *Classified Specialist, Department of Anaesthesia, Combined Military Hospital, Dhaka*

Correspondence *Muhammad Delwar Hussain, Email: drdelwarhussain@yahoo.com*

analgesic effect by central blockage of perception of pain with sub-anaesthetic doses.[4]

Research has demonstrated significant reductions in post-operative pain score as well as opiate consumption with low dose ketamine administration without side effects associated with its induction doses.[5] Pain in the immediate post-operative period should be prevented in order to smooth extubation, awakening and the recovery period.[6] A safe analgesic, which could be used routinely, should have little or no potential for respiratory depression, should be readily available in the operation theatre and should not require any counter signature.[6] Ketamine in dose of 0.5 mg/kg fulfills these requirements. Literatures provide little information where ketamine had been used for the treatment of post-tonsillectomy pain in Ear Nose Throat surgeries. The present study investigates the advantages of pre-induction low dose ketamine in reducing post-operative analgesia requirement and the complications in relation to pain and other analgesic drugs.

Materials and Methods

This prospective comparative study was carried out in the Department of Anaesthesia of Combined Military Hospital Dhaka from July 2016 to June 2017. Prior permission was taken from the hospital ethical committee explaining the purpose and the procedure of the study. Informed consent was taken from the study subjects. Surgeons were appraised about the study protocol. A total number of two hundred and forty patients requiring tonsillectomy surgeries under general anaesthesia were selected for the study. Selected patients were of both sexes, age ranging from 15 to 30 years, weight ranging from 30 to 70 kg, American Society of Anesthesiologist (ASA) grade I and II. Those who were hypersensitive to thiopental, ketamine and pethidine, hed bleeding disorder, were on anticoagulant therapy and not well motivated about the study were excluded from the study. The patients were divided into two groups: conventional general anaesthesia (control group, 120 cases) and low-dose ketamine with general anaesthesia (ketamine group, 120 cases). All patients were examined pre-operatively on day before operation and haemodynamic status was recorded. The post-operative pain severity was measured with Visual Analogue Scale (VAS) and Verbal Rating Score (VRS) which are quantitative and qualitative scales respectively. The patients were oriented about a 10 cm VAS scale explaining that one end of the scale indicates no pain and the other is the worst possible pain. The VRS was explained as no pain, mild, moderate and severe (0−3 points). All patients were taught to express their post-operative pain management as excellent, good, fair and poor according to their satisfaction. Patients were randomised by drawing of shuffled coloured envelopes and were put in either control group or ketamine group. Each patient received either ketamine hydrochloride 0.5 mg/kg body weight or saline prepared in a 5 mL syringe intravenously before induction of anaesthesia and the time was noted. The type and duration of surgery were also noted. After pre-oxygenation for 3 minutes with 100% oxygen, general anaesthesia was induced with diazepam 0.1 mg/kg, pethidine hydrochloride 1.5 mg/kg, thiopental sodium 5 mg/kg followed by suxamethonium chloride 1.5 mg/kg to aid tracheal intubation. After tracheal intubation, the patients were ventilated with 66% nitrous oxide in oxygen. Halothane 0.5% was added to maintain the anaesthesia. Further neuromuscular block was maintained by using vecuronium bromide as needed. At the end of the surgery, neuromuscular blocking was antagonised by neostigmine methyl sulphate 0.04 mg/kg and atropine sulphate 0.02 mg/kg body weight. Basic standard monitoring, i.e., heart rate, noninvasive blood pressure and arterial oxygen saturation were recorded at ten minutes interval throughout the perioperative period. Duration of anaesthesia was recorded in minutes from induction to complete recovery after reversal. The first post-operation visit was performed in recovery room in 30 minutes. On obtaining desirable condition in recovery, patients were discharged to post-operative ward where they were observed for 24 hours after surgery. The patient was conscious and could answer verbally at this time. During the recovery period, patients' comfort and symptoms were recorded. Post-operative pain was managed with pethidine hydrochloride (1.5 mg/kg) intramuscularly upon first complaint of moderate pain (>05 on VAS, >02 on VRS) and then repeated 8 hourly. Then the patients were visited at intervals of 30 min, 1 hour, 2, 4, 8, 12 and 24 hours after surgery and following variables were recorded: (i) Time of first request for analgesia injection and

type and dosage; (ii) Number of patient's requests for analgesia and their degree of satisfaction regarding pain management; (iii) Total dosage of analgesia in 24 hrs; (iv) Visual Analogue Scale-VAS; (v) Verbal Rating Scale-VRS; (vi) Adverse effects such as nausea, vomiting, respiratory depression, sedation, hallucinations or no complications. The data collected from all 120 patients in each group were analysed by SPSS 10.0 Statistical software.

Results

Majority of the patients (46.67%) belonged to age group 15−18 years and lowest (10%) in the age group 27−30 years. Among the 240 patients 132 (55%) were male and 108 (45%) were female with male to female ratio 1.3:1 (Table I). Vital parameters were observed and recorded at intervals. Mean heart rate (HR), mean arterial blood pressure (MBP) and arterial oxygen saturation (SpO2) were stable from immediate post-operative period (recorded as zero time) to next 24 hrs post-operatively (Table II). Pain intensity measured by VAS and VRS were recorded at the predetermined time intervals and was reduced significantly in ketamine group at all observation period compared with control group (Table III). Duration of surgery was recorded in minutes from surgical incision to complete the operation by the surgeon. In ketamine group total operation time was 47.45±1.20 minutes and in control group 46±0.58 minutes and the difference was not statistically significant. Time to first opioid request was longer in low-dose ketamine group (5.36±3.21 hours) than in control group (2.49±1.53 hours). Cumulative pethidine consumption over 24 hours was less in ketamine group (98.73±2.60 mg) than in control group (142.52±3.48 mg). Mean dose of pethidine consumption in each time was less in the ketamine group (Table IV).

Table I: Distribution of patients by demographic data (n=240)

Age group (in years)	Number	Percentage
15−18	112	46.67
19−22	72	30.00
23−26	32	13.33
27−30	24	10
Sex		
Male	132	55
Female	108	45

The degree of patients' satisfaction was found excellent in 42.50% cases, good in 34.17%, fair in 22.50% and poor in 0.83% in ketamine group whereas it was excellent in 0%, good in 5.83%, fair in 22.50% and poor in 71.67% in control group (Table V). Concerned surgeons also expressed their satisfaction with post-operative pain management. Post-operative complications like nausea, vomiting, pruritus, hypotension, respiratory depression, sedation and hallucinations in both the groups were recorded at pre-determined time intervals. These complications were less in ketamine group than in control group (Table VI).

Table II: Heart rate (HR/min) and mean blood pressure (MBP) of patients at different times

Time	Ketamine group (n=120)		Control group (n=120)	
	HR	MBP	HR	MBP
Base line	83.2±3.2	90.2±4.0	83.6±3.5	89.5±4.1
On intubation	100.6±7.8	95.3±4.2	103.4±8.4	96.1±4.3
At 10 min	88.8±5.2	91.1±3.9	96.3±4.8	93.4±3.8
On extubation	96.5±3.6	94.8±4.0	100.2±3.7	95.6±4.2
2 hrs post-op	86.4±4.4	92.6±3.8	88.6±4.5	93.4±3.9
4 hrs post-op	85.7±3.5	92.4±3.5	86.6±3.2	94.6±4.0
8 hrs post-op	86.8±3.1	92.2±3.2	87.2±3.5	91.5±3.7
12 hrs post-op	85.4±4.2	90.8±3.8	85.5±4.5	90.6±4.0
24 hrs post-op	84.4±3.5	91.1±3.4	84.4±3.1	90.8±4.1

Table III: Visual Analogue Scale (VAS) and Verbal Rating Score (VRS) of patients at different times

Time after operation	Ketamine group (n=120) Mean ±SD		Control group (n=120) Mean ±SD	
	VAS	VAS	VAS	VAS
2 hours	1.20±0.75	0.92±0.50	3.05±0.64	1.61±0.52
4 hours	1.00±0.65	0.85±0.41	2.95±0.60	1.67±0.48
8 hours	1.60±0.70	0.90±0.51	3.54±0.56	1.74±0.56
12 hours	1.30±0.65	0.81±0.46	3.30±0.58	1.75±0.52
24 hours	1.25±0.50	0.87±0.50	3.10±0.70	1.74±0.45

Table IV: Comparison of variables between ketamine and control groups

Variables	Ketamine group (n=120)	Control group (n=120)
Mean operation time (min)	47.45±1.20	46±0.58
First analgesia request time (hrs)	5.36±3.21	2.49±1.53
Total opioid consumption (mg)	98.73±2.60	142.52±3.48

Table V: Degree of patients' satisfaction in ketamine and control groups

Satisfaction	Ketamine group (n=120)	Control group (n=120)
Excellent	51 (42.50%)	0 (0%)
Good	41(34.17%)	7 (5.83%)
Fair	27 (22.50%)	27 (22.50%)
Poor	1 (0.83%)	86 (71.67%)

Table VI: Distribution of different types of post-operative complications in ketamine and control groups

Complications	Ketamine group (n=120)	Control group (n=120)
Nausea/vomiting	13 (10.83%)	28 (23.33%)
Pruritus	1 (0.83%)	3 (2.5%)
Respiratory depression	0 (0%)	1 (0.83%)
Sedation	4 (3.33%)	3 (2.5%)
Hallucinations	4 (3.33%)	1 (0.83%)
No complications	98 (81.66%)	84 (78.33%)

Discussion

The need for better post-operative analgesia has been stated repeatedly.[7] A recent report cites 14 references and concludes that almost 40% of patients consider their post-operative analgesia insufficient or even poor.[8] The reasons for the lack of proper post-operative analgesia are mainly fear of respiratory depression and addiction, both of which are not usually found in a normal recovery period with short term post-operative pain. Another problem is the shortage of registered staff to check narcotic drugs. An ideal analgesic drug would be one that is readily available to the anaesthetist in the operation theatre, does not require paper-work, is not a respiratory depressant and has low addictive potential. Ketamine has been used by researchers for this purpose for many years, but the clinical impression needs scientific investigation and validation.[6] The duration of action of ketamine as an anaesthetic agent is quite short, but its analgesic effect is of much longer duration.[9] The reason for this dual action lies in the pharmacokinetics of the drug. The intravenous drug initially decays fast, with an α half-life of 11−17 minutes and a β half-life of 150–186 minutes.[9,10]

The analgesic action is also thought to be due to a long-acting metabolite, nor-ketamine which is excreted in the urine for up to 24 hours.[11] The intravenous bolus dose at the beginning of a short procedure such as tonsillectomy and septoplasty should, therefore, maintain an analgesic action throughout the early post-operative period. A longer lasting effect could be obtained by giving the dose intramuscularly. Sadove et al[12] in a study using intramuscular ketamine in a dose of 0.44 mg/kg for post-operative pain in adults showed a significant analgesic effect lasting at least 60 minutes (which was the duration of their

observations). Among various drugs or techniques that prevent central sensitisation, only NMDA antagonist reverses the established sensitisation.[13-15]

Pre-emptive analgesia aims to prevent or reduce this sensitisation, and thus to reduce post-operative pain.[16] Clements and Nimmo[17] showed that the analgesic effect of ketamine occurs at lower plasma concentration (100 ng/mL) than anaesthetic effect (700 ng/mL). Therefore, in this study 0.5 mg/kg of ketamine was used prior to induction of anaesthesia, direct analgesic effect of which would have lasted only for about 15 minutes. But they observed reduction in the pain for much more prolonged period, and reduction in the cumulative pethidine required during first 24 hours. This result could be explained by prevention of central sensitisation prior to tissue injury during surgery. Other methods of prolonging the analgesic effect of ketamine would be to give a larger initial intravenous dose or a top-up dose towards the end of the anaesthetic procedure. Oral ketamine has also been used for analgesia.[18]

The results of this study demonstrated that addition of low-dose ketamine before induction of general anaesthesia in ENT surgeries delays the first request of opioid administration from about 2−5 hours in immediate postoperative period. It was observed that the dose of pethidine requirement in ketamine group was about two-thirds of the dose in control group. Results of pain scores indicated that patients in the control group had more pain than in the ketamine group throughout the 24 hours of assessment. These findings support the findings of Murray et al[19] who observed that less number of tonsillectomy patients who received ketamine awoke in pain, than those induced with thiopental alone. Findings of this study best correlates with the findings of Kianfar et al[20] who used low-dose ketamine (0.15 mg/kg) in addition to general anaesthesia in cholecystectomy patients and observed that the cumulative dose of morphine required was reduced by about 40% in the ketamine group.

In conclusion, it can be asserted that a small dose of ketamine given before surgical incision produces pre-emptive analgesia in patients undergoing tonsillectomy surgeries. Due to possible side effects of post-operative pain after oral surgeries and because conventional methods such as patient control analgesia (PCA) and opioid injection have disadvantages, pre-induction low-dose ketamine may be a suitable alternative to conventional methods of post-operative pain control.

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