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Original Article

An Evaluation of the Effectiveness of Preemptive Ketamine for Postoperative Analgesia in Elective Thyroidectomy

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Abstract

Background: The use of preincision low-dose ketamine as a preemptive analgesic modality has been widely suggested. However, findings from previous studies have remained inconclusive. **Materials and Methods:** Eighty-two patients scheduled to have elective thyroidectomy under general anesthesia were recruited. The patients were randomly allocated into one of two groups, to receive either 0.5 mg/kg of ketamine intravenously or an equal volume of normal saline, 10 min before surgical incision. At the end of surgery, pain scores, time to first request for analgesic and total opioid requirement in 24 h postoperatively were recorded. **Results:** There was no significant difference in the postoperative pain scores, time to first requirement for analgesic, postoperative opioid consumption and satisfaction with analgesia between the two groups. The median pain scores at recovery, 2, 6, 12, and 24 h postoperatively for the ketamine and saline groups were not significantly different (*P* values 0.208, 0.185, 0.412, 0.590, and 0.854 respectively). The times to first request for analgesic were 86.00 ± 56.58 min in the ketamine group and 79.90 ± 68.05 min in the saline group (*P* = 0.357). The 24-h opioid (morphine) consumptions were 11.00 ± 3.16 mg in the ketamine group and 13.21 ± 5.87 mg in the control group (*P* = 0.275). **Conclusion:** This study concluded that the administration of preincision low-dose ketamine (0.5 mg/kg) did not produce a preemptive analgesic effect in patients who had an elective thyroidectomy.

Keywords: Ketamine, pain, postoperative analgesia, preemptive analgesia, thyroidectomy

Introduction

Postoperative pain is a common concern among surgical patients.[1] Although frequently encountered, available evidence shows that it is still frequently undertreated, with up to 70% of surgical patients experiencing moderate to severe pain following surgery.[2] Inadequate management of postoperative pain is an established cause of increased morbidity and health care costs.[3] Consequently, an attempt has been made to improve outcomes in postoperative pain management by the employment of preemptive analgesic techniques.[4]

Preemptive analgesia is defined as an antinociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies postoperative pain.[5] Ketamine, an antagonist at N-Methyl D-aspartate receptors, has been suggested for use as a preemptive analgesic agent, due to the role played by these receptors in mediating nociceptive stimuli.[6] In addition, the wide availability and affordability of ketamine, especially in low-resource environments, is an added potential advantage. The use of ketamine for preemptive analgesia has however remained controversial, with some previous studies suggesting a preemptive effect while others did not.[4,7,8] Roytblat *et al*.[7] found a preemptive effect of ketamine which was clearly shown by a significant difference in postoperative opioid consumption between patient groups. Amanor-Boadu *et al*.[8] however, could not demonstrate an overall sustained preemptive effect, even though their study revealed a prolongation of the time to first request for analgesia in the ketamine group. Akbar *et al*.[9] also concluded that low-dose intravenously administered ketamine had a preemptive effect in reducing pain after appendectomies, while Nistal-Nuño *et al*.[10] failed to elicit this analgesic effect.

In view of these conflicting findings, and the continual need for cost-effective approaches to postoperative pain control, there

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is a need to investigate closely the usefulness or otherwise of preemptive analgesia using ketamine. Thus, we conducted this prospective randomized double-blinded study to determine the effectiveness of low-dose ketamine as a preemptive analgesic in the postoperative period following elective thyroidectomy.

Materials and Methods

The study was a prospective randomized controlled double-blinded study of 82 American Society of Anesthesiologists (ASA) physical status I and II adult female patients scheduled for elective thyroidectomy under general anesthesia. Exclusion criteria included patient refusal, history of cardiovascular disease, seizure and psychiatric disorders, history of chronic analgesic use, toxic goiter, anticipated difficult intubation/very huge goiter and previous history of allergy to the study agent.

Ethical clearance was obtained from the University of Ilorin Teaching Hospital Ethical Review Board and written informed consent was obtained from all patients following a detailed explanation of the procedure. All patients were reviewed the night before surgery by the investigator. History and thorough physical examination including airway assessment were carried out and findings recorded. Patients' demographic characteristics including age, sex, weight, height and ASA classification were also recorded. Signed informed consent was obtained from the patients for general anesthesia. Patients were also carefully educated on the pain scoring instrument to be used (Verbal Rating Scale).[9] Patients were fasted overnight and given 10 mg of diazepam orally the night before surgery and 2 h before induction of anesthesia. Patients were randomized into two groups (A and B) using simple random sampling techniques. Randomization was by balloting using a ballot box containing 82 balls of paper marked appropriately with 41 for each group. Patients randomly picked from the ballot box the night before surgery and balloting was done serially for all consecutive patients.

The balloting and administration of medication were carried out by a senior resident anesthetist who did not participate further in the management of the patient. The intraoperative and postoperative management as well as patient assessment were carried out by the principal investigator who was blinded to the groups.

Study medications were prepared by a trained assistant who took no further part in the management of the patients. The medications were prepared using 5 ml syringes containing either ketamine (Rotex Medica, Germany) 0.5 mg/kg or normal saline, both made up to 5 ml.

On arrival of the patient in the operation suite, monitoring was commenced and baseline vital signs, including noninvasive blood pressure, pulse oximetry (SpO_2) and electrocardiogram (ECG), were taken and recorded using a DASH 4000 multiparameter patient monitor (GE Medical Systems Information Technology, Inc. 8200 W. Tower Ave, Milwaukee, Wisconsin, USA). An intravenous (IV) line was established using a size 18G IV cannula. After preoxygenation with 100% oxygen for 3 min, anesthesia was induced with IV propofol 1.5–2 mg/kg and endotracheal intubation facilitated with suxamethomium chloride 1–1.5 mg/kg IV. Intraoperative analgesia was provided with IV fentanyl 2 μg/kg and incremental bolus doses of 0.5 μg/kg as required in the course of surgery. Group A received 0.5 mg/kg of ketamine (made up to 5 ml) intravenously 10 min before surgical incision, while Group B received an equal volume (5 ml) of normal saline 10 min before surgical incision. Maintenance of anesthesia was achieved with isoflurane 1%–1.5% and 50% oxygen in air, IV atracurium 0.5 mg/kg was used for muscle relaxation and maintained with top-up doses of 0.1–0.2 mg/kg repeated at 30 min intervals as required. Standard monitoring of the patient was continued throughout surgery including heart rate and blood pressure every 5 min and continuous SpO_2, capnography, and ECG monitoring. Intraoperative fluid therapy was provided with IV normal saline at a standardized rate to accommodate required maintenance and ongoing losses. Blood transfusion was administered when blood loss exceeded the allowable estimated value. Other relevant anesthetic care was standardized for both groups.

At the end of surgery, reversal of residual neuromuscular blockade was achieved with a combination of neostigmine 0.05 mg/kg and atropine 0.02 mg/kg given intravenously. Following the resumption of adequate spontaneous ventilation, the patient was extubated while deeply anesthetized (using isoflurane 1%–1.5% and 50% oxygen in air). Direct visualization of the vocal cords was performed and thereafter 100% oxygen, using face mask, was administered to the patient and breathing monitored until they were fully awake. The patient was then transferred and kept in the recovery room for 1 h where monitoring and observation were continued. Oxygen therapy was also continued by nasal prongs. Pain assessment was started when patients were fully awake (i.e., obeyed simple commands, in the recovery room), using the verbal rating scale for pain. Pain score was subsequently recorded at 2 h, 6 h, 12 h, and 24 h postoperatively.

Time to first request for analgesia (TFA), starting from the end of surgery to patient's first request for analgesic) for all patients was noted and recorded, along with pain score assessment and recording at that period. Intramuscular morphine 0.15 mg/kg was given when pain score exceeded 1 (mild pain), or upon request by the patient. The total 24-h morphine requirement in each patient was calculated and recorded. Background postoperative analgesia was provided with IV paracetamol 1 g infusion 6-hourly.

Data analysis

SPSS software version 16 (Chicago, IL, USA. Inc.,) was used for data analysis. Data were presented in frequencies, proportions, means and standard deviations. Continuous variables were summarized in means and standard deviations while categorical variables were summarized in frequencies and proportions and presented in tables and charts. Statistical

analysis of continuous variables was done using Student's *t*-tests while categorical variables were analyzed using Chi-square test (with Yate's correction in cases where >20% of expected count is <5). Pain scores were presented in range and median and Mann–Whitney *U*-test was used for comparison. A $P < 0.05$ was considered statistically significant.

Results

The two groups studied were comparable with respect to demographic characteristics, baseline clinical variables, and duration of anesthesia and surgery [Table 1].

Postoperative pain scores

The postoperative pain scores (VRS) in the immediate postoperative period (recovery room) and subsequently at 2, 6, 12, and 24 h postoperatively were comparable in both groups [Table 2]. *P* values at these intervals were 0.087, 0.430, 0.842, 0.991, and 0.975, respectively. The range and median values for pain scores in both groups revealed, at 12 and 24 h postoperatively, the maximum level of pain as "mild" and "moderate" for the ketamine and control groups, respectively [Table 3]. However, the difference was not statistically significant ($P = 0.590$ and 0.854, respectively).

Time to first request for analgesic

The mean time to the first request for analgesic (TFA) was comparable in both groups; 86.00 + 56.58 min in the ketamine group versus 79.90 + 68.05 min in the control group. Table 4 shows that less number of patients in the ketamine group (15 patients, i.e., 36.6%) requested for analgesia compared with those in the control group (20 patients, i.e., 48.8%). Although the mean TFA was longer (by approximately 6 min) in the ketamine group, this did not attain statistical significance ($P = 0.357$).

Twenty-four hour opioid consumption

The mean total amount of opioid analgesic required was not significantly different in the two groups, as shown in Table 5. The mean total intraoperative fentanyl given were 193.90 ± 44.99 μg and 196.34 ± 46.2 μg for the ketamine and control groups, respectively ($P = 0.810$). The mean total morphine required in the ketamine group was 11.00 ± 3.16 mg 13.21 ± 5.87 mg in the control group ($P = 0.275$).

Discussion

Our study did not demonstrate any preemptive analgesic effect of low-dose preincision ketamine (0.5 mg/kg) in elective thyroidectomy. Ketamine administration did not significantly improve the postoperative pain scores in the first 24 h following surgery, and the time to first request for analgesic (TFA) was not significantly different in the two groups. The total opioid consumption within 24 h was also comparable in both groups.

We observed that the postoperative pain intensity scores in this study were within the mild-to-moderate range. This is possibly due to the fact that the postoperative pain intensity following thyroidectomy is relatively low, compared with other more extensive procedures. Thyroidectomy has generally been considered as being only moderately painful.[12,13] Kalmovich *et al*.[14] noted that the pain level following thyroidectomy decreased steadily from the first postoperative evening, with the peak average pain being at the moderate level.

Comparing previous studies,[5,7-9] we also noted that the dose of ketamine used did not necessarily correlate with outcomes, with the use of similar doses often still being associated with conflicting results. This suggests that other than the ketamine dose used, other peri- and intra-operative factors probably also play a significant role in determining a preemptive effect. Some studies[15,16] in animals and humans have previously suggested that the use of adjuvant drugs as part of the general anesthetic technique can attenuate the central sensitizing effects of surgical stimuli, leading to increased difficulty in detecting a preemptive effect.

Kissin[17] had earlier identified certain reasons which may make it difficult to establish the existence of preemptive analgesia. These included (i) misleading terminology, (ii) incomplete

Table 1: Demographic variables in the two groups

Variable	Ketamine, *n* (%)	Control, *n* (%)	Total, *n* (%)	t/χ^2	*P*
Age group (years)					
20-29	2 (4.9)	3 (7.3)	5 (6.1)	0.567	0.967[Y]
30-39	5 (12.2)	5 (12.2)	10 (12.2)		
40-49	15 (36.6)	16 (39.0)	31 (37.8)		
50-59	17 (41.5)	13 (31.7)	30 (36.6)		
≥60	2 (4.9)	4 (9.8)	6 (7.3)		
Mean±SD	48.07±8.38	47.68±9.92		0.192[t]	0.848
Weight (kg), mean±SD	63.81±6.43	66.46±8.30		−1.617[t]	0.110
Height (m), mean±SD	1.63±0.04	1.64±0.05		−0.982[t]	0.329
BMI (kg/m^2), mean±SD	23.92±2.52	24.53±2.47		−1.108[t]	0.271
ASA grade					
I	38 (92.7)	36 (87.8)	74 (90.2)	0.139	0.709[Y]
II	3 (7.3)	5 (12.2)	8 (9.8)		

[t]Independent samples *t*-test, [Y]Yates corrected Chi-square. SD: Standard deviation, ASA: American Society of Anesthesiologists, BMI: Body mass index

Table 2: Distribution of patients according to pain scores

Postoperative pain scores	Number of patients			χ^2	*P*
	Ketamine, *n* (%)	Control, *n* (%)	Total, *n* (%)		
At recovery room (30 min)					
No pain	20 (48.8)	11 (26.8)	31 (37.8)	4.886	0.087
Mild	15 (36.6)	18 (43.9)	33 (40.2)		
Moderate	6 (14.6)	12 (29.3)	18 (22.0)		
At 2 h					
No pain	12 (29.3)	9 (22.0)	21 (25.6)	1.690	0.430[Y]
Mild	28 (68.3)	27 (65.9)	55 (67.1)		
Moderate	1 (2.4)	5 (12.2)	6 (7.3)		
At 6 h					
No pain	23 (56.1)	20 (48.8)	43 (52.4)	0.343	0.842[Y]
Mild	17 (41.5)	18 (43.9)	35 (42.7)		
Moderate	1 (2.4)	3 (7.3)	4 (4.9)		
At 12 h					
No pain	29 (70.7)	27 (65.9)	56 (68.3)	0.018	0.991[Y]
Mild	12 (29.3)	13 (31.7)	25 (30.5)		
Moderate	0 (0.0)	1 (2.4)	1 (1.2)		
At 24 h					
No pain	30 (73.2)	31 (75.6)	61 (74.4)	0.050	0.975[Y]
Mild	11 (26.8)	9 (22.0)	20 (24.4)		
Moderate	0 (0.0)	1 (2.4)	1 (1.2)		

[Y]Yates corrected Chi-square

Table 3: Range and median values of postoperative pain scores

Pain scores	Number of patients		*U*	*P*
	Ketamine (*n*=41)	Control (*n*=41)		
At recovery room				
Range	0-2	0-2	620.000	0.208
Median	1	1		
2 h postoperative				
Range	0-2	0-2	722.500	0.185
Median	1	1		
6 h postoperative				
Range	0-2	0-2	762.500	0.412
Median	1	1		
12 h postoperative				
Range	0-1	0-2	793.500	0.590
Median	0	0		
24 h postoperative				
Range	0-1	0-2	825.500	0.854
Median	0	0		

U: Mann-Whitney U test, 0: No pain, 1: Mild pain, 2: Moderate pain, 3: Severe pain, 4: Excruciating pain

afferent anti-nociceptive block in the preemptive group, (iii) presence of a partial preemptive effect in the control group, thus minimizing the difference in outcome compared with the active treatment group, (iv) inadequate noxious stimuli during the primary and secondary phases of the surgical injury to generate a sufficient difference between study groups, and (v) outcome measurement problems. It is possible that an interplay of these and other perioperative factors contributed significantly to our findings.

Our findings are comparable to that of Amanor-Boadu *et al*.[8] which compared two groups of patients (preincision ketamine and postincision ketamine groups) who had gynecological surgeries. Even though the study reported a significant delay in the TFA for the preincision ketamine group, a definite preemptive effect could not be demonstrated, as the postoperative pain scores (VAS) and 24 h opioid requirement were not significantly different. The same dose of ketamine (0.5 mg/kg) as used in this study, as well as standard general anesthetic technique, was used. Similarly, in agreement with our findings, Adam *et al*.[18] could not establish a preemptive effect of ketamine in patients who had mastectomy. This was despite their use of a significantly lower dose of preincisional ketamine (0.15 mg/kg).

In the study by Singh *et al*.[19] (involving patients who had laparoscopic cholecystectomy), 3 Groups A, B and C received preincision ketamine doses of 1.00 mg/kg, 0.75 mg/kg and 0.5 mg/kg respectively while a fourth Group D (control) received isotonic saline. Their results showed that the mean pain scores were significantly higher in the control group compared with the study Groups A, B, and C at most of the time intervals. Similarly, the total postoperative opioid consumption was also significantly higher in the control group, compared with the ketamine groups. This is in contrast to our results. However, this may not be unconnected with the use of laparoscopic technique, which minimizes the degree of surgical trauma, thereby considerably lessening pain

Table 4: Time to first request for analgesic

Variable	Number of patients			U/χ^2	*P*
	Ketamine, *n* (%)	Control, *n* (%)	Total, *n* (%)		
Request for analgesic					
Yes	15 (36.6)	20 (48.8)	35 (42.7)	1.246	0.372[F]
No	26 (63.4)	21 (51.2)	47 (57.3)		
Time to first request for analgesic (min)					
Mean±SD	86.00±56.58	79.90±68.05		122.500[U]	0.357
Median	60.00	45.00			

[F]Fishers exact Chi-square, [U]Mann-Whitney *U* test. SD: Standard deviation

Table 5: 24 h opioid consumption

Variable	Ketamine, *n* (%)	Control, *n* (%)	*U/t*	*P*
Total fentanyl given (µg), mean±SD	193.90±44.99	196.34±46.62		0.810
Total morphine given (mg), mean±SD	11.00±3.16	13.21±5.87	−1.112[t]	0.275

[U]Mann-Whitney *U* test, [t]Independent samples *t*-test. SD: Standard deviation

from tissue injury. Thus, a low-dose preemptive ketamine, which could have been insufficient for a major surgery may be adequate for a minimally invasive procedure such as laparoscopic cholecystectomy. The findings of Ahmed *et al*.[20] also indicated that preemptive administration of ketamine markedly reduced the postoperative pain scores and also prolonged the TFA after total abdominal hysterectomy. The authors, however, reported a complete withdrawal of opioid analgesics throughout the intraoperative period. This could be a reason for the observed variance with our findings, as the omission of intraoperative opioid analgesia could have contributed to an improved appreciation of a preemptive effect of ketamine. A similar explanation could be adduced for the results of Akbar *et al*.,[9] who also demonstrated reduction in postoperative pain scores, prolongation of the TFA and reduction of postoperative opioid consumption in the preincision ketamine group in their study on patients scheduled for appendectomy. Their omission of intra-operative opioid possibly also modified their outcome differently to ours. In addition, the mean duration of surgery was also significantly less, compared to our study. This could have had an effect on the degree of pain experienced postoperatively and influenced analgesic consumption. The use of standardized general anesthesia technique, the same dose of preincision ketamine, and standard incision in all patients are, however, key factors which are comparable with our study.

Roytblat *et al*.[7] reported a 40% decrease in the postoperative opioid use after cholecystectomy with mean morphine doses (over 24 h) of 29.5 mg and 48.7 mg in the preincision ketamine and control groups respectively. However, the use of a patient-controlled analgesia (PCA) device in their study is a significantly improved approach to postoperative pain treatment, which was not used in our work, due to nonavailability. It is possible that this contributed to the difference in findings. However, in another study[10] among patients undergoing colon surgery, in which a PCA device was used, the TFA, opioid requirements, and the measured cumulative consumption of morphine revealed no statistically significant difference between the groups. This is contrary to the expectation that the use of the PCA for postoperative opioid administration, and the homogeneity of surgical procedure (open colon surgery) could have improved the accuracy of the results.

Fu *et al*.[21] also reported a significant reduction in PCA morphine consumption postoperatively, in the preemptive ketamine group. Their study compared the analgesic effect of a presurgical loading dose of ketamine (0.5 mg/kg), followed by a continuous infusion, versus a single postsurgical ketamine dose of 0.5 mg/kg in the control group. However, the total ketamine doses received were different between both groups, and hence likely to have influenced the analgesic requirement postoperatively. In addition, surgical procedures employed were heterogeneous, with possibly different degrees of pain stimulation, and thus contributing further to the difference between their study and ours.

As earlier noted, thyroidectomy is associated with a relatively low postoperative pain intensity. Hence, it is possible, as proposed by Kissin,[17] that there was inadequate noxious stimulation in our study to generate sufficient difference between the study groups. This could have had an effect on our result. Furthermore, general anesthesia (used in our study) involves the administration of many adjuvant drugs such as opioid analgesics, IV, and inhalational anesthetics, which may exert some partial preemptive effect, leading to a masking of the desired preemptive effect. This was probably responsible for the decision of some researchers to withhold opioid use intraoperatively, as noted earlier. Our study ensured the use of intraoperative opioid (fentanyl), in contrast to these studies. This is owing to our conviction that omission of adequate intraoperative analgesia especially in the control group could be ethically controversial. Our inability to elicit a preemptive analgesic effect of ketamine could however probably be traceable to this factor.

Conclusion

Based on the above findings, we conclude that administration of preincision IV low-dose (0.5 mg/kg) ketamine did not produce a preemptive analgesic effect in patients who had elective thyroidectomy.

Limitations

Nonavailability of the PCA device was an important factor which probably limited the quality of postoperative analgesic delivery and measurement.

Recommendations

In view of our inability to elicit a preemptive effect of ketamine, we recommend that attention and resources should be further devoted to investigating other drugs that are potentially useful as preemptive analgesics.

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Conflicts of interest

There are no conflicts of interest.

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