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Commentary Open Access

The Efficacy of Preemptive Ketamine Administration in Bilateral Superficial Cervical Plexus Block After Thyroid Surgery

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Abstract

Background: Peripheral tissue injury initiates peripheral sensitization; in addition, it triggers excitability of the central neurons known as central sensitization. N-methyl–D-aspartate (NMDA) receptors are largely involved in the pathogenesis of central sensitization. The concept of preemptive local anesthetic administration seems hopeful in management of postoperative pain. The addition of ketamine as NMDA receptors antagonist reduces the incidence of chronic pain and the chance for development of hyperalgesia and allodynia. Our study hypothesis is to evaluate effects of adding ketamine to bupivacaine in bilateral superficial cervical plexus block (BSCPB) on acute and chronic pain after thyroid surgery.

Patients and Methods: Sixty (ASA I, II) 18 to 60 years old undergoing thyroid surgery were simply randomized into two equal groups, thirty patients received BSCPB using 9 ml bupivacaine 0.25% solution mixed with 1 ml normal saline (Bupivacaine group) and thirty patients received BSCPB using 9 ml bupivacaine 0.25% solution mixed with 1 ml ketamine 50 mg/ml (Ketamine group). Patients were instructed about the use of a 10 cm Visual Analog Scale (VAS) (0=no pain to 10=worst possible pain). Pain level was recorded at PACU admission every 3 h for the first 24 hours. The analgesic requirement during the first 24 h after surgery was recorded. Any side effects were recorded. The incidences of chronic pain, wound hyperalgesia and allodynia after six months were recorded.

Results: Intraoperative fentanyl requirements were significantly reduced in ketamine group. At post-anesthesia care unit, acetaminophen requirements during the first 24 hours after surgery were significantly reduced in ketamine group. The incidence of wound hyperalgesia and allodynia were significantly lower in ketamine group.

Conclusion: Pre-incisional BSCPB using bupivacaine 0.25% in addition to 50 mg ketamine demonstrated significant reduction in intraoperative and postoperative analgesic requirement after thyroid surgery. The incidences of chronic pain, wound hyperalgesia and allodynia were significantly reduced after six months in ketamine group.

Introduction

Pre-emptive regional blockade are standard techniques for decreasing postoperative analgesic drug requirement. Preincisional Bilateral Superficial Cervical Plexus Block (BSCPB) is reported to be easier to perform with similar efficacy and fewer anesthesia related complications than alternative techniques [1], the earlier suggestion that the deep cervical plexus block provides better postoperative analgesia was not established and in fact it appears that analgesia is better after superficial block alone [2]. N-Methyl-D-Aspartate (NMDA) receptors are activated by C-fiber inputs triggered by surgical tissue trauma via nociceptive transmitter release in the dorsal horn of the spinal cord. The activation of these receptors enhances central nervous system sensitization and, therefore, the intensity of perceived postoperative pain. It has been proposed that analgesic drugs might more adequately prevent this central sensitization when administered before the tissue trauma; this is the theory behind the concept of preemptive analgesia [3]. There is a growing body of evidence that ketamine, a non-competitive antagonist at NMDA receptors [4], can facilitate postoperative pain management [5]. In addition; Ketamine reduces the incidence of wound hyperalgesia and allodynia [6]. Our study hypothesis is to evaluate effects of adding ketamin to bupivacaine in Bilateral Superficial Cervical Plexus Block (BSCPB) on acute and chronic pain after thyroid surgery.

Patients and Methods

After the study was approved by an Investigational Review Board, an informed written consent was obtained from patients participating in the study. The study is registered in the Pan African Clinical Trial Registry (www.pactr.org) database, with unique identification number PACTR201201000348300.

Sixty (ASA I, II) 18 to 60 years old patients scheduled for elective thyroid surgery were randomized into two equal groups, thirty patients received BSCPB using 9 ml bupivacaine 0.25% solution mixed with 1ml normal saline (Bupivacaine group) and thirty patients received BSCPB using 9 ml bupivacaine 0.25% solution mixed with 1 ml ketamine 50 mg/ml (Ketamine group). Randomization was performed by random numbers using sealed envelopes without sex stratification. Sealed envelopes indicate the group of assignment. An independent anesthesiologist, who did not participate in the study or data collection, read the number contained in the envelope and made group assignments. Patients were blindly randomized into two groups; the process of inclusion into the study went on until the requested number of patients was reached.

Patients were excluded from the study if their preoperative

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medication included opioid or non-opioid analgesics, corticosteroids, or non-steroidal anti-inflammatory drugs. Coagulation disorders, pregnancy, age less than 18 years, patient refusal, and emergency re-operation within the first 24 hours were also exclusion criteria. The injection was given with unlabelled syringes prepared by independent anaesthologist not involved in the patients care or in pain assessment. The specific treatment given was unknown to the patient, anesthesiologist, surgeon, or nurses in charge of pain assessment. All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been assigned.

On the evening before surgery, patients were instructed about the use of a 10 cm Visual Analog Scale (VAS) (0=no pain to 10=worst possible pain). Anesthesia was standardized. Patients were pre-medicated with midazolam (0.01 mg/kg) 2 hours before surgery. General anesthesia was induced using propofol (2 mg/kg) and fentanyl (1 μg/kg). Tracheal intubation was facilitated by the administration of atracurium 0.5 mg/kg. General anesthesia was maintained with isoflurane (0.5-1.5%) in 100% oxygen. Additional doses of fentanyl (0.5 μg/kg) were administrated for variations of Systolic Blood Pressure (SBP) and Heart Rate (HR) of more than 20% when compared with the values measured before operation. All the patients were admitted to the PACU.

BSCPB was performed by an independent anesthesiologist familiar with the technique, not involved in the study, pain assessment or data collection. 10 ml of the prepared mixture according to study group were injected in each side, during block placement, patients were lying supine with their heads slightly extended and rotated to the lateral side opposite to the block.

At the midpoint of the posterior border of Sternocleidomastoid (SCM) muscle, injection was performed subcutaneously along the posterior border of the muscle in cranial and caudal directions. Intraoperatively, MBP and HR were recorded at induction, incision, end of resection, and extubation. The duration of surgery and fentanyl requirements were also recorded. Postoperative laryngoscopy was performed to evaluate laryngeal palsy before transfer to the PACU.

Postoperative pain was assessed at rest and movement in the form of deglutition by independent physicians who were completely blinded to patients group assignment, not sharing in the study design or data collection, using Visual Analogue Scale (VAS) ranging from 0 (no pain) to 10 (worst imaginable pain). Pain level was recorded at PACU when the patient was able to communicate every 3 h for the first 24 h during rest and movement during deglutition. All patients received 15 mg/kg i.v. acetaminophen every 6 h; the first dose was given 40 min before the end of surgery. Supplementary doses of acetaminophen i.v. was given to patients with a VAS higher than 4. Any episodes of bradycardia (HR <50 beats/min), hypotension (SBP <90 mmHg), nausea, vomiting, and excessive sedation were recorded.

Pin-prick hyperalgesia was tested using a von Frey hair on the skin starting from outside the hyperalgesic area where no pain sensation was experienced and advancing toward the centre of the incision until the patient reported a distinct change in perception and feeling pain. Pin-prick hyperalgesia was compared in two regions of the body: a control site on the inner forearm and a test site approximately 10 cm from the surgical wound. Allodynia was tested by a brush, which was applied in the same manner as the von Frey hair. Pin-prick hyperalgesia and allodynia were evaluated at 6 months after surgery during the follow up visit by independent physicians who were completely blinded to patients' group assignment, not sharing in the study design or data collection.

The primary outcome was intraoperative fentanyl requirements. The secondary outcomes measures were acetaminophen requirements during the first 24 h after surgery and the incidence of chronic pain in the form of hyperalgesia and allodynia after surgery. All adverse events related to surgery and the regional anesthetic technique was recorded.

Statistical Methods

Student *t* test was used for analysis of continuous variables. Chi-squared statistic was used to test the differences in proportions. Descriptive statistics were reported as percentages for proportions while, mean and standard deviation (with ranges) for continuous values. The results were considered significant at the 5% critical level (a two-sided) P value (0.05).

A sample size analysis determined that 28 patients per group were required to detect difference of at least 20 % in fentanyl consumption between groups with a power of 80%, α of 0.05 and allocation ratio of 1:1, so we included 30 patients in each group.

Results

There is no significant difference between the two groups regarding the patients' demographics, type and duration of surgery (Table 1).

Regarding intraoperative and postoperative analgesic requirements, Intra-operative fentanyl requirements were significantly reduced in ketamine group with a mean value of 40 ± 10.5 μg in comparison to bupivacaine group with a mean value of 90 ± 25.5 μg (p=0.027). Acetaminophen requirements during the first 24 hours after surgery were significantly reduced in ketamine group with a mean value of 250 ± 75 mg in comparison to bupivacaine group with a mean value of 875 ± 205 mg (p=0.012). Eighteen patients (60%) in bupivacaine group required acetaminophen infusion during the first 24 h after surgery which is statistically significant in comparison to 5 (16%) patients in ketamine group who required acetaminophen infusion (p=0.004) (Table 2).

No patient in either group reported sedation, hallucinations, nightmares, or diplopia, and no differences were noted in the incidence of nausea and vomiting between the two groups.

Six months after surgery, the incidence of burning pain was significantly higher in the bupivacaine group, 9 (30%) patients in

	Bupivacaine group (n=30)	Ketamine group (n=30)
Age (years) mean ± SD	48.8 ± 3.63	49.1 ± 3.88
Gender		
Male	9(30%)	21(70%)
Female	10(33%)	20(66%)
Weight (Kg) mean ± SD	84.7 ± 9.2	83.3 ± 9.4
Height (cm) mean ± SD	175 ± 21	172 ± 23.6
Duration of surgery (min)	79.4 ± 12.9	84.4 ± 14.5
Type of surgery†:		
- Total Thyrodectomy	4	5
- Subtotal thyrodectomy	10	9
- Hemithyrodectomy	9	6
Lobectomy	7	10

Student t test was used
†Chi-squared test was used

Table 1: Patients characteristics in both groups.

	Bupivacaine group (n=30)	Ketamine group (n=30)
Intra-operative fentanyl requirements (µg)	90 ± 25*	40 ± 10.5
Acetaminophen requirements during the first 24 h after surgery (mg)	875 ± 205*	250 ± 75
Number of patients required acetaminophen during the first 24 h after surgery†	18 (60%)*	5 (16%)

Student t test was used.
† Chi-squared test was used.
*Statically significant change (p<0.05)

Table 2: Analgesic requirements in the studied groups.

Chronic Pain characteristics	Bupivacaine group (n=30)	Ketamine group (n=30)
Type of Pain		
t Throbbing	1 (3.3 %)	1 (3.3%)
Aching	3 (10%)	2 (6.6%)
Troublesome	2 (6.6%)	1 (3.3%)
Burning	9 (30%)*	3 (10%)
Stabbing or Pricking	11 (36%)*	4 (13%)
Wound allodynia	8 (26%)*	2 (6.6%)
Wound Hyperalgesia	5 (16%)*	1 (3.3%)

Chi-squared test was used
*Statically significant change (p<0.05)

Table 3: Chronic pain characteristics in each group of patients 6 months postoperatively.

comparison to 3 (10%) patients in ketamine group (P=0.028). In addition, stabbing or pricking pain was significantly reduced in ketamine group, 4 (13%) patients in comparison to 11 (36%) patients in bupivacaine group (P=0.012). Significantly higher number of patients in the bupivacaine group developed wound hyperalgesia, 8 (26%) patients in comparison to 2 (6.6%) patients in ketamine group (P=0.02). Significantly higher number of patients in the bupivacaine group developed wound allodynia, 5 (16%) patients while, only one patient developed allodynia in ketamine group (P=0.036) (Table 3).

Discussion

This prospective, randomized, double blinded trail revealed that BSCPB using bupivacaine 0.25% as a local anesthetic in addition to ketamine 50 mg as NMDA receptor antagonist demonstrated significant reduction in intra-operative and postoperative analgesic requirement during the first 24 hours after thyroid surgery. The incidences of chronic pain, wound hyperalgesia and allodynia were significantly reduced six months after surgery.

NMDA receptor had been isolated in peripheral nervous system; in addition tissue injury induces sensitization of the nervous system. Peripheral sensitization is a reduction in the threshold of nociceptive afferent terminals at the site of injury, and central sensitization is an increase in the excitability of the spinal neurons. Much interest has focused on the potential role of N-methyl-d-aspartate receptor antagonists in preventing central sensitization and wound hyperalgesia [3].

The benefit of preemptive NMDA receptor antagonists on postoperative pain was formerly studied [7]. NMDA receptor antagonism accounts for most of its analgesic effects [4]. Another mechanism may be the synergistic or additive interaction among opioids. A potentiation between the effects of opioids and NMDA antagonists on wind–up of C fiber-evoked responses of spinal dorsal horn neurons had been reported. Furthermore, NMDA antagonists seem to have additional advantage of attenuating analgesic tolerance to opioids [8].

Previous experimental studies [9-11] demonstrated the existence of NMDA receptors in the peripheral nervous system suggesting the peripheral pain relieving role of ketamine, stimulation of these receptors produced mechanical hyperalgesia that could be inhibited by local treatment with NMDA receptor antagonists.

Ketamine is increasingly used in both acute and chronic pain settings in the developing world. Many studies previously evaluated the analgesic effect of ketamine, Roytblat et al. [12] and Tverskoy et al. [13] had demonstrated the benefit of intraoperative ketamine in reducing postoperative pain, wound hyperalgesia and postoperative opioids requirements. Menigaux et al. [14] found that intraoperative small dose ketamine reduced postoperative morphine requirements. The results of De Kock et al. [15] suppose that a sub-anesthetic dose of ketamine reduces wound hyperalgesia.

Pre-emptive use of ketamine is effective in reducing pin-prick hyperalgesia, and touch allodynia. Unfortunately, there are several issues for future investigation such as the most effective dose, timing of administration, necessity for continuous infusion and emergence complication [16]. Emergence phenomena from ketamine are very common in the form of disturbances of sensory perception. These sensory disturbances include transient blindness or double vision, distortion of body image, colour hallucinations, floating sensation and depersonalization. The reported frequency of ketamine hallucinations varies from 5 to 30%. Increased incidence is associated with female sex, rapid intravenous boluses and large doses of ketamine [17]. Our patients did not develop sedation, hallucinations, nightmares or diplopia which is explained by the use of small sub-anesthetic doses of perineural ketamine and consequently minimum amount of systemic absorption.

Warncke et al. [18] reported that ketamine as NMDA receptor antagonist blocked the development of punctuate hyperalgesia and wound up phenomena. Pedersen et al. [19] showed that ketamine had antinociceptive effects in acute inflammatory pain. Ketamine also improves postoperative rehabilitation at 1 month and reduces persistent postoperative pain up to 6 months in orthopedic surgery [20].

Previous study concluded that superficial cervical block is an alternative to combined block for parathyroidectomy, with similar onset time of surgical block, pain score during surgery and time to first analgesic requirement [21].

Stoneham et al. [22] compared superficial and deep cervical plexus blockade and found that the intraoperative requirement was similar between the groups. Pandit et al. [2] compared the superficial cervical plexus blockade with combined blockade and found no significant difference between the groups regarding number of patients needing postoperative analgesia and the median time to first analgesic requirement. Dieudonne et al. [23] concluded that the use of BSCPB in patients undergoing thyroid surgery produced significant reduction in postoperative analgesic requirement. Aunac et al. [24] concluded that the use of superficial and deep cervical plexus block significantly reduced intraoperative and postoperative analgesic requirements in the immediate postoperative 24 hours. Eti et al. [25] concluded that the use of BSCPB is associated with statistically significant prolonged first analgesic requirement time in post-thyrodiectomy patients. The use of preemptive BSCBP significantly reduced postoperative analgesic

requirement in patients undergoing thyroid surgery under general anesthesia [26].

Conclusion

Pre-incisional BSCPB using bupivacaine 0.25% in addition to 50 mg ketamine demonstrated significant reduction in intra-operative and postoperative analgesic requirement after thyroid surgery. The incidences of chronic pain, wound hyperalgesia and allodynia were significantly reduced in ketamine group after six months.

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