



KETOROLAC ADMINISTRATION WITH KETOROLAC AND BILATERAL SUPERFICIAL CERVICAL PLEXUS BLOCK'S COMPARISON TO TOTAL POST-THYROIDECTOMY ANALGESIC RESCUE NEEDS

Sandi Fathir¹, Suwarman², Muchammad Erias Erlangga³

¹ Faculty of Universitas Padjajaran /Hasan Sadikin General Hospital, Bandung, West Java, Indonesia

² Faculty of Universitas Padjajaran /Hasan Sadikin General Hospital, Bandung, West Java, Indonesia

³ Faculty of Universitas Padjajaran /Hasan Sadikin General Hospital, Bandung, West Java, Indonesia

* sandi19003@mail.unpad.ac.id

ARTICLE INFO	ABSTRACT
Published: May 29 th , 2023	<i>Thyroidectomy is generally performed by a surgeon with a short operating duration. Inadequate postoperative pain treatment results in several physiological and psychological outcomes, including prolonged hospital stays and the development of chronic pain. This study aims to compare the administration of ketorolac with a combination of ketorolac and bilateral superficial cervical plexus blocks to the total need for analgetic rescue after thyroidectomy surgery. This study used an experimental study with a single-blind randomized control trial method for both study groups. After surgery, group A was given an IV injection of 30 mg ketorolac, while group B was given IV injections of 30 mg ketorolac and bilateral superficial cervical plexus block under ultrasound guidance and 10 ml of 0.25% bupivacaine on each side of the neck before surgery was completed. Both groups would be monitored for 2 hours. The average value of total analgetic rescue needs in the patient group given ketorolac was 195.24 ± 72.72 mcg. While the total need for analgetic rescue in the group of patients who were given a combination of ketorolac and bilateral superficial cervical plexus blocks was 44.05 ± 19.21 mcg. The results of the unpaired T-test showed a p-value of 0.001. There is a significant difference in the total need for analgetic rescue in patients receiving ketorolac.</i>
Keywords: Thyroidectomy, Bilateral superficial cervical plexus block, Analgetic rescue	
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INTRODUCTION

Thyroidectomy is a medical procedure for removing the thyroid gland and can be performed for both benign and malignant diseases, such as thyroid nodules, hyperthyroidism, obstructive or substernal goiter, differentiated (papillary or follicular) thyroid cancer, medullary thyroid cancer (MTC), anaplastic thyroid cancer, thyroid lymphoma, and thyroid metastases from primary extrathyroidal cancers (most commonly renal cell and lung cancer) (Haugen, 2017).

Thyroid surgery can carry a risk of mild pain. Symptoms such as discomfort when swallowing, burning sensation in the throat, nausea, or vomiting are often felt, especially on the first postoperative day. Prevention of pain problems can be done with the use of nonsteroidal anti-inflammatory drugs or with regional anesthesia (Harahap et al., 2017; Patoir et al., 2017). The 2012 American Society of Anesthesiologists (ASA) practice guidelines state that inadequate treatment of postoperative pain results in prolonged hospital stays leading to the development of chronic pain (Papioian et al., 2020). The use of postoperative NSAIDs as acute pain inhibitors helps reduce opioid overuse (Gupta & Bah, 2016; Stasiowska et al., 2015).

The use of NSAIDs helps reduce costs and is proven to work on peripheral nociceptors by blocking cyclooxygenase (COX) enzymes and centrally in the dorsal horn of the spine to inhibit prostaglandin-E2 (PGE2) production through COX-2. The ASA guidelines note that patients should receive a 24-hour regimen of NSAIDs, COX inhibitors, or acetaminophen as part of their multimodal postoperative pain management regimen (Motamed, 2022). Postoperative pain after thyroid surgery is important to pay attention to. Inadequate postoperative pain control can increase stress hormone levels, increase insulin resistance, increase catabolism, and other perioperative complications (Kang et al., 2017; Sen & Bathini, 2015). Several studies have assessed pain based on analgesic dose or directly based on post-thyroidectomy VAS scores (Anekar & Cascella, 2021).

Patient Controlled Analgesia (PCA) is a method of administering analgesics as postoperative analgesia. PCA is the administration of intravenous opioids as needed and under the control of the patient. This technique is based on the use of a microprocessor-controlled infusion pump that delivers a programmed dose of opioids when the patient presses the PCA button (Motamed, 2022). PCA has two delivery methods: demand dosing (fixed dose given by the patient himself intermittently) and continuous infusion added to the requested dose (infusion rate fixed according to the patient's requested dose). The majority of intravenous PCA instruments use both the opioid and morphine classes of drugs (Jung et al., 2021).

According to the World Federation of Societies of Anesthesiologists (WFSA), acute pain can be treated with an analgesic ladder. Acute postoperative pain can be treated by administering a combination of intravenous analgesics with regional anesthesia (Mayhew et al., 2018). The administration of analgesic drugs based on the WFSA analgesic ladder is the administration of non-opioid analgesics such as non-steroidal anti-inflammatory drugs or acetaminophen with or without adjuvants for mild pain. For moderate pain, weak opioids such as hydrocodone, codeine, and tramadol are given with or without non-opioid analgesics, and with or without adjuvants (Anekar & Cascella, 2021). Mild postthyroidectomy pain can use NSAIDs with or without adjuvants (Anekar & Cascella, 2021; Sen & Bathini, 2015). A peripheral nerve block is a simple, safe and effective postoperative analgesia method. Bilateral superficial cervical plexus block (BPSSB) can be used as preoperative analgesia or to treat postoperative pain in cases of neck surgery because it can block nerve branches originating from the superficial cervical plexus. BPSSB is a procedure with a low complication rate (Kannan et al., 2018).

BPSSB, is a simple, safe, effective method of postoperative analgesia with a low complication rate. The BPSSB technique can reduce the need for intra and postoperative opioid analgesia, as well as reduce postoperative nausea and vomiting, so this study was conducted to determine the administration of a combination of ketorolac and bilateral superficial cervical plexus blocks to the total analgetic rescue requirement after thyroidectomy surgery. The study is expected to lead readers to a wider range of knowledge regarding ketorolac and thyroidectomy analgesic rescue, and how to implement the contextually necessary procedures properly.

METHOD

The subjects of the study were patients who were going to have thyroidectomy surgery at Dr. Hasan Sadikin who fulfilled the inclusion and exclusion criteria. The inclusion criteria in this study were patients who underwent thyroidectomy with a transverse incision, patients aged 18-60 years, and physical status according to the American Society of Anesthesiologists (ASA) I-II. Meanwhile, the exclusion criteria in this study were the patient takes pain medication before surgery and history of neurological or psychiatric disorders that may affect the patient's communication skills. The research was conducted from 12 October 2022 to 11 January 2023. The research was conducted after obtaining approval from the Ethics Committee of RSUP Dr. Hasan Sadikin Bandung with Ethics Number: LB.02.01/X.6.5/344/2022.

This study used an unpaired numerical comparative analytic design with 2 groups. The number of samples in this study were 42 people divided into group A (n=21) who would receive a single bolus of ketorolac and group B (n=21) who would receive a combination of ketorolac with bilateral superficial cervical plexus blocks. The selection of research subjects was carried out based on consecutive sampling and divided into groups using permuted block randomization. It is an experimental research with a single blind randomized control trial method.

Data analysis procedures included descriptive analysis and hypothesis testing. Assessment of data normality was carried out using the Shapiro-Wilk test, then deploying the unpaired T-test. Categorical data analysis was performed using the Chi-Square Test. The data would be stated to be statistically significant when the p value <0.05 and the 95% confidence interval. The data obtained were recorded in a form and then processed through the SPSS version 25.0 for Windows program.

RESULT AND DISCUSSION

The characteristics of the study subjects were described based on age, body mass index (BMI), duration of surgery, sex, and education. The distribution of patients by characteristics is described in Table 1.

Table 1. Comparison of the Characteristics of the Research Subjects

Variable	Group		p-value*
	A (n=21)	B (n=21)	
Age (years)			0,413
Mean ± Std	49,4 ± 9,78	47,05 ± 8,46	
Median	52	48	
Range (min-max)	24-59	30-60	
BMI (kg/m²)			0,406
Mean ± Std	26,75 ± 2,16	27,28 ± 1,91	
Median	27,34	27,41	
Range (min-max)	21,48-28,84	21,48-29,97	

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Duration of Surgery (minutes)			0,921
Mean ± Std	165,24 ± 16,1	164,76 ± 14,7	
Median	160	160	
Range (min-max)	140-190	140-190	
Sex			0,214
Male	4 (19%)	5 (23,8%)	
Female	17 (81%)	16 (76,2%)	
Education			0,105
Did not graduate high school	0 (0%)	0 (0%)	
High school	15 (71,4%)	16 (76,2%)	
College	6 (28,6%)	5 (23,8%)	

* Note: The p value is calculated based on the unpaired t test if the data is normally distributed. An alternative to the Mann Whitney Test if the data is not normally distributed. Categorical variables were carried out using the Chi-Square Test.

Age, BMI, and length of operation variables have normally distributed data. Numerical data analysis was tested using an unpaired t-test. The statistical test results for age, BMI, and length of surgery obtained $p > 0.05$, so there was no significant difference in the mean between the variables age, BMI, and length of operation in the two groups

Categorical data analysis was performed by Chi-Square Test. The results of the statistical test obtained a value of $p > 0.05$ which means it is not significant, so there is no significant difference in the proportion between the variables of sex and education in the two groups.

Based on these two results, the two groups were homogeneous and comparable.

Comparison of Total Requirement for Analgesic Rescue

A comparison of the total analgetic rescue needs in patients receiving ketorolac and the combination of ketorolac and bilateral superficial cervical plexus blocks was analyzed using an independent T-test (Table 2).

Table 2. Comparison of Total Requirement for Analgesic Rescue

Variable	Group		p-value*
	A (n=21)	B (n=21)	
The total requirement for analgetic rescue			0,001*
Mean ± Std	195,24 ± 72,72	44,05 ± 19,21	
Median	175	50	
Range (min-max)	125-350	25-75	

* Note: The p value is calculated based on the unpaired T test if the data is normally distributed and the Mann-Whitney test if the data is not normally distributed.

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The results of the unpaired T test showed a p value <0.05 which means that there was a significant or statistically significant difference.

Comparison of First-Time Emphasis Analgetic Rescue

The comparison of time to suppression of first analgesic rescue in both groups was analyzed using independent T test as presented in Table 3.

Table 3. Comparison of First Time Emphasis Analgetic Rescue

Variable	Group		p-value*
	A (n=21)	B (n=21)	
Analgetic rescue time			0,0001*
Mean $\pm$ Std	262,14 $\pm$ 17,14	713,81 $\pm$ 98,44	
Median	260	670	
Range (min-max)	240-290	600-930	

* Note: The p value is calculated based on the unpaired T test if the data is normally distributed, the Mann-Whitney test if the data is not normally distributed. Significance value based on p value <0.05 .

The results of the unpaired T test showed a p value <0.05 , which means that there was a significant difference in the time of pressing the first analgesic rescue in subjects with groups A and B.

Based on the results of statistical tests, it was found that the total analgetic rescue requirement in group B who received a combination of ketorolac and bilateral superficial cervical plexus blocks was lower than group A ($p < 0.05$; Table 2). Based on the test results above, the hypothesis is accepted.

Discussion

The group of subjects given ketorolac, the mean age was 49.4 years. The group of subjects given combination ketorolac with bilateral superficial cervical plexus blocks, the mean age was 47.05 years. The results followed of a systematic review which states that the average age of patients undergoing thyroidectomy is between 45-50 years. Other literature also mentions that most thyroidectomy operations in Indonesia are performed on patients aged 45-55 years (Lee et al., 2018). Pain scale scores are reported to vary. The elderly reported needing fewer analgesics than young people. This is related to several factors such as differences in psychosocial abilities in processing pain stimuli, changes in pharmacokinetics and pharmacodynamics of drugs with increasing age (Widyawigata et al., 2019).

In group A and B, the majority of the subjects were female (81% and 76.2%). The results of a systematic review also revealed the same thing that the patients who underwent thyroidectomy were mostly women (Lee et al., 2018; Widyawigata et al., 2019). The factors underlying sex differences in the experience of pain are multifactorial and complex. The production of thyroid

auto antibodies is more susceptible to occur in women (Slijepcevic et al., 2015). A study showed that women showed a lower pain threshold, a greater ability to discriminate the sensation of pain, a higher degree of pain, and a lower tolerance for pain (Templeton, 2020; Vallerand & Polomano, 2000).

The average BMI of the subjects in groups A and B were 26.75 kg/m² and 27.28 kg/m². Previous studies have found that patients treated with thyroidectomy have increased body weight compared with patients treated with other antithyroid medications (Blanchard et al., 2019). Obese people tend to be more susceptible to pain and often require high doses of opioids. This is due to the disruption of drug distribution by an increase in the amount of adipose tissue and extracellular fluid in obesity (de Hoogd et al., 2017; Patanwala et al., 2014; Zengin et al., 2021).

In groups A and B, the average operating time was 165.24 and 164.76 minutes. Thyroidectomy surgery is generally performed in a short operating duration, which is 2-4 hours (Wiederhold et al., 2022). Surgery will cause cells to become damaged and release chemicals such as histamine, bradykinin and prostaglandin E₂ which have a vasodilator effect and increase blood vessel permeability resulting in local edema. Tissue pressure increases and nociceptor stimulation occurs. When nociceptors are stimulated, substance peptide P and calcitonin gene-related peptide will stimulate inflammatory processes, vasodilation, and increased vascular permeability. Serotonin has a vasoconstrictive effect followed by vasodilation. All of this stimulation of nociceptors causes pain (Yam et al., 2018).

In groups A and B, the majority of subjects had the same level of high school education (71.4% and 76.2%). Previous research reported that a person's education level can be a significant predictor of postoperative pain. This is caused by various reasons, one of which is a lack of understanding of the preoperative information received. Understanding good preoperative information is reported to be useful in reducing postoperative pain, anxiety and accelerating healing (Lanitis et al., 2015).

The results of this study indicate that the average value of total analgesic rescue needs in group A is 195.24 mcg and in group B is 44.05 mcg. The results of the unpaired T test showed a value of $p = 0.0001$, which means that there was a significant difference in the total need for analgesic rescue in the two groups.

The use of NSAIDs is proven both peripherally and centrally by blocking the cyclooxygenase enzyme which inhibits the conversion of arachidonic acid into prostaglandins thereby preventing pain receptor sensitization in response to injury (Gupta & Bah, 2016). Administration of NSAIDs will result in a significant reduction in opioid requirements.

A bilateral superficial cervical plexus block can be used as preoperative analgesia or to treat postoperative pain in cases of neck surgery because it can block nerve branches originating from the superficial cervical plexus. The goal of a peripheral nerve block is to block the transmission of impulses distal to the nerve terminals, thereby stopping pain signals from being sensed by the cortex. Impulse blockade can be brief or prolonged depending on the drug or technique used (Wiederhold et al., 2022). During thyroid and parathyroid surgery, bilateral superficial cervical plexus blocks were performed (Lee et al., 2018). This cervical plexus includes branches deep into

the neck muscles and phrenic nerves (C3, C4, and C5) that have connections to the superior cervical sympathetic ganglion, hypoglossus, and spinal accessory nerves (Wiederhold et al., 2022).

The combination cervical plexus block was an effective technique for reducing pain during and after thyroidectomy. This condition was due to bilateral superficial cervical plexus blocks increasing the effectiveness of intraoperative analgesia, reducing the amount of general anesthesia required during thyroidectomy, and reducing the severity of postoperative pain. Another study concluded that superficial cervical plexus blocks are safe, easy to perform and effective for reducing opioid consumption and increasing analgesic action after carotid endarterectomy (Kale et al., 2015). Other researchers have also revealed that this block appears to be a cheap, safe, and effective alternative to conventional general anaesthesia (Kim et al., 2018).

The total analgetic rescue required after thyroid surgery in the group with BPSSB was less than the group without BPSSB. Consumption of total opioids and analgesics was reduced by BPSSB in the first 24 hours postoperatively and there were no significant side effects. So that the BPSSB technique in thyroidectomy under general anesthesia can reduce the scale of postoperative pain, reduce the need for total analgesia, and the time needed for the first analgetic rescue is longer (Atisook et al., 2021).

The average value of analgetic rescue time in group A was 262.14 minutes and 713.81 minutes in group B. These results are in accordance with the results of previous studies which explained that patients who were given bilateral superficial cervical plexus blocks after surgery had a longer time of suppression of the first analgesic rescue (Warschkow et al., 2012).

Ketorolac has an onset of action in 20-30 minutes and a duration of action of 4-6 hours. This is in line with group A which at the time of PCA suppression for the first time for analgetic rescue for 262 minutes (4 hours 22 minutes) after ketorolac administration (Mahmoodi & Kim, 2022), whereas the onset of action from bupivacaine is 10-20 minutes with a duration of action of 4-10 hours (Padur et al., 2016). In the study in group B, it was found that the first PCA suppression time for analgetic rescue was 713 minutes (11 hours 53 minutes).

The multimodal analgesia technique is a technique for administering analgesics using an opioid, non-opioid analgesic agents, or with peripheral nerve blocks. The main goal of the multimodal analgesia technique is the optimal management of post-surgical pain so that the side effects of drugs are minimized. The concept of multimodal analgesia is the presence of sparing opioid effects aimed at enhancing analgesia by combining two or more drugs with different mechanisms of action and having an additive or synergistic effect. The consequences of administering these analgesics tend to be less, side effects will be reduced, but the analgesic effect will remain optimal. Ideally the administration of the two drugs differs in how they work, one works on peripheral sensitization, and the other works on central sensitization (Kehlet & Wilmore, 2002).

This study did not assess subjectivity for the degree of subject pain using pain assessment instruments. This is because the researchers used PCA, which is subjectively the patient will suppress PCA if they feel pain and this study was carried out in surgery with a mild risk of pain scale.

CONCLUSION

The total number of analgetic rescue requirements after thyroidectomy surgery in the administration of the combination of ketorolac and bilateral superficial cervical plexus blocks was lower than that of ketorolac administration. The administration of the combination of ketorolac and bilateral superficial cervical plexus block has a longer time of the suppression of the first analgetic rescue than the administration of ketorolac.

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