Migration Letters

Volume: 21, No: 4, pp. 515-525

ISSN: 1741-8984 (Print) ISSN: 1741-8992 (Online)
www.migrationletters.com

Comparison of Bolus Intravenous Lidocaine Administration with Continuous Intravenous Lidocaine on the Incidence of Postextubation Cough in Thyroidectomy Postoperative Patients

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Abstract

Background: Post-extubation cough following thyroidectomy is a dreadful complication. Intravenous lidocaine has been chosen by many as a prophylactic measure. This study aims to compare bolus vs continuous intravenous lidocaine administration on the incidence of postextubation cough in patients after thyroidectomy.

Methods: This study was an experimental study with a double blind randomized controlled trial design. Cough incidence was assessed using the original Minogue scale. The study was conducted at Dr. Hasan Sadikin General Hospital Bandung on 40 thyroidectomy patients. Statistical analysis of numerical data used unpaired T test and Mann Whitney while categorical data used Fisher's Exact Test.

Results: The incidence of cough was higher in group A bolus compared to group continuous intravenous lidocaine, with significant statistical difference (p value <0,05) at 12 and 24 hours after extubation. .

Conclusion: Continuous intravenous lidocaine is proven to be more effective in reducing the incidence of postextubation cough after thyroidectomy.

Keywords: *bolus intravenous lidocaine; continuous intravenous lidocaine; lidocaine; postextubation cough; postoperative complications; thyroidectomy.*

Introduction

Thyroidectomy is a surgery with a high prevalence of postoperative cough with possible risk factors being endotracheal tube stimulation, airway fluid secretion, anesthetic gases and surgical manipulation. Coughing may increase the risk of neck hematoma and postoperative bleeding which will increase postoperative morbidity of thyroidectomy.

Intravenous lidocaine administration decreases the incidence of cough and blunts the increase in heart rate and mean arterial preassure (MAP) during extubation.Lidocaine has an effective effect on preventing cough at a dose of 0.5-2 mg. Lidocaine is a dose dependent drug so that the use of lidocaine at a dose of 1.5-2 mg/kgBB intravenously can reduce the cough reflex more significantly and effectively at 3-5 minutes after injection compared to other doses. Intravenous bolus administration of lidocaine is often used but the time of use still varies because it is difficult to determine the ideal time for

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administration. Some studies suggest lidocaine administered preoperatively may be more beneficial against post-extubation cough with an intravenous lidocaine half-life of approximately 1.5 hours. The effective serum concentration of lidocaine to prevent cough is at 3.0 mcg/mL which can be achieved by intraoperative continuous intravenous administration.

Currently there are no studies comparing bolus intravenous lidocaine administration with continuous intravenous for the prevention of postextubation cough complications in thyroidectomy patients, so from the above background, the authors conducted a study aimed at comparing bolus intravenous lidocaine administration with continuous intravenous lidocaine for the prevention of postextubation cough complications in thyroidectomy postoperative patients.

Subjects and Methods

The research design was experimental and was conducted in a double blind randomized controlled trial on both research groups. The subjects in this study were patients who underwent thyroidectomy surgery who met the inclusion criteria, namely patients aged 18-50 years with ASA (American Society of Anesthesiologists) physical status I and II. Research subjects who were excluded from the study were patients with a history of allergy to the drugs to be used, a history of asthma or previous pulmonary disorders, active smokers, a history of cardiac abnormalities or arrhythmias, patients with sinus bradycardia (pulse < 60 beats/minute), women with sinus bradycardia (pulse < 60 beats/minute).60 beats/minute), pregnant women, patients with symptoms of perioperative upper respiratory tract infection, currently receiving angiotensin converting enzyme inhibitor (ACE inhibitor) therapy, currently using bronchodilator drugs or steroid drugs, liver function abnormalities, kidney function abnormalities and subjects were excluded from this study if the surgical procedure extended > 3 hours and complications occurred during surgery.

The sample size was determined based on the calculation of the sample size for unpaired numerical comparative analytic research in 2 groups with a sample size for each group of 20 people. The sample size was determined based on the calculation of the sample size for unpairednumerical comparative analytic research of 2 groups with the following formula:

$$n_1 = n_2 = 2\left(\frac{(Z_\alpha + Z_\beta)S}{X_1 - X_2}\right)^2$$

Where:

Z_α= standard deviation alpha

Z_β= standard deviation of beta

S = combined standard deviation.

X -X12 = minimum difference in means considered meaningful

Where:

$$S_g^2 = \frac{\left[s_1^2 \times (n_1 - 1) + s_2^2 \times (n_2 - 1) \right]}{n_1 + n_2 - 2}$$

$$Z_\alpha = 1,64$$

$$Z_\beta = 1,28$$

Type 1 error is set at 5%, the hypothesis is one-way so type 2 error is set at 10%,hence the value of

The amount of difference between the mean and standard deviation is determined basedon the standardized range (|max-min|/SD = 1). Based on this formula, the value is entered into the sample size formula as follows:

$$n_1 = n_2 = 2\left(\frac{\left(Z_\alpha + Z_\beta \right) S}{X_1 - X_2} \right)^2$$

$$n_1 = n_2 = 2\left(\frac{(1,64 + 1,64) * 1}{1} \right)^2$$

$$18+1,8=19,8\approx 20$$

$$= 2(8,52) = 17,04 \approx 18$$

Thus the minimum sample size for each group is 18 people plus the possibility of 10% sample exclusion so that the sample size for each group is samples per group, so the total sample size for 2 groups is 40 people.

The study was conducted after obtaining a research permit with Number DP.04.03/X.2.2.1/2533/2023 from the Ethics and Research Committee of Dr. Hasan Sadikin Hospital / Padjadjaran University with ethical approval number No. LB.02.01/X.6.5/7/2023 to be conducted at Dr. Hasan Sadikin Hospital Bandung with ethical clinical trial government was identified NCT06040034 at https://clinicaltrials.gov/

The research sampling technique was carried out by consecutive sampling, namely by taking each research subject who met the inclusion and exclusion criteria based on the order of patient arrival. The allocation of subjects into one of the research groups was carried out by the permutation block method. The sample members were then divided into 2 groups, namely group A was given lidocaine intravenously bolus 1.5 mg/kgBB before induction and group B was given lidocaine bolus followed by continuous intravenous 1.5 mg/kgBB/hour until the end of surgery with the research subject and the person assessing the cough not knowing the type of drug given.

Cough was assessed at extubation, 5 minutes after extubation, 1 hour after extubation, then 4 hours, 6 hours, 12 hours, and 24 hours after extubation. Cough was assessed using the original Minogue scale. Demographic and clinical characteristics, including age, height, weight, ASA level, gender, duration of anesthesia and duration of surgery were recorded. The incidence and severity of cough after extubation were recorded and recorded.

Data analysis included descriptive analysis and hypothesis testing. Numerical data were presented as mean, standard deviation, median and range. Then for data on patient characteristics in the form of categorical data, coding is given and presented as a frequency distribution and percentage. Data were recorded in the research form that had been made, then editing, verification, coding and data entry were carried out, then data analysis was carried out. Statistical analysis according to the purpose of this study.

Data were presented as percentage (%) for categorical variables and mean ± standard deviation (SD) for numerical variables. The statistical analysis began by conducting a

characteristic test of the two groups to test whether the two groups were homogeneousso that they were suitable for comparison or not. If there were significant confounding variables, covariance analysis was performed through binary logistic regression analysis.

In numerical data, a normality test is first carried out which aims to determine whether the data is normally distributed or not normally distributed. The statistical test used to test whether the data is normally distributed or not is done with Shapiro Wilks (because n each group is less than 50). Statistical tests to compare the mean of numerical variables between 2 groups with unpaired T test if the data is normally distributed and alternative Mann Whitney test if the data is not normally distributed. While statistical analysis for categorical data was tested with the chi-square test if the Chi-Square conditions were met if not met, the Fisher's Exact test was used for 2 x 2 tables and Kolmogorov Smirnov for tables other than 2 x 2. The Chi Square requirement is that there is no expected value less than 5 as much as 20% of the table. For paired numerical data, the p value is tested with a paired T test if the data is normally distributed with an alternative Wilcoxon test if the data is not normally distributed.

The criterion for significance used is the p value with the provisions that the $p \leq 0.05$ value is statistically significant or meaningful, and $p > 0.05$ is insignificant or not statistically meaningful. The data obtained were recorded in a special form and then processed through the Statistical Product and Service Solution (SPSS) 25.0 for Windows program.

Results

The study was conducted at Dr. Hasan Sadikin Hospital Bandung from February 2, 2023 to May 1, 2023 on 48 subjects who underwent thyroidectomy surgery under general anesthesia with 8 patients included in the exclusion criteria because the surgical procedure extended more than 3 hours and 40 patients who met the inclusion criteria and were not included in the exclusion criteria. The subjects were then divided into two groups, group A as the control group, which received intravenous lidocaine bolus 1.5 mg/kgBB followed by continuous administration of NaCl 0.9% 1.5 mg/kgBB/hour and group B received intravenous lidocaine 1.5 mg/kgBB followed by continuous administration of lidocaine 1.5 mg/kgBB/hour with each group consisting of 20 research subjects.

The characteristics of the study subjects based on age, weight, height, BMI and education history between group A and group B were not found to be significantly different ($p > 0.05$). Group A had an average age of 43.15±9.821 years with an average body weight of 55.85±12.036 kg while the average height was 1.57±0.055 meters with an average BMI of 22.69±5.320 kg/m^2 . Group B had an average age of 42.60±11.962 years with an average weight of 58.35±10.012 kg and an average height of 1.56±0.080 meters with an average BMI of 24.16±4.813 kg/m^2

Table 1. Comparison Table of Characteristics of Research Subjects Between Groups A and B

Variables	Group A n=20	Group B n=20	P-value
Age (years)			0,904
Mean±Std	43,15±9,821	42,60±11,962	
Median	44,50	47,50	
Range (min-max)	24,00-57,00	19,00-56,00	

Variables	Group A n=20	Group B n=20	P-value
Gender			1,000
Male	3	3	
Female	17	17	
Body weight (kg)			0,253
Mean±Std	55,85±12,036	58,35±10,012	
Median	52,00	60,00	
Range (min-max)	36,00-87,00	35,00-74,00	
Height (m)			0,567
Mean±Std	1,57±0,055	1,56±0,080	
Median	1,58	1,56	
Range (min-max)	1,45-1,70	1,40-1,75	
BMI (kg/m2)			0,277
Mean±Std	22,69±5,320	24,16±4,813	
Median	21,65	22,45	
Range (min-max)	16,44-41,38	17,86-36,19	
Operation duration (minutes)			0,883
Mean±Std	127,00±20,673	128,50±20,654	
Median	120,00	120,00	
Range (min-max)	90,00-150,00	90,00-165,00	
Duration of anesthesia (minutes)			0,904
Mean±Std	157,75±20,097	159,00±19,708	
Median	150,00	150,00	
Range (min-max)	120,00-180,00	120,00-180,00	
Extubation time (seconds)			1,000
Mean±Std	8,10±1,294	8,10±1,410	
Median	8,00	8,00	
Range (min-max)	6,00-11,00	6,00-11,00	

Notes: For numerical data, the p value is tested with an unpaired T test if the data is normally distributed with an alternative Mann Whitney test if the data is not normally distributed. Categorical data p value was calculated based on the Chi-Square test with alternative Kolmogorov Smirnov and Exact Fisher tests if the conditions of Chi-Square are not met. The significance value is based on $p<0.05$.

Comparison of cough incidence between groups A and B at T0, T1, T2, T3, T4 and T5 found that the incidence of cough was more in group A (mostly grade 1 cough)than group B (mostly grade 0) but not significantly different ($p>0.05$). While measurements at T6 and T7 showed that the incidence of cough in group A was also more (mostly grade 1 and 2) compared to group B (grade 1) with significant differences ($p<0.05$).

Table 2. Comparison Table of Cough Incidence in Group A and Group B

Variables	Group		P-value
	A (lidocaine bolus) (n=20)	B (continuous lidocaine) (n=20)	
Incidence of cough T0			1,000
Grade 0	20	20	
Grade 1	0	0	
Grade 2	0	0	
Grade 3	0	0	
Incidence of cough T1			0,289
Grade 0	16	20	
Grade 1	4	0	
Grade 2	0	0	
Grade 3	0	0	
T2 cough incidence			0,108
Grade 0	14	20	
Grade 1	6	0	
Grade 2	0	0	
Grade 3	0	0	
Incidence of T3 cough			0,429
Grade 0	17	20	
Grade 1	3	0	
Grade 2	0	0	
Grade 3	0	0	
Incidence of T4 cough			0,799
Grade 0	19	20	
Grade 1	1	0	
Grade 2	0	0	
Grade 3	0	0	
Incidence of T5 cough			0,174
Grade 0	13	18	

Variables	Group		P-value
	A (lidocaine bolus) (n=20)	B (continuous lidocaine) (n=20)	
Grade 1	6	2	
Grade 2	1	0	
Grade 3	0	0	
Incidence of cough T6			0,006*
Grade 0	9	19	
Grade 1	9	1	
Grade 2	2	0	
Grade 3	0	0	
T7 cough incidence			0,0001**
Grade 0	4	18	
Grade 1	13	2	
Grade 2	2	0	
Grade 3	1	0	

Notes: For ordinal data, the p value is tested with the Mann Whitney test The value of significance is based on the p value <0.05.

The incidence of side effects found in groups A and B were tachycardia, bradycardia, hypertension and hypotension, but the comparison of the incidence of these side effects between groups A and B did not have a significant difference (p>0.05).

Table 3. Comparison Table of Side Effects in Group A and Group B

Group			
Variables	A (lidocaine bolus) (n=20)	B (continuous lidocaine) (n=20)	P-value
Side effects			
Nausea	0	0	1,000
Vomiting	0	0	1,000
Tachycardia	5	7	0,490
Bradycardia	3	2	1,000
Hypertension	3	1	0,605
Hypotension	4	5	1,000
Arrhythmia	0	0	1,000

Notes: For numerical data, the p value is tested with an unpaired T test if the data is normally distributed with an alternative Mann Whitney test if the data is not normally distributed. Categorical data p value was calculated based on the Chi-Square test with alternative Kolmogorov Smirnov and Exact Fisher tests if the conditions of Chi Square are not met. Significance was based on p<0.05.

Continuous intravenous lidocaine administration resulted in a lower incidence of cough compared to bolus lidocaine administration. Based on numerical data analysis using the Mann Whitney Test for the p value on the variable cough incidence T6 and cough incidence T7 is smaller than 0.05 (p value <0.05) which means significant.

Discussion

The characteristics of the study subjects based on age, weight, height, BMI and education history between group A and group B were not found to be significantly different (p>0.05) so that the two groups were considered homogeneous and suitable for comparison. The incidence of post-extubation cough at T6 and T7 was found to be more in group A than group B with a significant difference (p<0.05), while the incidence of cough at T0, T1, T2, T3, T4 and T5 was found to be more in group A than group B but there was no significant difference (p>0.05).

Intravenous lidocaine administration to inhibit post-extubation cough at a dose of 1.5 mg/kgBB bolus at the beginning of the action in both groups has an effective effect to prevent coughing with cough incidence immediately after extubation (T1) and 5 minutes after extubation (T2) there is no significant difference even though the statistical impression is not significant but in group A there is still a grade 1 cough incidence with a mild cough category of 4 people, while in group B there is no cough incidence at T1 to T4.

In statistical data obtained cough incidence at T5 with group A 6 people experienced grade 0 cough as many as 6 people and 1 person had a cough with grade 2 severity, while in group B 2 people experienced grade 1 cough, although statistically the data results did not show significant significant differences, but it can be concluded that in group B there were fewer cough incidents with a lighter degree of cough symptoms experienced. From research references that have tried to examine the incidence of post-extubation cough by administering lidocaine 1.5 mg/kgBB bolus as was done in group A in this study, similar results were obtained, namely that there was still an incidence of cough that occurred even though it was not statistically significant, but occurred with a minimal amount. These results can be related to the concentration of lidocaine between group A and group B which is different, so that in group A the concentration will continue to decrease over time and there is still a number of cough incidents immediately after extubation compared to group B which uses continuous lidocaine so that plasma levels in the blood are still sufficient to prevent post-extubation cough because lidocaine given intravenously blunts sympathetic responses during laryngoscopy, endotracheal intubation to extubation so that there is no hemodynamic surge by weakening the cough response. [1,2,30,31]

The incidence of T1 to T5 cough in group A was more than that in group B, but the result was not significant (p>0.05). These results were related to the duration and half-life of lidocaine administration in both groups. Some studies state that lidocaine given before surgery is more beneficial against post-extubation cough with an intravenous lidocaine half-life of about 1.5 hours.[3] Research shows that lidocaine doses <1.5 mg/kgBB and doses >1.5 mg/kgBB have an effective effect on preventing cough.The effect of lidocaine is dose dependent so that lidocaine at a dose of 1.5-2 mg / kgBB intravenously can reduce the cough reflex significantly and effectively at 3-5 minutes after injection compared to other doses.[2,3]

In this study, group A was given lidocaine bolus with a half-life of 1.5 hours at the beginning of surgery, while group B was given continuous lidocaine until the end of surgery, so that the half-life of group B was 1.5 hours after surgery and the plasma concentration in group A had begun to decrease, while in group B the plasma concentration was still maintained so that the side effects of postoperative cough in some patients with continuous lidocaine administration began to be obtained when the plasma

concentration began to be low although the results were not significant and thedegree of severity was minimal at T6 and T7 ($p<0.05$).

This study shows that lidocaine serum concentrations that are maintained continuously are effective in relieving cough compared to bolus administration. Lidocaine concentrations between 2.3 g/mL and 3.0 g/mL can significantly reduce the incidence of post-extubation cough by administration through continuous intravenous infusion to maintain plasma concentrations because if given by bolus these concentrations are very difficult to achieve because the achievement of lidocaine plasma concentrations at three minutes is only 6-7.5 micrograms/mL while at five minutes, 2-3 micrograms/mL and will continue to fall over time.

This is not much different from studies that have been conducted on bolus lidocaine administration and also in other studies using continuous lidocaine. Previous studies have also assessed the benefits of lidocaine at 24 hours and 48 hours postoperatively with the result that benefits were obtained at 1 hour to 4 hours postoperatively.

The side effects of nausea, vomiting, tachycardia, bradycardia, hypertension, hypotension and arrhythmia between the two groups were not significantly different ($p>0.05$). The side effects that occurred in group A and group B were minimal.

In this study, the patient did not have severe side effects and complications and also did not experience a condition of continuous coughing until desaturation. Side effects in this patient were found to be minimal because the dose used in this study wasnot a toxic dose that could cause unwanted side effects. The recommended dose for initial loading is a maximum of 1.5 mg/kgBB given for 10 minutes, followed by a maximum continuous infusion of 1.5 mg/kgBB/hour. Although lidocaine doses are more effective at high doses, continuous lidocaine given systemically is recommended not to exceed 120 mg / hour. In this study, the bolus dose of lidocaine did not exceed 120 mg/hour (toxic dose). In addition, the duration of continuous lidocaine administration did not exceed 3 hours because from previous studies, continuous lidocaine administration for 4-8 hours in healthy people was not found to accumulate lidocaine in the body which could cause side effects. [32]

The results of this study can be compared with previous studies which showed no significant difference in the incidence of side effects in groups A and B. However, the incidence of side effects needs to be studied further using a larger sample size.

The conclusion of this study is continuous intravenous lidocaine administration of 1.5 mg/kgBB/hour resulted in a smaller incidence of postextubation cough after thyroidectomy surgery compared with bolus intravenous lidocaine administration of 1.5 mg/kgBB.

This study can be used as a basis for further research on the comparison of continuous intravenous lidocaine administration of 1 mg / kgBB / hour with continuous intravenous lidocaine 1.5 mg / kgBB / hour on the incidence of postextubation cough in patients after thyroidectomy surgery. Based on this study, it can be recommended touse lidocaine bolus dose of 1.5 mg/kgBB followed by continuous intravenous lidocaine dose of 1.5 mg/kgBB/hour to reduce the incidence of post-extubation cough in patients after thyroidectomy surgery.

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