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Preemptive intravenous ibuprofen application reduces pain and opioid consumption following thyroid surgery

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ABSTRACT

Objective: The primary aim of this study was to investigate the effects of preemptive a single dose IV ibuprofen on postoperative 48 h opioid consumption and postoperative pain in patients undergoing thyroidectomy.
Methods: The study included 40 patients aged 18 to 65, scheduled for elective thyroidectomy. Patients were randomly divided into 2 groups. Control group (n = 20) received 100 mL saline solution 15 min before surgery, while study group (n = 20) received 800 mg IV ibuprofen in 100 mL saline. The same general anesthesia protocol was applied in both groups, and all operations were performed by the same surgical team using the same technique. Postoperative analgesia was assessed using a visual analogue scale (VAS) and the amount of consumption of 48 h postoperative fentanyl with patient-controlled analgesia (PCA) and additional analgesia requirements were recorded. When additional analgesia was required, 1000 mg IV paracetamol was used.
Results: VAS scores in the ibuprofen group were found lower than the control group in the all-time points ($p < 0.05$). Opioid consumption in the 48 h was significantly higher in the control group than the ibuprofen group ($p < 0.001$). Using of rescue analgesia was significantly higher in the control group than the ibuprofen group, statistically ($p < 0.05$). A significant difference was observed between two groups in terms of side effects of fentanyl consumption (nausea and vomiting) ($p < 0.001$).
Conclusion: To use preemptive a single dose IV ibuprofen decreases pain scores and postoperative opioid consumption in patients following thyroidectomy. Additionally, this application increase the patient comfort reducing nausea and vomiting in early postoperative period.

1. Introduction

Thyroidectomy is a commonly performed surgery for either benign or malignant thyroid pathologies. It is a very painful procedure because of the region of operation is in a sensitive skin area of the body [1]. With the help of the advanced equipment and the operative techniques, the surgical complications like hoarseness and hypocalcemia were decreased, but postoperative pain is still a significant problem after thyroidectomy [2]. Postoperative pain following thyroidectomy may be important especially in the early time after surgery [3]. This problem should be treated because it disrupts the comfort of the patients and prolongs the length of hospital stay [4]. Different forms of treatment like the use of opioids and nonsteroidal anti-inflammatory drugs, local or regional anesthesia have been expressed for prevent this problem [3,5,6]. Opioids used cause possible side effects such as nausea and vomiting that increases the patient discomfort and the hospitalization time [1].

Preemptive analgesia is an analgesic treatment applied before surgical procedure [7]. Ibuprofen is a propionic acid derivative and a nonsteroid antiinflammatory drug (NSAID). It has features like antiinflammatory, antipyretic, and analgesic effects and it is one of the most commonly used NSAIDs. It has been used in the treatment of mild, moderate pains and also in the treatment of severe pains in combination with opioids since 2009 in the USA. Additionally, it has been shown that intravenous (IV) ibuprofen can be used in the treatment of postoperative pain [8].

The aim of this study was to investigate the effects of a single preemptive dose of IV ibuprofen on postoperative pain and opioid consumption in patients undergoing elective thyroidectomy.

2. Material and methods

The study was performed between January 2017 and March 2018. A total of 40 patients aged 18 to 65 with American Society of

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Anesthesiologists (ASA) physical status I–III undergoing elective thyroidectomy with general anesthesia were admitted to this prospective, randomized, double-blinded study.

Patients graded ASA IV or above, with allergies to the agent material, severe hepatic or renal failure, a history of long-term nonsteroid antiinflammatory and opioid analgesic use, a history of gastrointestinal bleeding, peptic ulcer or inflammatory bowel disease, diabetes or other neuropathic diseases, patients weighing < 40 kg, patients incapable of using a patient-controlled analgesia (PCA) device were excluded.

The study protocol was explained to patients one day before surgery. The information about the visual analogue pain scale (VAS) and the PCA device to be used for analgesia after surgery were given to them, separately. Written consent was obtained from all patients. The study was double-blind, randomized and placebo-controlled. Patients were divided into 2 groups with a random computer program. The control group (n = 20) was administered 100 mL IV saline, and the ibuprofen group (n = 20) was given 800 mg IV ibuprofen (İntrafen 800 mg/8 mL, Gen İlaç, Istanbul, Turkey) in 100 mL saline, 15 min before surgery. No premedication was performed. Standard electrocardiography (ECG), peripheral oxygen saturation (SpO_2), and noninvasive blood pressure monitoring were performed in all cases, and all measurements were recorded at 5-minute intervals during surgery.

Anesthesia in both groups was induced with IV 2 mg/kg propofol (Propofol®, Fresenius Kabi, Germany), 2 μg/kg fentanyl and muscle relaxation with IV 0.6 mg/kg rocuronium (Esmeron®, Glaxo Smith Kline, England). Following intubation, 0.1 mg/kg rocuronium was administered when necessary for muscle relaxation. Maintenance anesthesia was established with 2% sevoflurane (Sevorane®, AbbVie, England), 50% N_2O in 50% oxygen (tidal volume = 6–8 mL/kg, frequency = 10/min). Depth of anesthesia was monitored by bispectral index (BIS) and the value of BIS was maintained between 40 and 60.

All operations were performed by the same surgical team using the same technique. At the end of the operation, 0.06 mg/kg neostigmine (Neostigmin® Ampoule 0.5 mg/mL, Adeka, Samsun, Turkey) and 0.02 mg/kg atropine (Atropine Sulfate® Ampoule 0.5 mg/mL, Galen, Istanbul, Turkey) were applied for the antagonism of the muscle relaxant. Tracheal extubation was performed when extubation criteria were fully met in the operating room, and then the patient was taken to the postanesthesia care unit (PACU).

All patients were attached to a PCA device after surgery in the recovery room. The PCA device was set to a 10 mcq concentration, a 10-minute lockout and a 25 mcq bolus dose with no basal infusion, maintained for 48 h. No other analgesic treatment than PCA was administered to patients. When postoperative pain remained despite the use of PCA, 1000 mg IV paracetamol (Perfalgan® 10 mg/mL, Bristol-Myers Squibb, France) was applied to patients. Assessment of VAS pain scores were made at the first 30 min, 1, 2, 4, 8, 12, 24, and 48 h in the postoperative period. All postoperative pain assessments were conducted with blinded respect to the patient's group.

The postoperative complications like nausea and vomiting, respiratory depression, dizziness, peripheral edema, diarrhea were recorded in the PACU and in the ward. Nausea was recorded by each patient as none, light, moderate or severe. When occurred of nausea and vomiting, the patient's nurse was instructed to administer metoclopramide 10 mg IV.

The primary outcome of the study was the total amount of fentanyl consumption in the 48-hour postoperative period.

Ethics committee approval was obtained, and written informed consent was obtained from all patients. The study was conducted adhering to the Declaration of Helsinki.

2.1. Statistical analysis

Statistical analysis was performed using SPSS for Windows version 23.0 software program (SPSS Inc., Chicago, IL, USA). The distribution of the variables was evaluated for normality using the Kolmogorov–Smirnov and histogram tests. Descriptive statistics are expressed as the mean ± standard deviation (SD). Categorical variables were analyzed using the chi-square test. The normally distributed data comprising continuous variables were analyzed using Student *t*-test. Otherwise, the Mann–Whitney *U* test was used. A value of $p < 0.05$ was considered statistically significant.

Table 1
Demographic data of both groups (age, height, weight and gender).

	Groups	N	Mean ± Std. deviation	*p*
Age	Control	20	45.40 ± 12.015	0.862
	Ibuprofen	20	44.80 ± 9485	
Height	Control	20	169.45 ± 8382	0.076
	Ibuprofen	20	164.75 ± 7489	
Weight	Control	20	80.40 ± 9265	0.052
	Ibuprofen	20	74.35 ± 9377	
Gender male	Control	7	_	0.490
	Ibuprofen	5	_	
Gender female	Control	13	_	
	Ibuprofen	15	_	

N: number; Std.: standard; $p < 0.05$: statistically significant.

3. Results

Forty patients (28 females, 12 males) were included in the study. Twenty patients received IV ibuprofen, and 20 patients received 0.9% NaCl solution, preoperatively. While the mean age of the study group was 44.8 ± 9.485, the control group was 45.4 ± 12.015. No patient dropped out of the study during the procedures.

Demographic data for the patients were shown in Table 1. No differences were determined between both groups in terms of age, height, weight and gender ($p > 0.05$).

Average of blood pressure, heart rate, SpO_2, and respiration numbers were similar between the two groups at all measurement times.

VAS scores were assessed in all patients. VAS scores at 30th minute and 1, 2, 4, 8, 12, 24 and 48th hours were lower in the ibuprofen group than the control group ($p < 0.05$) (Table 2) (Fig. 1).

Fentanyl consumption was lower in the ibuprofen group compared to the control group during postoperative 48 h (748.85 ± 155.645 and 255.45 ± 171.429 mcq, respectively) ($p < 0.001$) (Table 2).

Using of postoperative rescue analgesic (paracetamol IV) was found significantly higher in the control group (n = 8) according to the ibuprofen group (n = 2) ($p = 0.028$) (Table 2).

In terms of side-effects, statistically significant differences were determined between two groups. The mean vomiting episode was 1.8 ± 1.704 in the control group, whereas 0.05 ± 0.224 in the ibuprofen group ($p < 0.001$). While the mean amount of nausea episodes was 5.35 ± 1.268 in the control group, in the study group was 0.55 ± 0.999 ($p < 0.001$). The violence of all nausea episodes was light or mediate grade. Additionally, no difference was observed between two groups in terms of intraoperative bleeding and postoperative hematoma.

4. Discussion

The results of this study showed that a single dose of 800 mg IV ibuprofen given 15 min before elective thyroid surgery reduces the need for postoperative opioid consumption and the pain scores during the first 48 h postoperatively. In addition, preoperatively using IV ibuprofen significantly reduced rescue analgesic need and the side effects related with fentanyl consumption.

The multimodal analgesia application in terms of postoperative pain management has been expressed to be more effective according to the traditional administration. It has been reported that IV ibuprofen can be used as a component of multimodal analgesia [9]. We administered multimodal analgesia by using preemptive IV ibuprofen, fentanyl as an

Table 2
The mean verbal analog scores (VAS) of groups according to time, the amounts of fentanyl consumption, the side effects related with opioid consumption (nausea and vomiting), and using of rescue analgesia.

	Groups	N	Mean ± Std. deviation	*p*
min30	Control	20	7.80 ± 2067	0.003
	Ibuprofen	20	4.40 ± 3619	
h1	Control	20	6.75 ± 2291	0.003
	Ibuprofen	20	4.00 ± 2974	
h2	Control	20	6.95 ± 2212	0.003
	Ibuprofen	20	4.30 ± 2867	
h4	Control	20	6.30 ± 2386	0.018
	Ibuprofen	20	4.30 ± 2867	
h8	Control	20	5.60 ± 1875	0.002
	Ibuprofen	20	3.30 ± 2250	
h12	Control	20	5.00 ± 2340	0.007
	Ibuprofen	20	3.00 ± 1919	
h24	Control	20	5.10 ± 2808	0.017
	Ibuprofen	20	3.00 ± 2753	
h48	Control	20	3.60 ± 2186	0.002
	Ibuprofen	20	1.55 ± 1276	
Fentanyl consumption	Control	20	748.85 ± 155.645	< 0.001
	Ibuprofen	20	255.45 ± 171.429	
Nausea	Control	20	5.35 ± 1268	< 0.001
	Ibuprofen	20	0.55 ± 0.999	
Vomiting	Control	20	1.80 ± 1704	< 0.001
	Ibuprofen	20	0.05 ± 0.224	
Using of rescue analgesia	Control	8	–	0.028
	Ibuprofen	2	–	

N: number; Std.: standard; h: hour; min: minute; $p < 0.05$: statistically significant.

opioid in form of PCA and rescue IV paracetamol in the postoperative period.

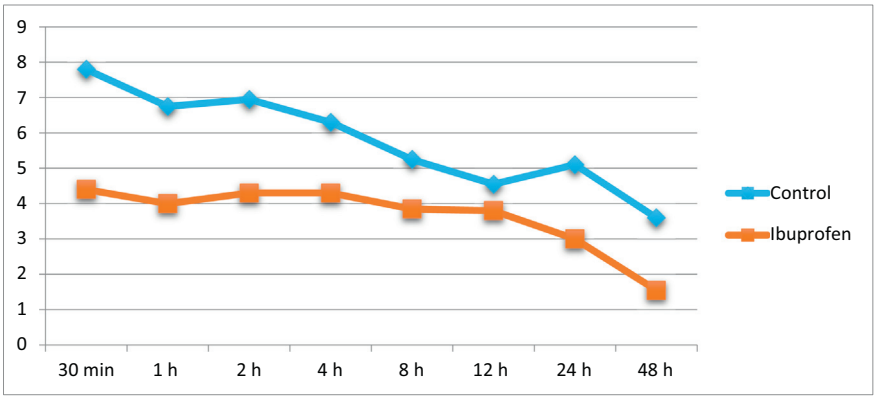
Ibuprofen is a well-known NSAID which has features like analgesic, antiinflammatory, and antipyretic. Although it's oral form has been used for 40 years, IV form firstly presented to selling in America in 2009. It's analgesic, antipyretic, and antiinflammatory effects are related with reversible and competitive inhibition of the cyclooxygenase enzyme-2 (COX-2) [10].

Pain after thyroidectomy arises from the wound incision, hyperextension of the neck, retraction of the wound edges during surgery and dissection itself [5]. Effective postoperative pain treatment provides early mobilization, a shortened hospital stay, and increased patient comfort. Preemptive analgesia is a method of postoperative pain management. This method includes the analgesic application before onset of painful stimuli [11]. Although there are some studies reported that the preoperative analgesia is unimportant [12], the effectiveness of preemptive analgesia is expressed in several other studies. For this purpose, the using of agents like bupivacaine, lidocaine, clonidine, ketorolac, oral ibuprofen, gabapentin, and pregabalin have been reported in the literature [5,6,13]. However, the using of IV ibuprofen is limited.

There are several studies in which a single preemptive dose of IV ibuprofen was used to postoperative pain in the literature [6,8]. In a study involved pediatric tonsillectomy, it has been reported that the IV ibuprofen application reduced the postoperative fentanyl use [8]. In other study has been reported that preemptive IV ibuprofen administration eased stress and inflammatory response by reducing catecholamine, cortisol, and cytokine levels after laparoscopic cholecystectomy [14]. In another study, IV 400 mg ibuprofen in a single dose has been used 30 min before cholecystectomy surgery and has been reported that a single preemptive dose of IV ibuprofen reduced 24-hour opioid consumption and pain scores in the postoperative period [6]. In contrast to this study, in other study that used 400 mg ibuprofen dose, it has been reported that no statistically significant change according to control group in terms of morphine consumption postoperatively in the patients undergoing orthopedic and abdominal surgery. In the same study has been also reported that 800 mg ibuprofen is more effective in terms of reduces pain and morphine consumption in the postoperative period [15]. There is a study as preemptive single dose drug application to reducing postoperative pain and opioid consumption before thyroidectomy surgery in the literature. In this study which a single dose of 1200 mg gabapentin given to patients 2 h before thyroid surgery, has been showed that postoperative morphine consumption and pain scores decreased during the first 24 h postoperatively [13]. In our study, we used IV 800 mg ibuprofen in a single dose, 15 min before thyroid surgery. This study showed that a single preemptive dose of IV 800 mg ibuprofen decreased opioid consumption during 48 h and caused of lower pain scores in the postoperative period.

Studies in the literature have also reported that the reducing of opioid consumption causes decreasing of opioid related side effects like vomiting and nausea [6,16]. In our study, we used IV 800 mg ibuprofen in a single dose, 15 min before surgery. Our purpose of to use it in this way was to provide of the drug to reach a peak plasma concentration during of surgical stimulus and early postoperative period. However, when opioid was inadequate to decrease postoperative pain, IV 1000 mg paracetamol in form of rescue dose was used. More vomiting and nausea were observed in related with opioid consumption in the control group according to the ibuprofen group. In addition, we observed that IV ibuprofen in a single dose administration significantly reduced the using of rescue analgesic compared to the control group.

NSAIDs are known to increase bleeding in a dose related manner because of they are inhibit thromboxane [17]. In a study, a single dose of ibuprofen was given just before lumbar surgery and it was seen that amount of intraoperative hemorrhage was not increased significantly [18]. We no observed a significantly difference between control and



Note: min: minute; h: hour.

Fig. 1. The relation between pain scores and time in the groups in postoperative period.
Note: min: minute; h: hour.

ibuprofen groups in terms of intraoperative hemorrhage and postoperative hematoma in our study.

There are a few limitations of this study. The first limitation of this study is not being designed in a comparative manner with another analgesic. The second limitation is that the 800 mg ibuprofen was applied to patients only preoperatively and was not maintained postoperatively. Our aim was already to see the efficacy of a single dose ibuprofen.

In conclusion, the using of a single preemptive dose 800 mg ibuprofen resulted in better pain scores and lower postoperative opioid consumption in the postoperative first 48 h in patients undergoing thyroidectomy. It also reduced the need of rescue analgesic drug and the side effects associated with opioid consumption such as nausea and vomiting in the postoperative period. Finally, we suggest to application of preemptive a single dose IV 800 mg ibuprofen 15 min before thyroid surgery for increasing of postoperative patient comfort.

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Compliance with ethical standards

Conflict of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name the institution/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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