EFFICACY OF THREE IV NON-OPIOID-ANALGESICS ON OPIOID CONSUMPTION FOR POSTOPERATIVE PAIN RELIEF AFTER TOTAL THYROIDECTOMY: A RANDOMISED, DOUBLE-BLIND TRIAL*

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Abstract

Objectives: In a randomized, double-blind trial, the synergistic action of intravenous parecoxib, metamizol or paracetamol on postoperative piritramide consumption was compared in patients recovering from total thyroidectomy during the first 24h while evaluating pain intensity and patient satisfaction.

Methods: 120 patients were randomly allocated to four patient groups treated with normal saline and/or one of non-opioid analgesics (parecoxib 40mg twice daily, metamizol 1g three times daily, paracetamol 1g three times daily) in addition to piritramide using the PCA pump. Beginning in the recovery room (PACU), patients were asked every 2h for 6 hours and afterwards once every 6h to quantify their pain experience and patient satisfaction while piritramide consumption was recorded.

Results: Upon arrival in the PACU piritramide consumption was high and decreased thereafter significantly in all groups ($P<0.05$). There were no significant differences between groups in incremental and cumulative piritramide consumption during the investigation. Also, VAS scores were high upon arrival in the PACU and dropped in all groups continuously after surgery: At 2h and 4h after surgery they were significantly lower in parecoxib group compared with NaCl ($P<0.01$). For overall patient satisfaction, no significant differences were observed. Pain relief scores at 24h were significantly higher in parecoxib group as compared to metamizol and paracetamol ($P<0.01$). Mild PONV was observed frequently in all groups and was treated with metoclopramide.

Conclusion: There is no clear-cut difference between the non-opioid drugs used, even though parecoxib seems to be superior in regard to VAS scores and piritramide consumption. However, the clinical significance is debatable.

Key words: piritramide; non-opioid analgesics; postoperative pain management; PCA-pump; thyroidectomy.

Introduction

Thyroid surgery is a procedure with moderate pain intensity of short duration postoperatively[1-2]. A variety of analgesic techniques with controversial results have been used to relieve pain after

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thyroid surgery[2-8]. In a study by Gozal et al, the mean pain level on a visual analog scale (VAS) ranging from 0 to 10 was 6.9 cm and 90% of the patients received morphine on the first postoperative day[9]. Other studies have confirmed the need for opioid analgesia in the early postoperative period[4-6]. Because of its ability to titrate to individual needs, IV patient controlled analgesia (PCA) is considered as the "gold standard" for delivery of IV opioids for the management of postoperative pain[10]. It is used not only in major surgery, but also in minor surgery for providing postoperative analgesia[11-12].

Opioids, however, have a range of side effects such as nausea and vomiting as well as dizziness and respiratory depression. In addition, thyroid surgery as cervical procedure carries a high risk of postoperative nausea and vomiting (PONV), particularly when performed in women[13-14]. Therefore, because of their synergistic action, a combination of opioid and non-opioid analgesics are often used to enhance analgesic efficacy and reduce side-effects of opioids caused by intravenous patient-controlled analgesia (PCA)[6,15].

Although the majority of PCA studies were conducted with morphine alone and in combination with many other drugs to augment analgesic effect or to reduce the adverse events[16-26], piritramide has been used in parts of Europe and South America as the analgesic opioid of choice for the management of postoperative pain[27]. Its relative analgesic potency compared with morphine is approximately 0.7. Its duration of action lasting for 4 to 6 hours is relatively long; hemodynamic changes are not expected to occur and the incidence of postoperative nausea and vomiting as happening with other opioids is less profound[28]. Only few studies have evaluated the consumption of piritramide administered by a PCA in combination with various non-opioid analgesics after different surgical procedures[11,29-31].

Since there is obviously no randomized study that compares IV administered parecoxib, metamizol or paracetamol on piritramide consumption in the early postoperative period of thyroid surgery, the aim is therefore to perform a prospective, randomized, double-blind, placebo-controlled study in patients undergoing total thyroidectomy. The primary objective is to compare postoperative piritramide consumption alone or in combination with parecoxib, metamizol or paracetamol for providing pain relief in adult patients recovering from thyroid surgery during the first 24 hours. Secondary objectives are to compare the pain intensity and patient satisfaction.

Methods

The investigative protocol was approved by the institutional review board at our teaching hospital on December 9, 2003 and all patients provided written informed consent before enrolment. The study began in March 2004 and ended in August 2007. Inclusion criteria were the following: Patients between the ages of 18 and 75 years and ASA physical status I-III. All patients were in a euthyroid state at the time of surgery. Patients with a history of significant cardiac, pulmonary, hepatic, or renal disease, morbid obesity, chronic pain and drug or alcohol abuse, and contraindications or previous adverse reaction to any of the drugs used in the study were excluded. Also not included were patients unable to cooperate.

Patients meeting the inclusion criteria and scheduled for thyroid surgery under general anesthesia were instructed the night before surgery about the use of PCA for postoperative pain relief as well as scales for the determination of pain intensity and patient satisfaction. After informed consent, one hundred and

Table 1
Patient groups (30 in each group) and treatment with normal saline (NS) and/or drug

Group	Treatment	15 min prior to extubation	8h postop.	12h postop.	16h postop.	24h postop.
A	Placebo	NS	NS	NS	NS	NS
B	Parecoxib	40 mg	NS	40 mg	NS	NS
C	Metamizol	1g	1g	NS	1g	NS
D	Paracetamol	1g	1g	NS	1g	NS

twenty patients were assigned to one of four groups, based on a computer-generated randomization table (http://www.randomization.com).

The four study groups were A) placebo, B) parecoxib 40 mg, C) metamizol 1g, and D) paracetamol 1g (Table 1). The drugs were dissolved in 100 ml normal saline and given via IV infusion over 15 min. Patients of the placebo group received only 100 ml of normal saline. In all groups 10 min before extubation 2 mg piritramide (Dipidolor®, Janssen-Cilag) was injected. In the postoperative period piritramide was offered in form of a patient-controlled analgesia by means of a PCA pump as an electronically steered syringe pump.

Thyroid surgery was performed by two surgeons under neuromonitoring, using similar surgical technique and similar surgical drains. Patients, surgeons, and anesthesiologists responsible for follow-up in the postoperative period were blinded to group allocation; other caretakers were also unaware of the analgesic drug that would be used for each patient during the study. The study solutions were clear so that they could not be recognized by the anesthesiologists collecting the data and were prepared by one of the researchers who was not involved in the intraoperative and postoperative treatment of these patients. The observation time extended during a period of 24 hours after surgery. However, to ensure patient safety, a sealed opaque envelope containing the randomized treatment assignment was kept with each patient in the operating room and ward to permit immediate unmasking in case of an emergency making this step necessary.

For premedication, midazolam 7.5 mg (Dormicum®, Roche Pharma AG Grenzach-Wyhlen, Germany) was administered orally 60 min before the surgical procedure. On arrival in the operating room, standard monitors were applied. A crystalloid infusion (Infusionslösung E153®, Serumwerk Bernburg AG, Bernburg, Germany) was started after placing an 18-gauge catheter in the non-dominant hand for fluid administration intraoperatively. A second 18-G catheter in the other hand was used for the administration of anesthetic drugs; this catheter was removed upon discharge from the recovery room (postanesthesia care unit, PACU).

After the administration of oxygen via an anesthetic breathing circuit and facemask for 3 minutes, 1 mg vecuronium bromide (Norcuron®, Organon GmbH, München, Germany) was given as pre-block while anesthesia was induced with 2 mg/kg propofol (Propofol® 1%, Fresenius Kabi Deutschland GmbH Bad Homburg, Germany) intravenously, followed by 80 mg suxamethoniumchlorid (Lysthenon® 2%, Nycomed Deutschland GmbH Konstanz, Germany) to facilitate endotracheal intubation. After intubation, mechanical pressure controlled ventilation was initiated at a flow rate of 1 L/min in a semiclosed system (Cicero; Dräger, Lübeck, Germany) and nitrous oxide in oxygen at a ratio 1 : 1 was administered throughout surgery. The inspired oxygen and end-tidal concentrations of carbon dioxide (CO2) were measured continuously at the proximal end of the endotracheal tube using a calibrated infrared gas analyzer (Dräger PM 8050, Dräger, Lübeck, Germany). Ventilation was adjusted to maintain end-tidal CO2 between 34-38 mmHg (4.5-5.0 kPa).

Muscle relaxation was obtained with vecuronium bromide 0.6 mg/kg and monitored by the train-of-four stimulation method using a peripheral nerve stimulator. Anesthesia was maintained with a supplemental infusion of 3-6 mg/kg/h propofol and 3-10.5 μg/kg/h remifentanil (Ultiva®, GlaxoSmith Kline GmbH & Co. KG München, Germany) required to maintain an adequate depth of anesthesia with mean arterial pressure and heart rate within 20% range of preoperative values.

Fifteen minutes before the expected end of surgery, each patient was treated according to list of randomization (Table 1). Then, infusion of propofol and remifentanil were ceased and residual muscle relaxation was reversed with 0.5 mg atropine and 5 to 10 mg pyridostigmine at the end of the procedure when necessary. The lungs of each patient were ventilated with 100% oxygen at a flow rate of 5 L/min. Spontaneous recovery of neuromuscular function was confirmed by train-of-four monitoring. The trachea was extubated when adequate spontaneous ventilation (tidal volume >5 ml/kg) and response to verbal commands were established. The pre-programmed PCA equipment (Master PCA, Fresenius Vial Infusion Technology, Brezins, France) was provided with a 50-ml disposable syringe, and 45 mg piritramide in 45 ml

saline solution was prepared for each patient. The PCA administered boluses of 2 ml (= 2 mg piritramide) with a lockout interval of 10 min and a maximal volume of 30 ml in 4 h. A bolus of 2 mg piritramide was first injected 10 min prior to the extubation in the operating room. Postoperative pain was then treated by self-administration of IV piritramide using the PCA pump already mentioned.

Thereafter, the patients were directly transferred to the recovery room, where further clinical observations were done by an independent, blinded observer who was unaware of the administered study drugs. On arrival patients were asked every 2 hours for the first 6 hours and afterwards once every 6 hours to quantify their pain experience on a visual analog scale (VAS) between 0 and 10, with 0 representing no pain and 10 the worst imaginable pain. Likewise, pain relief was assessed by the patient on a 0-3 verbal rating scale (VRS) (0 = no relief, 1 = mild, 2 = moderate, 3 = complete) before the patient was transferred to the ward and after 24 h. Patient satisfaction with the effectiveness of pain therapy was inquired at 6 hour intervals by using a 4 point-scale which shows the verbal expressed satisfaction of assigned numerical values: 1 = poor, 2 = moderate, 3 = good, 4 = very good. The cumulative piritramide consumption within 24 hours postoperatively was recorded after 2, 6, 12 and 24 hours on the display of the PCA pump.

Data were first processed in Microsoft® Excel 2000 and then with the statistical program SPSS for Windows in the version 15.0 (SPSS Inc. Chicago, Illinois, USA) evaluated. The primary efficacy measure was accumulated piritramide consumption. Sample size was calculated to detect a difference between groups of 30% (α = less than 0.05 and ß = 0.2; power = 0.8). The power analysis was based upon a variation (SD) of piritramide consumption from pilot data. Based on these assumptions a priori power analysis suggested a sample size of 30 patients for each group.

For examination of normal distribution, the Kolmogorov Smirnov test was applied. One-way analysis of variance (ANOVA) in normal distributed continuous variables and Kruskal-Wallis-test in non-normal distributed or ordinal variables between the groups were used. When significant differences were determined, pairwise intergroup comparisons using a post hoc Bonferonni-Test or Mann-Whitney-U-Test were followed. Within-group comparisons were made using repeated-measures analysis of variance for piritramide consumption. Categorical data were analyzed using $\chi 2$ or Fisher's exact test as appropriate. Differences were judged significant at $P < 0.05$.

Results

One hundred and twenty patients, scheduled for elective thyroid surgery under general anesthesia, were enrolled and randomized in the study with 30 patients in each group. Because there were no dropouts and no protocol violations in any of the patients studied, a complete data set was obtained in all 4 groups. Table 2 contains the demographic and patient-referred data in each group. The four groups were similar with respect to sex, age, body mass index (BMI) and ASA physical status. There was also no significant between-group

Table 2
Demographic and patient-referred data of the four groups

Group	Placebo (n = 30)	Parecoxib (n = 30)	Metamizol (n = 30)	Paracetamol (n = 30)
Sex Female Male	 27 3	 23 7	 25 5	 25 5
Age (yr) Mean and SD	 47.9 ± 11.8	 48.3 ± 14.2	 43.8 ± 13.7	 44,5 ± 15.1
BMI (kgm^{-2}) Mean und SD	 29.7 ± 5.9	 26.9 ± 5.1	 28.9 ± 5.4	 27.6 ± 6.8
ASA physical status II/III	 19/11	 19/11	 15/15	 19/11

Data are presented as mean ±·SD. There were no significant differences among the four groups.

Fig. 1

Piritramide consumption in mg (mean and standard deviations) in four groups over 24 hours postoperatively. There is no significant difference between the groups.

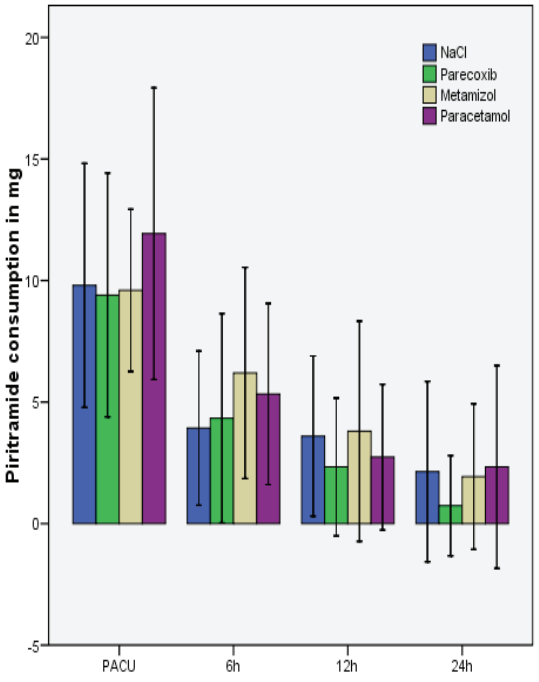
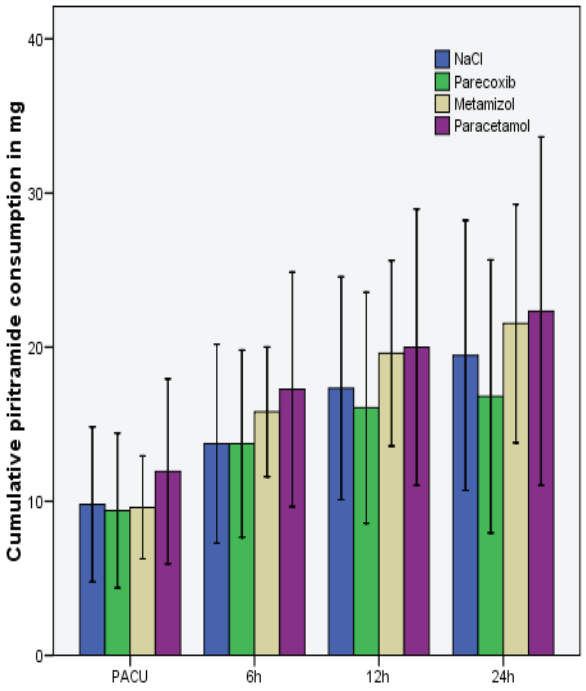


Fig. 2

Cumulative PCA-piritramide consumption (mean and standard deviations) in four groups at different investigation times. There is no significant difference between the groups.



difference with respect to anesthetic drug usage, total blood loss, total fluid administration or duration of anesthesia and surgery.

Piritramide consumption is presented in Figure 1. Upon arrival in the PACU piritramide consumption was similarly high and decreased thereafter significantly in all the groups receiving non-opioid-analgesics over 24h with one exception in the paracetamol group between 12 and 24h. In the placebo group the significant decrease was only found by comparing the first two investigation times and 12 with 24h. However between the four groups, the incremental piritramide consumptions in the PACU and after 6, 12 and 24 hours showed no significant differences. Likewise, the frequency of PCA bolus demands did not differ in the four groups (Table 3). Also with the cumulative PCA-piritramide consumption no significant difference could be found between the groups (Figure 2). However, the cumulative piritramide consumption was slightly lower in the parecoxib group at 12 and 24 hours, while the patients of the paracetamol group had the highest piritramide consumption as compared to the other groups.

VAS pain scores are presented in Figure 3. In all groups, VAS scores were highest upon arrival in the recovery room. The highest mean value was found in the NaCl group with 5.3 and the lowest with 4.3 in the metamizol group. Afterwards the VAS scores dropped in all groups almost continuously after surgery. A significant between-group difference was found at 2 and 4h after surgery: Pain scores at 2h after surgery were significantly lower in the parecoxib and metamizol group compared with NaCl ($P = 0.003$; $P = 0.005$). Additionally, pain scores at 4h were significantly lower in parecoxib group compared with NaCl and paracetamol ($P = 0.001$; $P = 0.01$).

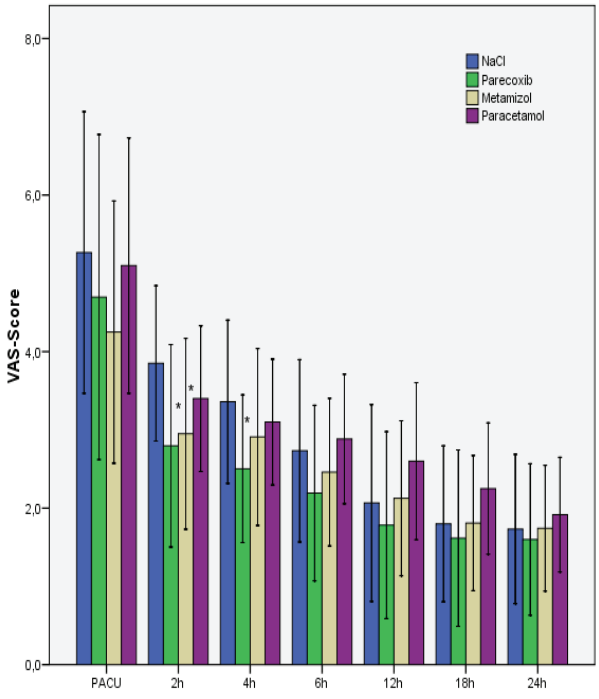
For overall patient satisfaction, assessed on the 4 point-scale, no significant differences among the four groups were observed at any time. In the PACU, satisfaction was moderate and improved to good/very good after 24h (Table 3). In pain relief score, there were no significant differences among groups at 2h after surgery; however, at 24h the scores were significantly higher in patients who received parecoxib as compared to metamizol ($P = 0.008$) and paracetamol ($P = 0.003$)

Table 3
Number of PCA bolus demands, pain relief score and patient satisfaction in the four groups (mean values and standard deviations).

Group	Placebo (n = 30)	Parecoxib (n = 30)	Metamizol (n = 30)	Paracetamol (n = 30)
No. of PCA bolus demands*				
overall demands	9.7 ± 4.4	8.4 ± 4.5	10.8 ± 3.9	11.2 ± 5.7
Pain relief scores				
2h	1.6 ± 0.5	1.8 ± 0.6	1.7 ± 0.5	1.7 ± 0.5
24h**	2.1 ± 0.3	2.3 ± 0.5	2.0 ± 0.3	2.0 ± 0.0
Satisfaction scores*				
2h	2.5 ± 0.6	2.7 ± 0.6	2.6 ± 0.7	2.4 ± 0.8
6h	3.1 ± 0.8	3.3 ± 0.7	3.2 ± 0.6	3.0 ± 0.6
12h	3.4 ± 0.7	3.6 ± 0.5	3.4 ± 0.6	3.2 ± 0.6
18h	3.6 ± 0.6	3.6 ±0.6	3.5 ± 0.5	3.4 ± 0.6
24h	3.7 ±0.5	3.6 ± 0.6	3.7 ±0.5	3.5 ± 0.5

* no significant differences between groups.
** Pain relief scores were significantly higher in parecoxib group when compared with metamizol and paracetamol after 24h (P = 0.008; P = 0.003).

Fig. 3
*Visual analog scale (VAS, mean and standard deviations) in four groups over 24 hours postoperatively (0 = no pain; 10 = worst imaginable pain). *P<0.01 NaCl versus parecoxib and metamizol at 2 h; *P<0.01 parecoxib versus NaCl and paracetamol at 4h.*



(Table 3). No drug reactions, such as dizziness and respiratory depression occurred in our study. However, mild postoperative nausea and vomiting (PONV) were observed frequently in all the groups, which were treated with 20 mg metoclopramide as an antiemetic in the PACU and on the ward. In addition, in the metamizol group there was one patient with a heavy subcutaneous bleeding at the surgical wound with upper airway obstruction immediately on arrival in the PACU.

Discussion

Our results showed that pain was most intense immediately after recovering from remifentanil based anesthesia for thyroid surgery and decreased to low levels in all groups after surgery. Accordingly, the required piritramide consumption was high in the PACU and there was no opioid-sparing effect as demonstrated by the lacking significant differences in piritramide consumption between the 4 groups.

The early intense pain after thyroidectomy is complex. Beside the surgical pain itself it may be caused by cervical hyperextension with postoperative

muscular pain[32] as well as postoperative irritation and discomfort because of intraoperatively placed endotracheal tube and wound drains, which are kept in place for 24 hours. Indeed, patients complain of pain at the incision site, sore throat, posterior neck pain, and occipital headache[15]. Furthermore, remifentanil-based anaesthesia has been shown to be associated with postoperative periincisional hyperalgesia[33-36], a fact which may have contributed to overall pain in our patients. The early intense pain in our study may also partly be explained by a bolus dose of 2 mg piritamide with a lockout time of 10 min which is routinely prescribed in Germany[11]. Smaller bolus doses with a short lockout time have been shown to reduce piritramide consumption by enabling the patient to titrate analgesic effect more effectively; however they obviously do not reduce opioid-related side effects[30]. A background infusion of opioid was not provided due to a possible increased risk of respiratory depression; furthermore it may induce acute tolerance with increased pain intensity, thus decreased analgesic effects and increased frequency of PONV and dizziness[17]. However, PCA without a background infusion may result in the opioid concentration being in the target range for appropriate pain treatment. Accordingly, it offers better analgesic efficacy and results in more patient satisfaction. Numerous randomized control studies have been published evaluating efficacy, side effects and patient satisfaction with PCA[19,23-24,26,37]. Therefore opioid analgesia with PCA is justified, at least in the early postoperative period after thyroidectomy[3,5,15,38-40].

Incremental and cumulative PCA-piritramide consumption showed no significant difference between the groups. However, the cumulative piritramide consumption was slightly lower in the parecoxib group at 12 and 24 hours, while the patients of the paracetamol group had the highest piritramide consumption as compared to the other groups. A reason for the missing clear opioid sparing effect in paracetamol and metamizol groups may be the doses of these drugs administered in our study: 40 mg parecoxib twice a day given is the maximum dosage recommended by the manufacturer for IV application in adults. In contrast, we used 1g paracetamol and 1g metamizol three times daily (TID), whereas the maximum doses recommended by the manufacturers is 1g four times daily (QID). In a newly published study, both parecoxib (80 mg/24h) and paracetamol (5g/24h) effectively reduced postoperative opioid requirements after thyroid and parathyroid surgery[41]. However, a lack of statistical significance on postoperative cumulative piritramide consumption was also found in different surgical procedures when parecoxib was given 40 mg twice daily and metamizol and paracetamol 4g daily were administered[11,29,31,42-44]. May be the results were also different if we had evaluated the pre-emptive efficacy of non-opioid-analgesics administered preoperatively[5,44-45].

Apart from the lacking superiority of one of the investigated drugs in combination with piritramide given over a PCA, a significant reduction in the visual analog scales (VAS pain scores) was registered only at 2h after surgery in parecoxib and metamizol as compared to the NaCl group while at 4 hour after surgery VAS scores in parecoxib versus NaCl and paracetamol were significantly lower. Thereafter, however, VAS scores were all ≤3. Therefore, it may be difficult to demonstrate an additional benefit with an analgesic when baseline pain is low in all groups. In regard to patient satisfaction there was a continuous increase over the study period and after 24h almost all patients in all groups rated their satisfaction with pain management as good or very good which is consistent with previous data where most patients were satisfied with PCA pain management[17,46]. The pain relief score after 24 hours showed statistical superiority of parecoxib versus metamizol and paracetamol. However, whether this is also of clinical relevance, is debatable.

In the metamizol group, one patient had a heavy subcutaneous bleeding at the surgical wound causing upper airway obstruction which occurred immediately on arrival in the PACU and made surgical intervention with ligature of the spurting hemorrhage necessary. Other drug reactions, such as dizziness and respiratory depression did not occur in our study. However, mild postoperative nausea and vomiting (PONV) were observed frequently in all the groups and were treated with mild antiemetics in the PACU and on the ward. Ondansetron and dexamethasone for effective management of PONV were not used[15,47]. PONV is the most common side effect after thyroid

surgery[15]. Patients undergoing thyroid or parathyroid surgery are at high risk for the development of PONV with a decreased rate in women by using propofol for maintenance of anesthesia[14,48-49]. Use of opioids might increase the incidence of PONV[49]. Therefore, the combined use of opioids with NSAIDs can reduce PONV in thyroid surgery[15,44-45,51].

Non-opioid analgesics including parecoxib, metamizol (dipyrone) and parecetamol are routinely used for the IV treatment of postoperative pain. Both parecoxib and metamizol are considered nonsteroidal anti-inflammatory drugs (NSAIDs), albeit one is a selective COX-2 inhibitor while the other is not selective. Parecoxib is the only parenterally administered selective COX-2 inhibitor which has the most supportive data for its beneficial effects as a part of multimodal analgesia and offer benefits with regard to its adverse effect profile[23,52]. Metamizol is still widespread used in Europe and South America. In addition to its analgesic properties it has antispasmodic and antipyretic effects, particularly in patients with visceral pain. In other countries it is banned because of an association with life-threatening blood agranulocytosis although the strength of the association has been a matter of much debate[53-57]. However, in the discussion of metamizol-induced agranulocytosis the overall risk of NSAIDs with regard to their potentially life-threatening adverse effects should be considered in comparison with other non-opiod analgesics which are not devoid of serious side effects[53]. Nevertheless, because of the risk of agranulocytosis after metamizol patients should probably be monitored for blood dyscrasias and, extremely rarely, broad-spectrum antibiotics with hematopoietic growth factors be administered if agranulocytosis occurs[29]. Paracetamol, on the other hand, is as para-aminophenol in a different chemical class and not considered anti-inflammatory. It can now also be administered intravenously and has thus gained renewed interest in this setting due to its minimal adverse effects.

A limitation of this study is that we used drugs which are not available in all countries. Also, we did not use the maximal doses recommended from the manufacturers with metamizol and paracetamol and we failed to monitor side effects of the drugs adequately. In addition, the results might have been different if non-opioid-analgesics had been given prior to surgery as preemptive analgesics. Furthermore, a comparison of the combined use of different drug classes (NSAID and paracetamol) given simultaneously as part of a multimodal treatment as in other studies might be worthwhile[39,58-59].

Conclusion

Pain is intense in the early postoperative period after total thyroidectomy and justifies the need for combined use of opioid and non-opioid analgesics. There is no difference in piritramide consumption in all groups at all investigation times and there is no clear-cut difference between the non-opioid drugs used, even though parecoxib seems to be superior in regard to VAS scores. However, the clinical significance of this finding can be debated.

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