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ORIGINAL ARTICLE

Ketoprofen is superior to metamizole in relieving postoperative pain after head and neck tumor operation

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Summary

Purpose: *Recently, nonsteroidal analgoantipyretics are recommended in the management of postoperative pain, with great attention to their safety. We conducted a randomized, single blind study to compare the analgesic efficacy and safety of ketoprofen and dipyrone (metamizole) after major head and neck surgery.*

Patients and methods: *60 patients received postoperatively 100 mg ketoprofen or 2.5 g metamizole i.v. every 8h over 72h with additional administration of tramadol in case of inadequate analgesia. Pain was assessed by visual numeric scale every 2h during the 72h.*

Results: *Patients in both groups had similar pain score during the first 2 postoperative days, while on the 3rd postoperative day patients in the ketoprofen group had significantly lower pain score ($p < 0.05$).*

Conclusion: *The efficacy of ketoprofen to achieve postoperative analgesia was comparable to metamizole during the first 48h, while ketoprofen was superior to metamizole during the 3rd postoperative day.*

Key words: head and neck cancer, ketoprofen, pain, operation

Introduction

Malignant tumors of the head and neck are conditions that require surgical treatment which implies resection of the entire tumor and a zone of normal-appearing surrounding tissue to the healthy tissue, including sometimes vital structures in this region. Due to excessive surgery, postoperative pain can seriously influence the quality of life of the patients. Adequate treatment of postoperative pain, in addition to its favorable psychological effect, is also considered to reduce the stress response to surgical trauma and to stimulate early patient mobilization, thus improving the procedure outcome [1,2].

In the pharmacotherapy of postoperative pain a large number of different analgesics is administered with different degrees of activity, intensity, safety and different ways of administration. Surgeons are currently moving away from systemic opioids; in addition to their well-recognized capacity for inducing respiratory depression, opioids prolong ileus and increase nausea and vomiting. Regional anesthesia coupled with nonsteroid antiiflammatory drugs (NSAIDs) administration appears to yield better results in terms of patient recovery [3]. Among analgesics at Ear, Nose and Throat Clinic, University Teaching Hospital Novi Sad, Serbia, a significant place in the suppression of postoperative pain belongs to nonopiate analgesic drugs with metamizole being traditionally among the most widely used analgesics, despite its well-known possibility to cause agranulocytosis [4]. However, after 2 cases of metamizole-induced agranulocytosis (one of them fatal) we tried to switch to other, safe and potent NSAIDs in the treatment of postoperative pain.

The aim of this work was to compare the efficacy of the relatively safe propionic acid derivative ketoprofen with metamizole in the treatment of the postoperative pain after major surgery of patients with malignant

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tumors in the head and neck region. We also recorded the possible appearance of complications associated with ketoprofen and metamizole therapy, excessive bleeding and agranulocytosis.

Patients and methods

This controlled, randomized, single blind study was performed at the Ear, Nose and Throat Clinic, University Teaching Hospital, Novi Sad, Serbia. The study protocol was approved by the independent Clinical Research Ethics committee, and a written informed consent was obtained from all patients before entering the study.

The study included 60 adult patients of both sexes, undergoing operations for cancer of the head and neck who were randomized to either ketoprofen (n=30) or to metamizole (n=30). Exclusion criteria were as follows: preoperative use of analgesics, allergy to NSAIDs, history of peptic ulcer and coagulopathy.

All patients were subjected to general anesthesia. The agents used for the induction of anesthesia were those considered appropriate by the anesthesiologist in charge of the patient. Balanced anesthesia with 40% oxygen in nitrous oxide, isoflurane, fentanyl and a neuromuscular blocking agent chosen by the anesthesiologist were used for maintenance. At the end of the surgical procedure the patients were extubated and transferred to the surgical Intensive Care Unit. Upon admission, the pain severity was evaluated using a visual numeric scale previously explained to the patient. On visual scale 0 denoted no pain while 10 denoted the most severe pain. During the first postoperative hour, patients in the metamizole group received metamizole 2.5 g i.v., while patients in the ketoprofen group received ketoprofen 100 mg i.v. The drugs were administered every 8h for the first 3-5 postoperative days, depending of the duration of pain. Patients with a score > 4 were considered inadequately treated for analgesia and received additional tramadol, a weak, synthetic opioid which is used in postoperative analgesia [5]. In case of insufficient analgesic activity of drugs the patients could ask for additional dose of tramadol (50 mg i.v.).

Except this, postoperative treatment was the same for both groups: all patients received parenterally ranitidine, systemic antibacterials for 7 days, plasma transfusions and diazepam every night.

The assessment of pain severity on the visual numeric scale was done by the nurse on duty every 2h except 6h during the night. The additional use of tramadol, side effects, possible excessive bleeding and significant changes in granulocyte number were recorded daily in each patient. Patients at increased risk for thromboembolic complications received low molecular heparin prophylaxis postoperatively.

Data are presented as a mean and standard deviation (SD). x^2 test was used to compare the visual numeric scale score between the groups. A p-value < 0.05 was considered statistically significant.

Results

All patients finished the study. There were neither drop outs, nor violations of the protocol.

The ketoprofen and metamizole groups were comparable with respect to gender, age, body mass index (BMI) and duration of operation (Table 1).

The majority of the patients (90%) were operated for malignancy of the head and neck region, while 6 of them (10%) had a major operation for histologically benign tumors (Table 2).

Pain assessment by visual numeric scale in the 1st, 2nd and 3rd postoperative day is presented in Figures 1-3, respectively.

Both medications decreased pain efficiently. The analgesia was more pronounced with ketoprofen but the difference was not significant during the first 2 postoperative days (Figures 1, 2). During the 3rd postoperative day the rating score was significantly lower in the ketoprofen group than in the metamizole group ($p< 0.05$) (Figure 3).

Table 1. Patient characteristics and duration of surgery

	Ketoprofen (n=30) Mean (range)	*Metamizole (n= 30) Mean (range)*
Sex (F/M)	5/25	3/27
Age, years (range)	60.2 (43-79)	54.8 (32-72)
Duration of surgery, min (range)	151.7 (50-250)	153.3 (60-300)
Body mass index	48.6	43.9

F: female, M: male

Table 2. Surgery characteristics

Type of operation	*Ketoprofen (no. of patients)*	*Metamizole (no. of patients)*	*Total* *No.*	*%*
Radical neck dissection	4	3	7	11.7
Laryngectomy	19	20	39	65.0
Resection of oropharyngeal cancer with neck dissection	4	–	4	6.7
Ear cancer with neck dissection	1	–	1	1.7
Extirpation of submandibular salivary gland	1	2	3	5.0
Resection of nose cancer	1	–	1	1.7
Surgery of laryngotracheal stenosis	–	2	2	3.3
Surgery of base of the tongue cancer with neck dissection	–	2	2	3.3
Extirpation of frontal sinus osteoma	–	1	1	1.7
Total	30	30	60	100

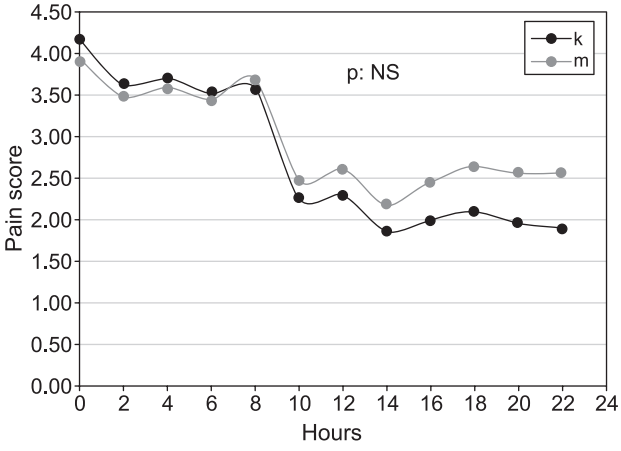

Figure 1. Pain assessment using numeric rating scale during the first 24 h after surgery. k: ketoprofen, m: metamizole, NS: non significant.

The 24h use of tramadol was the same in the ketoprofen (1 dose, 1 patient, first 4h postoperatively) and metamizole group (1 dose, 1 patient, first 4h postoperatively).

Both analgesics were well tolerated. There were no adverse effects recorded requiring special treatment. During the postoperative period, none of the patients developed excessive bleeding. Coagulation tests were within normal values at the end of treatment. No granulocytopenia was recorded. Bleeding from the wound and haematoma was the same in both groups and stopped without consequences (Table 3).

Discussion

Patients undergoing head and neck surgery often have significant pain because of the anatomic area in-

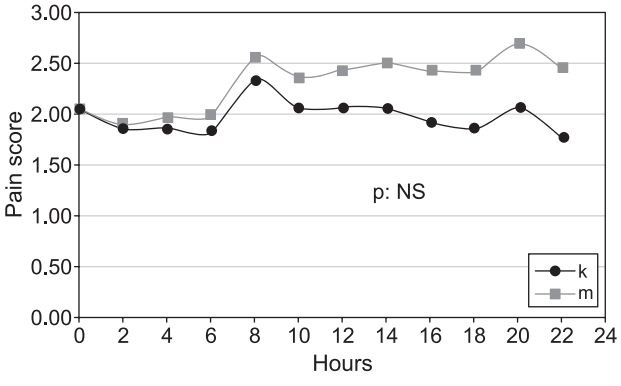

Figure 2. Pain assessment using numeric rating scale during the second 24 h after surgery. k: ketoprofen, m: metamizole, NS: non significant.

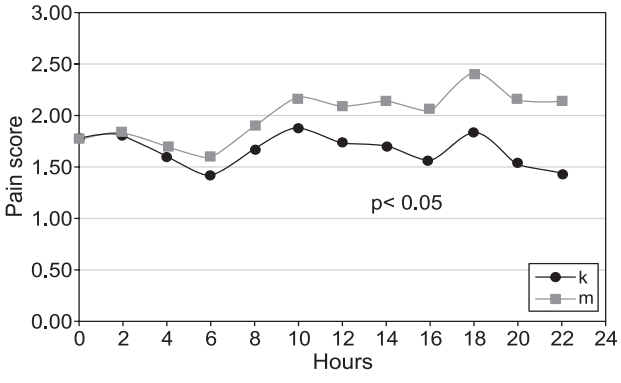

Figure 3. Pain assessment using numeric rating scale during the third 24 h after surgery. k: ketoprofen, m: metamizole.

Table 3. Adverse events in ketoprofen and metamizole groups of patients during the study period

Adverse events	*Ketoprofen (no. of patients)*	*Metamizole (no. of patients)*	*Total*
Nausea	3	4	7
Bleeding from the wound	3	3	6
Hematomas	3	2	5
Infections	3	1	4
Total	9	6	15

volved, the nature of surgery and trauma associated with anesthesia and surgery [6]. Postoperative pain control is one of the main goals in the postoperative treatment. In the postoperative care, opiate analgesics are used frequently [7,8]. However, due to their well-known toxicity, NSAIDs are increasingly used instead. Among them, metamizole has long been used as an analgesic for postoperative pain. Used intraoperatively or postoperatively it is equal or superior to paracetamol, diclofenac or parecoxib. It relieves somatic pain in many conditions accompanied by pain of mild and moderate intensity [9-11]. Metamizole possesses favorable gastric tolerability in comparison with other NSAIDs, and in therapeutic doses is almost free from gastrointestinal toxicity [12]. However, the risk of agranulocytosis with metamizole seems to be considerably higher than the previously estimated risks. Metamizole is also associated with other blood dyscrasias, and the prognosis of combined dyscrasias seems to be poorer than for isolated agranulocytosis [13]. Therefore, it is withdrawn in most countries of the western Europe and USA. In Serbia metamizole was also withdrawn for oral use. It is available only for parenteral use, mainly for the treatment of postoperative pain and pain due to malignancies [14].

Ketoprofen for parenteral use is particularly suitable in patients for whom oral administration of the medication is more complicated, as is the case in the majority of patients who had operations in the head and neck region. According to the existing data, it is an effective analgesic, which, under certain circumstances, can substitute pethidine or it is even superior to it [15, 16]. However, ketoprofen, like other NSAIDs, significantly inhibits platelet aggregation and thromboxane B(2) production in healthy volunteers, increases bleeding time and possesses significant risk of gastrointestinal complications [17,18]. This was the reason we did not use ketoprofen earlier as analgesic.

Our results showed that ketoprofen and metamizole were comparable in their analgesic activity. The intensity of pain was higher than 4 according to the visual analog scale only during the first hours after operation. The pain score fell markedly within the first 8h from 4-4.5 to 2-2.5 and remained at this level in both groups. Both analgesics were highly effective. The fact that in each group only one patient asked for additional dose of tramadol clearly implies that both analgesics were sufficient to relieve pain in the postoperative period. In all patients pain of mild and moderate intensity was relieved for the whole period between the two administrations, and this was measured by recording the intensity of pain every two hours.

Although both investigated drugs showed satisfactory analgesic effect lasting the whole investigated period, ketoprofen offered significantly better analgesia than metamizole during the 3rd postoperative day.

During the study no significant adverse effects were noticed nor had any of the patients been excluded from the study due to adverse events. Patients in both groups who developed postoperative bleeding on the first postoperative day received transfusion of fresh plasma. The bleeding stopped without withdrawal of either ketoprofen or metamizole. This finding is in agreement with another study conducted on patients with different pathology, such as tonsillectomy, which did not show greater frequency of bleeding after postoperative use of ketoprofen [19]. The practically equal number of patients with postoperative bleeding and hematomas in both groups indicates that the bleeding was not caused by analgesics. Data presented by other authors show that bleeding after similar operational interventions occurred also when only opiate drugs were used in the treatment of postoperative pain [20].

Analgesics were applied in regular time periods in order to maintain their concentration in the blood, thus preventing the appearance of pain. Such an effect is much more significant than pain restriction when it has already occurred, when a greater amount of medication is required with delayed start of action and longer duration of pain. Although according to some authors it is necessary to individualize the dose inter-

val, 8h standard interval between doses was sufficient for pain control in our study.

Conclusion

Ketoprofen proved a good and safe analgesic in patients operated for malignant tumors of the head and neck, as demonstrated by reduced postoperative pain score. The analgesic effect achieved by ketoprofen was at least comparable to metamizole. No increased risk of bleeding in patients receiving ketoprofen was seen. Therefore, ketoprofen, as a safe and effective NSAID can be used alone in the treatment of postoperative pain after head and neck operations.

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