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A double blinded randomized clinical trial of perioperative ketorolac 15 mg versus 30 mg, evaluated by visual analog score in orthopedic and ear-nose and throat patients

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ABSTRACT

Objective: Ketorolac is a non-steroid anti-inflammatory drug for intravenous use, with analgesic and anti-inflammatory effects and known for its potent influence on moderate to severe postoperative pain. The literature has shown that 30mg i.v. perioperative ketorolac is efficient, well-tolerated and decreases postoperative pain scores. There is no consensus in the literature on whether or not non-steroid anti-inflammatory drugs increase postoperative bleeding. This rare but possibly severe adverse reaction justifies further research into ketorolac dose-dependant postoperative pain scores. The study aims were to evaluate the difference between 15mg and 30mg perioperative i.v. ketorolac on postoperative VAS scores and secondary analgesia consumption after orthopedic or ear, nose and throat surgery.

Methods: A comparative double-blinded randomized controlled trial included 69 patients, aged 18-65 years, undergoing ear, nose and throat or orthopedic surgery. Patients were randomized to receive either 15mg or 30mg i.v. ketorolac 30 minutes prior to the end of the surgery. Postoperative pain was recorded at 0, 15, 30, 60 and 90 minutes after arriving at the post-anesthesia care unit. The total amount of supplement analgesia consumed was calculated when the patient left the postoperative care unit or after 90 minutes.

Results: A two-sided t-test showed the following: VAS t0: p=0.068 (95% CI 1.564 - 2.780); VAS t15: p=0.078 (95% CI 1.641 - 2.868); VAS t30: p=0.056 (95% CI 1.751 - 3.070); VAS t60: p=0.210 (95% 1.600 - 3.119); and VAS t90: p=0.124 (95% 1.120 - 3.230). The mean postoperative oral morphine equivalent was 9.1mg [5-20 mg] in the 15 mg group and 7.9 mg [2.5-20 mg] in the 30 mg group (two-sided t-test, p=0.526 95% CI -2.21-4.25).

Conclusion: Our study demonstrated that 15 mg i.v. perioperative ketorolac exerts the same postoperative pain relief as 30 mg and does not result in a higher secondary analgesia consumption.

Key words: *Ketorolac, pain, visual analog scale, postoperative, opioid consumption*

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used as part of multimodal pre-, peri- and postoperative pain management and are known to reduce postoperative morphine consumption and decrease the duration of admission [1-3]. Ketorolac is a NSAID for intravenous (i.v.) use, which can easily be administered to patients with postoperative nausea and vomiting [4]. It has both analgesic and anti-inflammatory effects and is known for its potent influence on

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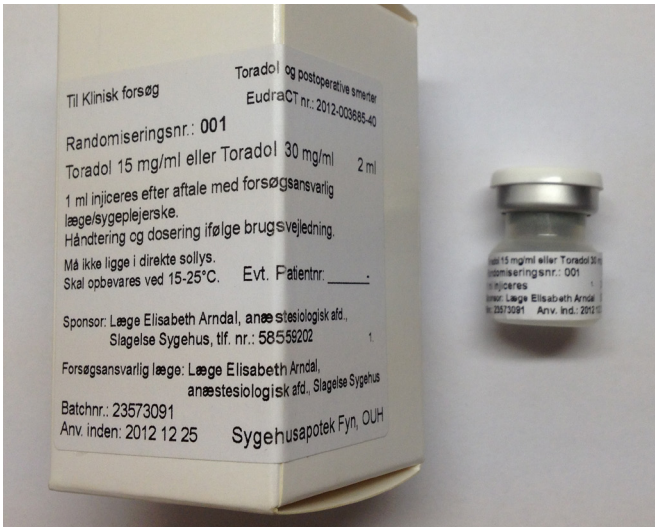


Figure 1. Trial drug, ketorolac.

moderate to severe postoperative pain [5, 6]. Ketorolac is used for multiple kinds of surgery, such as ear, nose and throat, dental, abdominal and orthopedic surgery [7,8]. Differences in surgical trauma and ketorolac doses govern the analgesic effect [9-11]. The literature has shown that 30mg i.v. perioperative ketorolac is efficient, well-tolerated and decreases postoperative visual analog scale (VAS) scores [12,13]. Ketorolac has known side effects, including affecting renal and platelet function and has also been reported to increase anastomosis leakage after bowel surgery [14,15]. There is no consensus in the literature on whether or not NSAIDs increase postoperative bleeding [16-18].These rare but possibly severe adverse reactions (SAR) justify further research into ketorolac dose-dependent postoperative pain scores. Our study aims were to evaluate the difference between 15mg and 30mg perioperative i.v. ketorolac on postoperative VAS scores and secondary analgesia consumption after orthopedic and ear, nose and throat surgery.

Materials and Methods

This comparative double-blinded randomized controlled trial included 69 patients and was carried out at the department of Anesthesiology, Slagelse Hospital, Denmark. The protocol was approved by the regional ethical committee and informed written consent was obtained from all participating patients prior to their inclusion in the study. The trial was conducted in accordance to the World Health Association Declaration of Helsinki. The study was registered at European Clinical Trials (EudraCT nr: 20012-003685-40) and was under continuous monitoring from the Good Clinical Practice (GCP) group, performed from 15.09.2012 to 15.09.2013.

Inclusion criteria: Age 18-65, able men and women (negative pregnancy test), ASA I and II (guideline of the American Society of Anesthesiology), ear, nose and throat surgery (tonsilectomi, adenoidectomi, removal of the submandibular or parotid gland, thyroidectomi, deviated septum, endoscopic sinus surgery, lateral or medial neck cyst, tympanoplasty) and minor orthopedic surgery. The surgeries were performed by different doctors.

Exclusion criteria: Gastrointestinal ulcer, coagulation disorder, chronic pain disorder, daily use of analgesics, NSAIDs or acetylsalicylic acid or prostaglandin allergy, pregnant or breastfeeding, ASA III or more or simultaneous treatment with lithium, probenecid or pentoxifyllin. Patients were included during their introductory visit with the anesthesiologist. The hospital pharmacy at Odense University Hospital, Denmark, created the randomization list and corresponding 2 ml caped vials containing the trial drug (Figure 1). Patients randomly received either 15 mg or 30 mg i.v. ketorolac 30 minutes prior to the end of the surgery (1:1 ratio). Postoperative pain was recorded at 0, 15, 30, 60 and 90 minutes after arriving in the post-anesthesia care unit (PACU) using a 0 to 10 cm VAS, where 0 represents no pain and 10 signifies the worst pain. Data registration ceased when the patient left the PACU or after 90 minutes, even if the patients were still in the PACU. The anesthesiologist nurse in the PACU could administer

Table 1. Demographic data.

Parameter	15 mg ketorolac	30 mg ketorolac
Number of patients	36	33
Age, mean, [range], years	42 [19-65]	43 [18-65]
Male:female ratio	14:22	17:16
Ethnicity		
Caucasian	30	30
Middle Eastern decent	5	2
Other	1	1
Weight, mean, [range] kg	75 [43-118]	81 [59-125]
Missing data, n	*n 4*	*n 3*

n (number of patients).

additional analgesia, except NSAID, as soon as the VAS upon arrival was registered. The total amount of supplement analgesia consumed was calculated when the patient left the PACU or after 90 minutes, even if the patients were still in the PACU. The total amount of all other pain medication, i.e., opioids, was converted into oral morphine equivalents.

All patients could leave the study at any given time if they so wished. The study would be terminated if ketorolac was unexpectedly withdrawn. SAR and suspected severe adverse reactions (SUSAR), if any, were reported to the Danish Medicines Agency in accordance with standard procedure. The collected data was entered into Microsoft Excel® and analyzed with STATA® version 14. Two-sided t-tests were chosen for statistical analysis as the variables were at the interval level. A p-value of less than 0.05 was considered to be statistically significant.

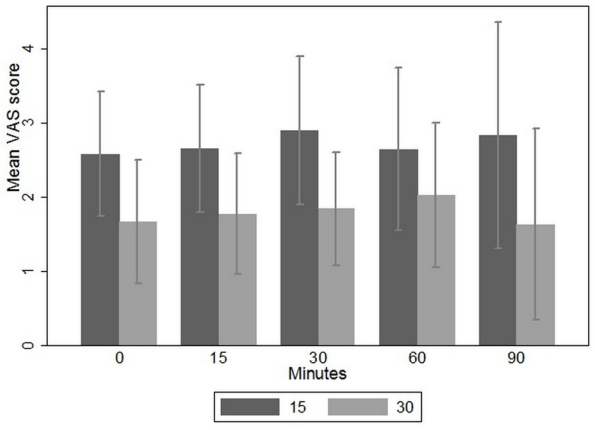
Results

A total of 69 patients perioperatively received a single dose of either 15 mg or 30 mg i.v. ketorolac. The baseline characteristics of patients were similar between the two study groups. Group demographics are presented in Table 1. Patients underwent either ear, nose and throat or orthopedic surgical procedures, the distribution of which can be reviewed in Table 2. The mean time of ketorolac infusion for both groups was 15 minutes before the end of surgery. 61 patients received perioperative i.v. synthetic morphine (fentanil or sufentanil). The perioperative oral morphine equivalent was 7.2 mg for both study groups (two-sided t-test, p=0.977 95% CI -1.19-1.16). A small number of patients (eight patients in the 15 mg group versus five in the 30 mg group) also received perioperative dexamethasone based on postoperative nausea and vomiting. Statistical analysis was not possible because of the limited sample size. Study parameters consisted of postoperative pain intensity scores through VAS and postoperative morphine consumption. VAS SCORES: Postoperative pain scores for both study groups are shown in Figure 2. The number of patients registered at each time point steadily decreased. VAS scores were registered for n patients

Table 2. Type of surgery and perioperative pain management.

Parameter		15 mg	30 mg
Surgery performed	Nasal septoplasty	12	6
	Tonsillectomy	8	5
	Total or hemithyroidectomy	6	5
	Endoscopic sinus surgery	3	4
	Middle ear surgery	1	3
	Major salivary gland excision	1	3
	Lateral neck cyst excision	1	1
	Adenoidectomy	1	1
	Combined head and neck	0	2
	Surgery	2	2
	Hand surgery	1	1
Infusion time, mean, *Missing data, n*	*(minutes to end of surgey)*	15 [1-75] *n 8*	15 [1-70] *n4*
Perioperative opioids, *number of patients*	Fentanyl	28	30
	Sufentanil	1	0
	Missing data	7	3
Perioperative oral morphine equivalent, mean, *mg*, [range] Missing data, *n*		7,2 [0-11.3] *n7*	7,2 [0-13.1] *n3*
Dexamethasone*	8 mg	5	5
	6 mg	1	0
	4 mg	2	0

SD: standard deviation. n (number of patients).* Only patients with post-operative nausea and vomiting were given perioperative dexamethasone.



Ketorolac 15 mg (dark gray) or 30 mg (light gray) . Visual Analog Scale (VAS) pain index was registered at the time t0, t15, t30, t60 and t90 minutes after arrival in the post anesthesia care unit. Vertical lines indicate 95% confidence interval. *n*= number of patients. The 15 mg group contained a total of 36 patients; t0 *n*=35, t15 *n*=32 , t30 *n*= 29, t60 *n*=18 , t90 *n*=12. The 30 mg group contained a total of 33 patients; t0 *n*= 29, t15 *n*= 27, t30 *n*= 26, t60 *n*=15, t90 *n*=11.

Figure 2. Postoperative pain scores after 15 mg or 30 mg perioperative i.v. ketorolac.

Table 3. Pain medication given in the post anesthesia care unit.

Parameter		15 mg ketorolac	30 mg ketorolac
Received pain medication* in post anesthesia care unit,	Yes	29	22
	No	7	11
Oral morphine equivalent dose, mg, mean, [range]		9.1 [5-20]	7.9 [2.5-20]
Paracetamol per oral 1 gram		17	14
Paracetamol intravenous 1 gram		3	2

*Paracetamol and/or opioid.

in the 15 mg and 30 mg group, respectively: at time0 (t0) n=35 / 29 and at (t90) n=12 / 11. One patient did not want to receive more pain medication even though VAS was in the range of 4-7 during the observational period. The decrease in VAS score registration was because of either missing data or terminated registration as the patient left the PACU. Two-sided t-test demonstrated: VAS t0: p=0.068 (95% CI 1.564 - 2.780); VAS t15: p=0.078 (95% CI 1.641 - 2.868); VAS t30: p=0.056 (95% CI 1.751 - 3.070); VAS t60: p=0.210 (95% 1.600 - 3.119); and VAS t90: p=0.124 (95% 1.120 - 3.230). SECONDARY ANALGESIC CONSUMPTION: 29 out of 36 patients in the 15 mg group and 22 patients out of 33 in the 30 mg groups received analgesics in the PACU. Patients received postoperative i.v. or per oral oxycodon and/or tramadol and/or morphine. The mean postoperative oral morphine equivalent was 9.1mg [5-20 mg] in the 15 mg group and 7.9 mg [2.5-20 mg] in the 30 mg group (two sided t-test, p=0.526 95% CI - 2.21-4.25). 20 out of 36 patients in the 15 mg group (56 %) and 16 out of 33 patients (48 %) in the 30 mg group also received i.v. or per oral paracetamol (see Table 3). The patients were allowed to receive all kinds of pain medication, including NSAID's, after they left the PACU. One out of 69 patients had postoperative bleeding more than 24 hours after discharge from the hospital not considered to be related to the study drug, however the patient had received 30 mg ketorolac during tonsillectomy. No SAR or SUSAR were reported.

Discussion

In our study, both groups were treated with the active drug, ketorolac, because we found it unethical to have an untreated or placebo group. The standard of care in our department calls for perioperative pain medication for all patients. Additionally, the effect of ketorolac compared to placebo had already been established by Gan et al. in 2012 [6] and Daniels et al. in 2013 [3].

The observed, slightly lower VAS scores for all observation time points in the 30 mg group were non-significant when compared to the 15 mg group. There was no statistically significant difference in the amount of perioperative opioids administered between the two groups, so besides the surgical trauma, it was just the ketorolac dose that differentiated them. To our knowledge, there are no other studies comparing 15 mg and 30 mg perioperative ketorolac. Daniels et al. [3] compared ketorolac and diclofenac with placebo in 239 patients undergoing orthopedic surgery. Patients in the ketorolac group received both 15 mg and 30 mg, but unfortunately the results were pooled so it was not possible to evaluate the ketorolac doses separately. Ketorolac was significantly better than placebo. De Oliveira et al. [11] identified 4 trials in their meta-analysis comparing 30 mg perioperative ketorolac to placebo. The analyses favored 30 mg ketorolac over placebo, though they did not highlight any studies testing 15 mg ketorolac.

In the work presented here, VAS scores over time (Figure 2) did not decrease, a somewhat surprising phenomenon. This may be based on the fact that the number of observations diminished over time so that

the number of patients in the 15 mg v.s.30 mg groups were 35 versus 29 at t0 and 12 versus 11 at t90. This is most likely because of terminated registration in the case patients experienced little or no pain, being discharged from the PACU, however this may also account for missing data. Thus, the few remaining patients kept the VAS score high. Perhaps the lasting patients did not receive sufficient pain medication, or possibly those that remained in the PACU were those with more pain than the average patient.

There was no difference in time of perioperative infusion between the two groups but in both cases, ketorolac was, on average, given 15 minutes before the end of surgery. According to the pharmacokinetics for ketorolac, it should be administered 30 minutes before the end of surgery for it to be effective when the patient wakes up. Therefore, one could argue that the VAS scores for t15 and not t0 show the real effect of the drug.

There was a non-significant difference in postoperative morphine equivalent consumption. There was no difference in postoperative paracetamol consumption. Therefore, the perioperative ketorolac dose did not affect postoperative analgesic consumption. Moeller et al. [18] investigated 34 patients undergoing functional endoscopic sinus surgery and septoplasty and showed that 30 mg ketorolac was as efficient as 25 mg fentanyl, its use not resulting in a higher employment of supplementary pain medication.

Moeller et al. (2012) reported no difference in postoperative bleeding up to 7 days after functional endoscopic sinus surgery and septoplasty. A meta-analysis by Gobble et al. [19] analyzed 27 studies using ketorolac with a total of 2314 patients and did not observe a statistically significant difference in postoperative bleeding. In sharp contrast, Chan and Panikh [20] found a significantly increased risk of post-tonsillectomy bleeding in adults that received ketorolac. Here, only one out of 69 patients had a registered postoperative bleeding. This was less than that reported in other studies but was potentially related to the limited number of patients in this study.

Strengths and weaknesses: We performed a GCP unit-monitored double-blinded randomized controlled trial that included 69 patients. We tested 15 mg versus 30 mg ketorolac in ear, nose and throat and orthopedic surgery patients, and this was never before conducted. The different types of surgical trauma were evenly distributed between the two groups. The procedures were performed by different doctors, possibly affecting the results. The study was limited by the relatively small sample size.

Having the limited sample size in mind, our study shows that 15 mg i.v. perioperative ketorolac yields the same postoperative pain relief as 30 mg and does not lead to a higher secondary analgesia consumption.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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