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Original Contribution

Intraoperative ketorolac dose of 15 mg versus the standard 30 mg on early postoperative pain after spine surgery: A randomized, blinded, non-inferiority trial☆

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ABSTRACT

Study objective: The primary aim of this study is to show the non-inferiority of 15 mg intraoperative dose of ketorolac as compared to the standard 30 mg ketorolac by looking at the visual analog scale pain (VAS) scores 4 h after an adult spine surgery.
Design: The study design is a prospective randomized non-inferiority clinical trial looking at non-inferiority of intraoperative 15 mg ketorolac from the standard 30 mg dose.
Setting: Quaternary care center.
Patients: 50 adult (18–65 years of age) undergoing lumbar decompression spine surgery.
Interventions: Group A received a single intraoperative dose of 15 mg ketorolac at the end of surgery and group B received single intraoperative dose of 30 mg ketorolac.
Measurements: The primary outcome was the visual analog scale (VAS) pain scores 4 h after an adult spine surgery. Secondary measures were morphine usage in the first 8 and 24 h postoperatively, numeric rating scores (NRS) up to 24 h, sedation, nausea, vomiting, respiratory depression, pruritus and bleeding complications.
Main results: Intention to treat analysis showed a mean increase in 4 h VAS pain score of 7.9 mm (95% CI: −4.5 mm to 20.4 mm) in patients administered 15 mg ketorolac. This difference was neither statistically ($P = 0.207$) nor clinically significant (<18 mm on VAS scale). A similar increase in the 15 mg group was noted through a per protocol analysis, 6.9 mm (95% CI: −6.6 mm to 20.5 mm, $P = 0.307$) greater in the 15 mg group. Non-inferiority of 15 mg was not confirmed. No significant difference was found in secondary endpoints.
Conclusions: Ketorolac 30 mg intravenous was not superior to 15 mg intravenous for post-operative pain management after spine surgery. However, 15 mg failed to meet the pre-specified criteria for non-inferiority to the 30 mg dose.

1. Introduction

Opioids have traditionally been the cornerstone of acute postoperative pain management. Problematic side effects such as nausea, vomiting, ileus, urinary retention, excess sedation, and respiratory depression are significant disadvantages with the use of opioids. Alternative treatments have been sought. The concept of adding a non-sedating non-opioid analgesic agent is appealing and has been validated by previous studies [1,2]. Nonsteroidal anti-inflammatory drugs (NSAID) are non-sedating and combine analgesic and anti-inflammatory properties ideal for pain after surgery.

Ketorolac is a potent intravenous NSAID, and a non-selective cyclooxygenase inhibitor which mediates pain, inflammation and fever [3]. It has been evaluated and used for treatment of moderate to severe pain including postoperative pain [4].

Standard parenteral dose recommended by manufacturer for healthy non elderly population is 30 mg based on a number of clinical trials and 15 mg for those ≥65 years of age [5].Previous studies have

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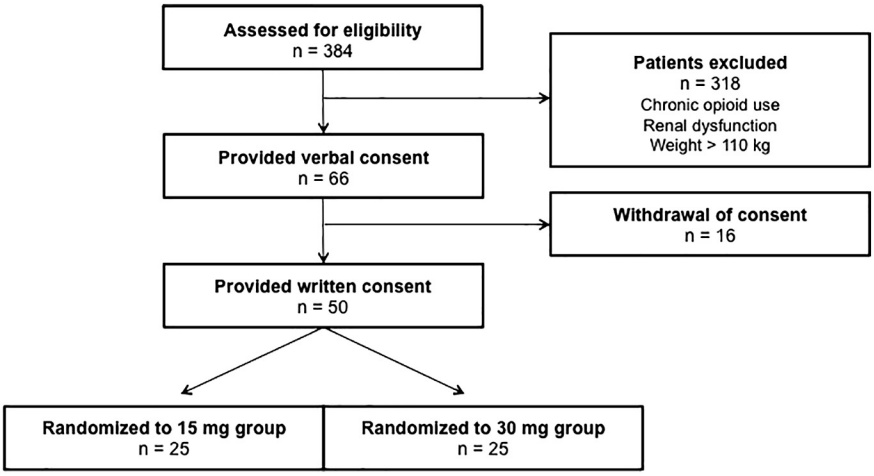

Fig. 1. Assessment and randomization of patients.

demonstrated the effectiveness of standard 30 mg intravenous ketorolac as an adjunct to opioids for postoperative pain relief [3,6–9]..

NSAIDs, including ketorolac, have an analgesic ceiling effect in which higher doses do not provide any additional pain relief but may increase the likelihood of side effects. Single dose intramuscular (IM) ketorolac have been studied in the past showing no difference in analgesia between the 30 and 90 mg dose [10]. Because of risk of drug toxicity and unwanted side effects, patients should be given the lowest effective ketorolac dose. Low dose ketorolac was studied in adolescents undergoing spine surgery and showed that a dose of 0.2 mg/kg (11 mg) provides supplemental analgesia postoperatively [6]. However, a literature review using a Medline (OVID) search did not locate adequate studies looking at intraoperative doses of ketorolac compared in terms of their efficacy and safety profile.

2. Outcomes

The primary aim of this study was to show the non-inferiority of 15 mg intraoperative dose of ketorolac as compared to the standard 30 mg ketorolac by looking at the visual analog scale (VAS) pain scores 4 h after an adult spine surgery. Minimum clinically significant decrease in VAS pain score was defined as 18 mm [11]..

Secondary objectives of this study aimed to assess morphine usage in the first 8 and 24 h postoperatively; a 10 mg decrease in morphine use in 24 h is considered clinically significant [9]. Other secondary objectives were overall morphine side effect such as sedation, nausea, vomiting, respiratory depression, pruritus and bleeding complications.

3. Materials and methods

3.1. Study design

The study was approved by the local ethics review board and patients provided written consent. The study design is a prospective, randomized, non-inferiority, clinical trial looking at non-inferiority of intraoperative 15 mg ketorolac from the standard 30 mg dose. The inclusion criteria were adult patients 18–65 years of age with a weight between 50 and 110 kg. Exclusion criteria were defined as previous lumbar laminectomy, current anticoagulant use with INR > 1.2, narcotic use > 4 weeks, known allergy or sensitivity to NSAID or morphine, renal insufficiency with creatinine > 100 μmol/L, known liver disease, history of gastrointestinal bleeding, pregnancy, history of bronchial asthma and NSAID use 2 days before surgery.

Patients were randomized into two groups by a computer generated random sequence number. Group A received a single intraoperative dose of 15 mg ketorolac at the end of surgery and group B received a single intraoperative dose of 30 mg ketorolac. Study drug was prepared by the hospital pharmacy and provided to the operating room in a blinded syringe. The patient, anesthesiologist, surgical team, and the nursing staff remained blinded to the intervention.

Patients received no pre-operative analgesia. Post-operative analgesia included intravenous morphine in the post-anesthesia care unit (PACU). If opioids outside of morphine were given in the 24 h post-operatively the doses were converted to morphine equivalents.

The anesthesiologist involved in the study was allowed to conduct his or her own anesthetic regimen for a lumbar decompression spine surgery. There was no restriction to the use of any volatile, sedatives, antiemetics, antibiotics, emergency drugs and other drugs needed by the patient for surgery. Fentanyl was used for intraoperative analgesia and use of any NSAID, longer acting opioids, such as morphine and hydromorphone, and short acting remifentanil were restricted.

The trial is registered at: https://clinicaltrials.gov/ct2/show/NCT01230463.

3.2. Statistical analysis

Power analysis using a non-inferiority margin of 6 mm (1/3rd the minimum clinically significant decrease in 4-hour VAS pain score), standard deviation of 20 mm [11], power of 80% and a two-sided 95% confidence interval resulted in a sample size of 175 per group (350 total). However, such a large sample was not feasible at our site given the high number of patients with chronic opioid use and the implementation of a microsurgical approach. Thus, we proceeded with a pilot study aimed at recruiting 50 total patients (25 per group).

The data are presented as mean ± standard deviation (SD), median (interquartile range [IQR]) or count (percentage [%]). Normality was assessed using a Shapiro-Wilk test. The primary outcome of the study,

Table 1
Baseline patient characteristics.

	15 mg ketorolac	30 mg ketorolac	P-value
Age (years)	53.0 (16)	54.0 (23)	0.420
Gender (males [%])	17 (68%)	17 (68%)	1.000
Height (m)	1.75 ± 0.1	1.73 ± 0.1	0.517
Weight (kg)	87.0 ± 15.0	85.8 ± 15.4	0.787
BMI (kg/m^2)	28.2 ± 3.8	28.4 ± 3.9	0.824
Preoperative Hgb (g/L)	146.8 ± 12.6	149.0 ± 12.2	0.530
Preoperative creatinine (μmol/L)	83.0 ± 16.3	75.0 ± 12.8	0.068

BMI = body mass index.