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Research paper

Pre-emptive ketorolac for prevention of intraoperative shoulder pain in patients undergoing cesarean section: A double blind randomized clinical trial

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ABSTRACT

Background: Shoulder pain is a commonly observed but mostly neglected consequence of cesarean section and little is known as well as explored about intraoperative shoulder pain. We conducted this randomized prospective double-blinded study to evaluate the efficacy of ketorolac in reducing the incidence and severity of intraoperative shoulder pain in patients undergoing cesarean section.
Methods: Two hundred ASA I and II patients scheduled to undergo elective cesarean section under spinal anesthesia were randomized to receive either intravenous ketorolac 30 mg (ketorolac group) or normal saline (control group). The primary outcome was the incidence of intraoperative shoulder pain. Secondary outcomes were severity of intraoperative shoulder pain, amount of intraoperative blood loss, incidence of hypotension, bradycardia and request for intraoperative rescue analgesia.
Results: The incidence of intraoperative shoulder pain in the control group was significantly higher than the ketorolac group ($P = 0.003$). Severity of shoulder pain and requests for intraoperative analgesia was significantly higher in the control group ($P = 0.012$, $P = 0.006$ respectively). Patients in the Ketorolac group experienced significantly higher incidences of bradycardia ($P = 0.037$).
Conclusion: 30 mg ketorolac administered intravenously just before the operation could decrease incidence and severity of intraoperative shoulder pain in patients undergoing cesarean section.
Clinical trial registration: ClinicalTrial.gov (Registration number: NCT02380898, first registered in 01/03/2015).

1. Introduction

Cesarean section (CS) is the most common abdominal surgery among women worldwide.[1] Shoulder pain, is very common but mostly neglected consequence of CS and little is known about intraoperative shoulder pain.[2]

Spinal anesthesia (SA) is most commonly used anesthesia technique in patients scheduled for CS. There are very well know complications of SA used during CS, but there are few studies exploring about intraoperative shoulder pain as one of its complications. Kikuchi et al reported that women undergoing CS under combined spinal epidural anesthesia experience very high incidences of intraoperative shoulder pain.[2]

This sharp type of pain noticed intraoperatively during CS is usually experienced in the shoulder area, and was described by the patients to originate from deep inside the shoulder. They also at times complain it to originate this from the right side of chest. The pain is found to go down to the upper arm and in the neck on right side sometimes. This pain at times leads muscle spasm. The reason for this pain is postulated to be due to sub-diaphragmatic clot, subdiaphragmatic air trapping, or because of peritoneal irritation resulting from them.[3]

Preventive analgesia using non-opioid analgesics is aimed to improve postoperative pain while minimizing side effects of opioids. Ketorolac is a nonsteroidal anti-inflammatory analgesic (NSAID) used frequently to treat postoperative pain as combined multimodal analgesia. Single dose ketorolac has been used in labor

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analgesia and it is found to be safe and effective both to mother and fetus.[4]

Considering this safety profile and efficacy in obstetrics as well as the opioid sparing role, we decided to use ketorolac to evaluate its efficacy in reducing intraoperative should pain in patients scheduled to undergo CS under SA.

2. Methods

After approval from the Medical Ethics Committee of the Faculty of Medicine of Assiut University, 200 primigravida healthy pregnant women (ASA I and II) having singleton pregnancy at term (more than equal to 37 weeks of gestation) were included in this study after obtaining their verbal and written informed consent. This randomized double-blind placebo controlled study was conducted between March to September, 2015.

Patients having allergy to study drug, gestational diabetes, cardiovascular or biliary disorders, asthma, renal impairment, preeclampsia, any chronic pain condition or trauma in the shoulder, forearms or upper limbs, history of previous abdominal surgery, patients with complication in current pregnancy, any contraindication to SA were excluded from the study.

Patients were randomly allocated using computer-generated randomization to receive either intravenous ketorolac 30 mg (ketorolac group) or equal volume of normal saline (control group). An independent person not involved in managing the patients perioperatively prepared the study drugs with matching random numbers to be used in designated patients. Neither the participants nor the investigators involved in collecting the data and assessing the outcomes of the study were aware of the identity of the target drugs used in the study.

All the patients preassessed before undergoing CS. They were fully explained by the investigator about use of numerical rating scale (NRS) in describing pain. They were fasted for 6 h before the operation. They were also premedicated with oral ranitidine (150 mg), oral sodium citrate (30 mL, 0.3 M) and intramuscular metoclopramide (10 mg) 1 h before operative as antiaspiration prophylaxis.

In the operating room in all patients a large bore intravenous access (preferably 18 gauges) was inserted in left dorsum of the hand and they were preloaded with 15 mL/kg of Ringer's solution intravenously. All patients were connected to standard routine monitoring [non-invasive blood pressure (NIBP), ECG and peripheral oxygen saturation]. All participants received either 30 mg Ketorolac intravenously in 4 mL volume (ketorolac group) or similar volume of normal saline (control group).

They were made to sit upright and spinal anesthesia was inserted using the midline approach after proper antiseptic cleaning and draping in the lumbar vertebral interspace of L_3-L_4 or a level below using a 25 gauge Quincke needle. After obtaining free flow of cerebrospinal fluids, 12 mg of hyperbaric bupivacaine and 0.2 mg morphine were injected intrathecally. All patients were then made to lie supine and a wedge was placed below right hip to give a left lateral tilt. Continuous NIBP monitoring at every 1–3 min interval was started. Block level was tasted using response to cold. After attaining a block level of at least up to T_6 surgeons were allowed to proceed with surgery. The surgical technique was similar in both the groups. To reduce the possibility of chemical peritonitis, both the surgeon and the assistants washed their gloves with saline just before proceeding with surgery.

The incidence of intraoperative shoulder pain was noted. To exclude abdominal or visceral origin of pain, a leading question was asked patients to indicate the site of that pain after any complain was received. The severity of that pain was assessed using the verbal numerical rating scale (0–10) at time of complaint. Based on the score the pain was categorized for analysis as mild (0–3), moderate,[4–7] and severe.[8–10] If the pain was more than mild, rescue analgesia was provided with intravenous fentanyl (25–50 mcg). Patients were prescribed to receive regular paracetamol (1 gm) oral or intravenous for persistent postoperative shoulder pain. Estimated blood loss was calculated using the difference in hematocrit values taken prior to and 24 h after cesarean delivery, according to the following formula:

$$\text{Estimated blood loss} = \text{EBV} \times [(\text{Preoperative hematocrit} - \text{Postoperative hematocrit}) \times / \text{Preoperative hematocrit}].$$

where EBV (estimated blood volume) in ml = the woman's weight in kg × 85.[5]

Hypotension (defined as >20% decrease in systolic blood pressure) was treated with bolus of intravenous fluid and ephedrine (6 mg). Bradycardia (heart rate< 60/min) was treated with intravenous atropine (0.5 mg).

2.1. Statistical analysis

In a pilot study to analyze sample size we found that 88 patients per group were sufficient to detect a relative difference of at least 20% in the incidence of shoulder pain, with a power of 80%, an alpha error of 0.05 and an allocation ratio of 1:1. Taking into account of dropouts, 100 patients were recruited in each group to give sufficient difference. Continuous data were presented as mean with SD or median with range. These data were analyzed using independent t-test. Categorical data were expressed as frequency or percentage and were analyzed using chi-square test. Pain intensity assessed by verbal numerical rating scale score was analyzed using the Mann Whitney and U test. All P values were two-sided, and the statistical significance was defined as a P-value of less than 0.05. All analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL).

3. Results

Total 254 patients from March until September 2015 were evaluated for eligibility, and 205 were initially included in our study, and 5 other were excluded as they required general anesthesia. Finally we completed the study with 200 patients (Fig. 1). Patients in both groups were similar in characteristics with regard to age, height, weight, and gestational age (Table 1). The operative and analgesic details are shown in (Table 2).

Incidence of shoulder pain was significantly higher in control group compared to ketorolac group (23% vs. 8%, P = 0.003). There was significant reduction in requests for intraoperative rescue analgesia for intolerable shoulder tip pain in the ketorolac group compared to control group (6% vs. 19%, P = 0.005). Higher incidence of intraoperative bradycardia was noticed in ketorolac group compared to control group (12% vs. 4%, P = 0.037). However, there were no significant differences between both groups with respect to the incidence of hypotension, time to sensory block, the highest level to sensory block and estimated blood loss (Table 2).

The overall NRS score for intraoperative shoulder pain at the time of first complaint was significantly higher in the control group compared to ketorolac group (P = 0.012) (Fig. 2). Also the severity of that initial pain was much higher (moderate to severe) in control group compared to study group (P = 0.031) (Table 3).

4. Discussion

We found in this study that 30 mg of intravenous ketorolac given before cesarean section can result in significant reduction of

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