Perioperative blood loss and diclofenac in major arthroplastic surgery

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Abstract

Introduction: Contemporary literature indicates precaution over the perioperative use of non-steroidal anti-inflammatory drugs, since they can potentially increase perioperative blood loss related to their mechanism of action. The aim of this study was to assess the influence of non-steroidal anti-inflammatory drugs on perioperative blood loss undergoing hip arthroplasty and its correlation with general and regional anesthesia.
Methods: This prospective study included 120 patients who had undergone elective unilateral total hip arthroplasty. Patients were allocated into four groups. Groups 1 and 2 were pretreated with diclofenac and operated in general and regional anesthesia. Group 3 and 4 weren't pretreated with any non-steroidal anti-inflammatory drug and were, as well, operated in general and regional anesthesia. Diclofenac was administered orally two times a day 75 mg (total 150 mg) and also as intramuscular injection (75 mg) preoperatively and 12 hours later on a day of surgery.
Results: The perioperative blood loss in the first 24 hours showed an increase of 29.4% in the diclofenac group operated in general anesthesia and increase of 26.8% in patients operated in regional anesthesia ($P < 0.05$) compared to control group. Statistical data evaluation of patients operated in general anesthesia compared to regional anesthesia, the overall blood loss in the first 24 h after surgery, showed an increase of 6.4% in the diclofenac group and increase of 3.6% in placebo group. This was not statistically significant.
Conclusion: Pretreatment with non-steroidal anti-inflammatory drugs (diclofenac) before elective unilateral total hip arthroplasty increases the perioperative blood loss significantly. Early discontinuation of non-selective non-steroidal anti-inflammatory drugs is advised.

Keywords: perioperative blood loss, non-steroidal anti-inflammatory drugs, hip arthroplasty.

Introduction

The anti-inflammatory, analgesic and antipyretic action of non-steroidal anti-inflammatory drugs (NSAIDs) are mediated through inhibition of prostaglandin synthesis by inhibiting cyclo-oxygenase (COX) (1). COX is the major enzyme in the biosynthesis of prostanoids. Following the discovery in the early 1990s of an inducible isoform of COX, it is now known that COX exists in at least two isoforms: COX-1 and COX-2. COX-1 exists in the stomach, intestine, kidneys and blood platelets. It synthesizes the prostaglandins that (a) regulate the normal physiological processes involved in protecting the gastrointestinal mucosa and (b) maintain the renal function and vascular homeostasis (2). This role of COX-1 has been referred as a 'housekeeping' function. In contrast, the inducible isoform COX-2, after expression induced by several cytokines or lipopolysaccharide, produces large amounts of prostanoids that mainly contribute to the pathophysiological process of inflammation. The therapeutic effects of NSAIDs are largely the result of inhibition of the enzyme COX-2, whereas the toxic effects (disturbing platelets, the gut and the kidney) are primarily due to the inhibition of COX-1. This leads to a lack of thromboxane synthesis and impaired platelet aggregation (3). Diclofenac as non-steroidal anti-inflammatory drug (NSAID) is used in the preoperative and perioperative period for alalgesia, for reduction of inflamation and reduction of oedema before major orthopaedic procedures. Beside these benifits, there are some unwanted side effects: rash, ringing in the ears, headaches, dizziness, drowsiness, abdominal pain, nausea, diarrhea, constipation, hearthburn. NSAIDs reduce ability of blood to clot and therfore increase bleeding after an injury (4,5). NSAIDs are widely used in orthopaedic surgery, and diclofenac is a very commonly used NSAID in Ortho-

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paedic Clinic in Clinical Centre of Vojvodina. There is concern over the perioperative use of NSAIDs since they have the potential to increase perioperative blood loss related to their mechanism of action (6). We decided to assess the effect of diklofenac on perioperative blood loss in routine practice in patients undergoing hip arthroplasty by means of a randomized and controlled study.

Methods

Randomized controlled study was performed in Orthopaedic Clinic, Clinical Centre of Vojvodina in Novi Sad, Serbia, during 2008. Investigation included 120 patients who were to undergo elective total hip replacement for coxarthrosis during spinal (intrathecal) and general anaesthesia. Patients were allocated and randomized to four equal groups of 30 patients. Group 1 and 2 which were pretreated with diclofenac and operated in general and regional anaesthaesia. Group 3 and 4 which weren't pretreated with any analgesic drugs and operated in general and regional anaesthaesia. Two groups of patients (who were operated in general and regional anaesthesia) were pretreated before surgery with diclofenac i.v., on a day before and on a day of surgery. Diclofenac injection were given i.v. three times a day. Other two control group (who were operated in general and regional anaesthesia) didn't get any analgesic drug. We used 75 mg of diklofenak-sodium (Diklofen˝ injection solution 75 mg/3ml Galenika AD, Belgrade). The exclusion factors were: any patients receiving NSAIDs, aspirin or anticoagulants before starting the trial, and any patients with a history of peptic ulcer, renal or liver dysfunction or allergy to any NSAID. On the day of surgery patients who were operated in general anaesthaesia, were premedicated with Midazolam. General anaesthesia was performed in each patient by administering of Propofol, Fentanyl. Rocuronium was used as non-depolarising neuromuscular blocker. Sevofluran and N_2O-oxidul as inhalated anaesthetics is used during general anaesthesia. Patients were intubated and connected to mechanical ventilation by volume controlled ventilation. Patients are also monitored by standard anaesthesiology parametres: noninvasive blood pressure, heart rate (from the electrocardiograph), transcutaneous oxygen saturation, respiratory rate, $EtCO^2$ and standard respiratory parameters. These standard anaesthesiology parameters was also observed during first 24 hours of operation. Ringer saline solution was given intravenously immediatey before starting surgery. A continous infusion of the same solution was administered during surgery and after surgery. A colloid solution (Haemaccel) was also given to match the volume of blood lost. On the day of surgery all patients who were operated in regional anaesthaesia, were premedicated with Midazolam 2 mg. Regional anaesthesia was performed in each patient by administering bupivacaine. Ringer saline solution was given intravenously immediatey before starting surgery. A continuous infusion of the same solution was administeted during surgery and after surgery. A colloid solution (Haemaccel) was also given to match the volume of blood lost. Adequate sedation was provided by the patient's request during the procedure: the anaesthesiologist administered midazolam 2 mg at a minimum interval of 5 min until the patient indicated that the desited level of sedation had been reached. Noninvasive blood pressure, heart rate (from the electrocardiograph), transcutaneous oxygen saturation and respitatory rate were continuously monitored during anaesthesia and in the intensive care unit during the first 24 h after surgery.

Perioperative blood loss

All operations were performed by the same orthopaedic surgeons team. Prophylaxis against thromboembolism was started in all patients on the evening before surgery with Fraxiparin 0.3 mg s.c. (protocol in our country). On the day of surgery, fraxiparin 0.3 mg s.c was given 24 h after the initial dose. Nurses in the operating room measured perioperative blood loss. Total blood loss was calculated by taking into account the amount in the suction bottles, the weight of the surgical sponges and the irrigation fluid used. The volume of blood collected in the high-vacuum wound drainage containers was measured for 24 h after surgery. The transfusion trigger for homologous packed cells was a haemoglobin concentration <8 g/L in the whole postoperative period.

Statistical analysis

The t-test tested for differences between the groups. $p<0.05$ was considered as significant.

Results

Patient characteristics data are given in Table I. The two groups did not differ for age, height, weight or gender. Likewise other variables, e.g. preoperative use of β-adrenoceptor receptor blocking drugs, patients who received sedation during surgery, the use of cement and a decline in blood pressure (>25% decrease in mean arterial pressure after cementation), showed no differences between groups. There was no difference in the duration of surgery in either group.

Perioperative blood loss

The volume of blood loss was significantly higher in patients pretreated with diclofenac than with placebo. The volume of blood loss was higher in patient operated in general anaesthaesia in both groups, but the blood loss wasn't statistically significant.

TABLE 1. Patients characteristic data

Group	Group 1: Diclofenac group (in general anaesthesia)	Group 2: Diclofenac group (in regional anaesthesia)	Group 3: Placebo group (in general anaesthesia)	Group 4: Placebo group (in regional anaesthesia)
Number of patients	30	30	30	30
Gender (m/f)	8/12	9/14	8/11	10/14
Age (yr)	56	59	61	58
Heigh (cm)	174	168	175	170
Weight (kg)	84	82	79	79
Duration of surgery (min)	112	107	123	116

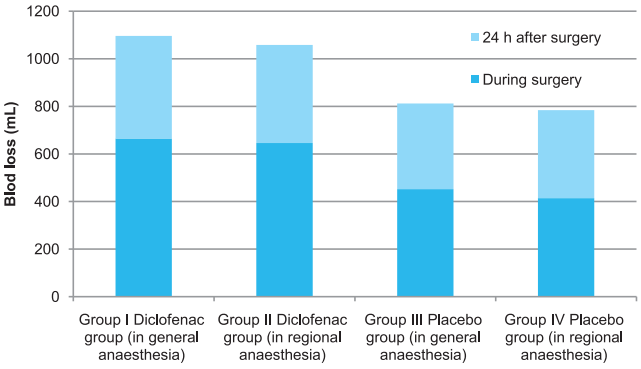

FIGURE 1. Total blood loss in Diclofenac and placebo groups

The volume of perioperative blood loss was 47.1% greater in the diclofenac group in general anaethesia and 56% greater in patients operated in regional anaesthesia compared with the placebo groups (P<0.05). The measured blood loss in the first 24 h after surgery also showed a 19.7% higher blood loss in the diclofenac group in general anaethesia and 11,4% higher in patients operated in regional anaesthesia compared with the placebo groups. This was not statistically different. The overall blood loss, i.e. the perioperative blood loss plus the blood loss in the first 24 h after surgery, showed an increase of 34.8% in the diclofenac group operated in general anaethesia and increase of 32.9% in patients operated in regional anaesthesia (P<0.05) (Table 2). The overall blood loss, i.e. the perioperative blood loss plus the blood loss in the first 24 h after surgery, in general anaesthesia compared to regional anaesthesia showed an increase of 5,2% in the diclofenac group and increase of 3.6% placebo group. This was not statistically significant (Figure I). Also measured perioperative blood loss and blood loss during first 24 h showed not statistically different. The study had an 86% power to demonstrate a 45% difference in expected blood loss at a P=0.05 level of significance. The number of homologous blood transfusions was nineteen in the diclofenac group and sixteen in the placebo group (not significant) during the whole period the patients remained in the hospital.

Discussion

The main finding is that pretreatment with diclofenac before total hip replacement surgery was associated with an increase in blood loss both during operation and for the first 24 h afterwards, in regional and in general anaesthaesia. Blood loss in regional anaesthaesia compared with general anaesthaesia is less but not statisticlly significant. Besides the useful anti-inflammatory, analgesic and antipyretic action of the NSAIDs, the study demonstrated an undesirable effect, namely increased blood loss. Researchers from the Case Western Reserve University School of Dental Medicine also recommend the discontinuation of NSAIDs prior to surgery to correct gum disease because blood loss is two times greater for those using the NSAIDs than those not taking it (7).

Study which compared diclofenac and melocsicam also showed that perioperative blood loss patients pretreated with diclofenac is significant and patient pretreated with meloxicam is less than after diclofenac (8). A. Schmidt et al. concluded that preoperative rectal diclofenac offers no advantage over paracetamol with respect to postoperative analgesia in tonsillectomy patients but increases intraoperative blood loss (9). R. Slappendel et al. from St. Maartenskliniek in Netherlands in their investigation finds that pretre-

TABLE 2. Blood loss during and after operation

Group	Group I Diclofenac group (in general anaesthesia)	Group II Diclofenac group (in regional anaesthesia)	Group III Placebo group (in general anaesthesia)	Group IV Placebo group (in regional anaesthesia)
Blood loss during surgery (ml)	665	646	452	414
Blood loss 24 h after surgery (ml)	431	412	360	370
Total blood loss (ml)	1096	1042	812	784

atment with ibuprofen before elective total hip surgery increases the perioperative blood loss significantly and that early discontinuation of non-selective non-steroidal anti-inflammatory drugs is advised (10). It has been suggested that NSAIDs that selectively inhibit COX-2 have fewer side-effects (11,12). The relationship berween platelet aggregation, thromboxane production and serum concentrations of the non-COX-2 selective drug as diclofenac has been examined (13). A single dose of diclofenac-sodium (75 mg) blocked platelet aggregation 2h after administration (13, 14). However, the effect was lost within 24 h. After diclofenac, had been given to healthy volunteers, platelet aggregation was inhibited for 6, 8 and 11 h, respectively. In the light of the half-life of diclofenac, these data suggest that diclofenac should be stopped 24 h before surgery (15,19). Although we tried to reduce as much possible the confounding factors in the study (one type of surgery performed one orthopaedic surgeon team), the use of fraxiparin for prophylaxis against thromboembolism could affect the outcome of the study. Diclofenac, but not the placebo, increases the prothrombin time (16,18). Other weaknesses of the study are the technique of measuring blood loss and the relatively high dropout rate. The study was probably not powerful enough to show whether an increase in blood loss resulted in an increased transfusion requirement or perioperative morbidity or mortality. These are much more important outcome measures for the patient compared with the actual measured blood loss. However, they are much more difficult to measure and therefore were not primary end-points of the study. It is concluded that ceasing NSAIDs sufficiently long before major orthopaedic surgery reduces perioperative blood loss (17). NSAIDs should be replaced before surgery with other analgesics, e.g. paracetamol, or possibly COX-2 selective anti-inflammatory agents, which have a better safety profile concerning peroperative blood loss. The study had an 86% power to demonstrate a 45% difference in expected blood loss at a P=0.05 level of significance. The number of homologous blood transfusions was nineteen in the diclofenac group and sixteen in the placebo group (not significant) during the whole period the patients remained in the hospital.

Conclusion

Pretreatment with diclofenac before major hip surgery either general or regional anaesthesia significantly increases blood loss. Considering the presence of relevant adverse effects, pretreatment with a non-selective NSAID is not recommended.

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