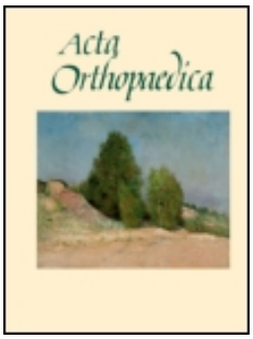

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Effects of celecoxib on blood loss, pain, and recovery of function after total knee replacement

A randomized placebo-controlled trial

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Background **Pain management after surgery has been used as a sales argument for the use of COX-2 inhibitors, but their potential positive and negative effects have not been fully investigated. We thus conducted a controlled evaluation of the effect of celecoxib on perioperative blood loss, pain relief and consumption of analgesics, range of motion, and subjective outcome in conjunction with total knee replacement (TKR).**

Method **50 patients were randomized to either placebo or celecoxib (200 mg) preoperatively and then twice daily. Total blood loss was calculated by the Hb balance method, taking the patient's pre- and postoperative hemoglobin and blood volume into account. Pain scores (VAS), range of motion, and subjective outcome (KOOS) were monitored postoperatively and during the first year after surgery.**

Results **No differences in total, hidden, or drainage blood loss were found between the groups. There were 30% lower pain scores during the first 4 weeks after surgery and lower morphine consumption after surgery in the celecoxib group, while no effect was seen on pain, range of motion, and subjective outcome at the 1 year follow-up.**

Interpretation **Celecoxib does not increase perioperative blood loss but reduces pain during the postoperative period after TKR. It is not necessary to discontinue celecoxib before surgery. The postoperative use of celecoxib did not increase range of motion or subjective outcome 1 year after TKR.**

Traditional non-steroid anti-inflammatory drugs (NSAIDs) are widely used as analgesics but their use is discontinued before major surgery in order to avoid increased perioperative blood loss (Fauno et al. 1993, Slappendel et al. 2002, Weber et al. 2003). Traditional NSAIDs inhibit the cyclooxygenase isoenzymes COX-1 and COX-2. Selective COX-2 inhibitors have been designed to avoid negative effects on hemostasis and gastric protection, while maintaining the analgesic and anti-inflammatory effects. In meta-analyses, COX-2 inhibitors appear to be as effective as traditional NSAIDs but are better tolerated (Pincus et al. 2004, Eisen et al. 2005, Moore et al. 2005, Schnitzer et al. 2005). In 2004, rofecoxib was withdrawn because of increased risk of myocardial infarction. After that, it has been debated whether this is specific for rofecoxib or whether it is a class-specific effect of COX-2 inhibitors. In a meta-analysis from 2003 (White et al. 2003) involving nearly 32,000 patients, celecoxib was found to give a lower risk of serious cardiovascular thrombotic events than paracetamol (RR 0.9). In contrast, another recent meta-analysis (Caldwell et al. 2006), involving about 13,000 patients, showed an increased risk of myocardial infarction with celecoxib (odds ratio 2.3), but no increased risk for the composite risk of stroke, cardiovascular events, and cardiovascular death. The differences might be explained by different search strategies and celecoxib dose (most patients in the analysis of Caldwell et al. were assigned to 800 mg celecoxib).

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Table 1. Patient characteristics

	Included to follow-up		Intention to treat	
	Placebo (n = 20)	Celecoxib (n = 24)	Placebo (n = 25)	Celecoxib (n = 25)
Sex (M/F)	12/8	7/17	14/11	8/17
Age (years)	69 (7.7) [a]	68 (6.3)	69	68
Weight (kg)	86 (11)	84 (13)	84	84
Height (cm)	173 (9)	168 (9)	173	169
Estimated blood volume (mL)	5,133 (689)	4,777 (745)	5,056	4,797
Men	5,591	5,523		
Women	4,446	4,470		
Time of surgery (min)	86 (12)	80 (9)	87	80

[a] Values in parentheses are SD.

In total knee replacement (TKR), rofecoxib has positive effects on pain relief and range of motion without increasing perioperative blood loss (Reuben et al. 2002, Buvanendran et al. 2003). With celecoxib, no negative effects on platelet function and bleeding time have been observed in healthy adults (Leese et al. 2000), but to our knowledge the effects of celecoxib on TKR patients have not yet been studied.

We therefore investigated the effect of celecoxib on blood loss, pain reduction and analgesic consumption, range of motion, and subjective outcome 1 year after TKR.

Material and methods

The study was designed as a randomized, placebo-controlled, double-blind trial and was performed in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2000. It was approved by the regional ethics committee (Dnr 03-286) and the Medical Product Agency in Sweden (Dnr 151:2003/47246). The study consisted of two parts: the first part was a radiostereometric analysis (RSA) of prosthesis fixation, which was regarded as the primary endpoint. This will be reported later, as a longer observation period is required. The second part consisted of clinical outcome variables, which were regarded as secondary outcome and which are reported in this article. The study was conducted from March 2004 through February 2005 at the Department of Orthopaedic Surgery, Linköping University Hospital, Linköping, Sweden. 50 patients suffering from osteoarthritis who met the inclusion criteria outlined below were consecutively recruited from the waiting list for elective primary unilateral TKR. The inclusion criteria included: age 50–80 years, ASA I to II, and capacity to give informed consent. The exclusion criteria included: a history of coagulopathy or of a thromboembolic event, plasma creatinine > 100 µmol/L in women and > 115 µmol/L in men, acute infection, malignant disease, unstable angina, myocardial or cerebral infarction within 1 year prior to operation, and allergy to NSAIDs or sulphonamides. All ongoing NSAID therapy was discontinued 7 days before surgery and for 3 weeks postoperatively.

Capsules containing either placebo or celecoxib (200 mg) were prepared by Apoteket AB (the Swedish pharmacy chain, Stockholm, Sweden). There, sets of capsules were randomly numbered 1–50 by a computer generator in 5 blocks of 10 sets. The content in every set of the capsules was automatically documented by the computer, printed out, and finally stored in a sealed envelope that was numbered according to randomization. A research nurse administered the numbered sets of capsules to the patients consecutively and the number of each set was traced on the evaluation form for each patient. Thus, all 50 patients randomly received either placebo or celecoxib 200 mg orally 1 hour preoperatively and then twice daily for 3 weeks. Patient characteristics are presented in Table 1. The randomization code was broken after 1 year, which exceeds the follow-up time for the variables in this study. Thus, both patients and observers were blinded as to treatment.

The patients received 2 g cloxacillin intravenously (i.v.) 30 min before surgery. Ringer's acetate solution was given i.v. as perioperative volume substitution. Subarachnoid spinal anesthesia with isobaric bupivacaine (Marcain spinal; AstraZeneca, Lund, Sweden) 17.5–20 mg was used. Midazolam or propofol was given i.v. for sedation if needed. After partial exsanguination of the limb by elevation for 1 min, a pneumatic tourniquet, located as high as possible on the thigh, was inflated to 300 mm Hg. All patients received Nex-Gen prostheses (Zimmer, Scandinavia) which were fixed to both the femur and the tibia with Palacos cum gentamicinum (Heraeus Medical, Germany) bone cement. All patients underwent a standardized procedure performed by 1 of 3 surgeons; 1 of them performed 42 of the 50 operations. Intraoperatively, the tibial component—an all-polyethylene construct—and the proximal tibia were marked with tantalum balls, diameter 0.8 and 1.0 mm, for later radiostereometric analysis. At the end of the surgery, approximately 15 min before release of the tourniquet, tranexamic acid 10 mg/kg (maximum dose 1,000 mg) was infused i.v. The dose was repeated after 3 h. A compressive bandage was applied before release of the tourniquet. The joint was drained with a single closed suction drain for 24 h postoperatively. Thromboembolic prophylaxis (5,000 IU subcutaneous dalteparin) was given postoperatively for 7 days. No patient was treated with other drugs that could affect perioperative blood loss—such as dextran, desmopressin, or NSAIDs.

For postoperative pain relief, all patients received paracetamol 1 g preoperatively and then routinely together with tramadol 50–100 mg 4 times a day during the hospital stay. If necessary, analgesia was complemented with ketobemidon (2.5–5 mg i.v. or s.c.) on demand. After discharge from hospital, only paracetamol and tramadol was used on patients demand. All consumption of analgesics was accounted for in an evaluation form during the stay in hospital and, after discharge, by the patient in a diary for 3 weeks after surgery. Pain was rated by visual analog scale (VAS, 0 = no pain and 10 = worst possible pain) preoperatively and postoperatively every day during the stay in hospital—in the morning before ambulation and rehabilitation exercises and on 4 additional occasions after 2, 4, 12, and 52 weeks.

The range of knee motion (ROM) was recorded by 1 of 2 physiotherapists preoperatively, each day during the hospital stay (after exercise) and after 2, 4, 12, 26, and 52 weeks. After discharge from the hospital, rehabilitation was continued under the supervision of physiotherapists. Subjective outcome was assessed using the knee injury and osteoarthritis outcome score (KOOS) (Roos et al. 1998, Roos and Toksvig-Larsen 2003), preoperatively and after 3 and 12 months.

Calculation of blood loss

Intraoperative blood loss was negligible because of the tourniquet. Calculation of blood loss after surgery was based on hemoglobin (Hb) balance. We assumed that blood volume on the fourth day after surgery was the same as that before surgery. The blood volume (BV) was estimated, taking sex, body mass, and height into account (Nadler et al 1962). Blood Hb concentration was measured preoperatively and on postoperative day 4. The Hb loss (in g) was then estimated according to the formula:

$$Hb_{loss\ total} = BV \times (Hb_i - Hb_e) \times 0.001 + Hb_t$$

where $Hb_{loss\ total}$ is the amount of Hb lost, Hb_i (in g/L) is the Hb concentration before surgery, Hb_e (in g/L) is the Hb concentration on the fourth day after surgery, and Hb_t (in g) is the total amount of allogenic Hb transfused.

Usually the Hb concentration of the drainage fluid is lower than in the circulating blood. Hence, we measured both the volume (Vdrain) and the Hb concentration (Hb drain, g/L) of the drainage fluid. One research nurse carried out all measurements. The Hb loss in drainage fluid (Hbloss drain) was calculated according to the formula:

$$Hb_{loss\ drain} = V_{drain} \times Hb_{drain}$$

The hidden Hb loss ($Hb_{loss\ hid}$) was calculated as follows:

$$Hb_{loss\ hid} = Hb_{loss\ total} - Hb_{loss\ drain}$$

The total blood loss (in mL), hidden blood loss (in mL) and blood loss in drainage (in mL) in relation to the patient's preoperative Hb_i (in g/L) were

Table 2. Total, hidden, and drainage blood loss

	Placebo (n = 20)	Celecoxib (n = 24)	95% CI for differences
Hb preoperative (mg/L)	140 (12.4) [a]	135 (9.4)	-1.6–11.6
Blood loss total (mL)	810 (314)	733 (316)	-110–264
Men	903	909	
Women	671	661	
Blood loss hidden (mL)	571 (278)	538 (315)	-142–208
Blood loss drainage (mL)	240 (96)	195 (88)	-10–100
No. of patients transfused	0	0	

[a] Values in parentheses are SD. Hb: blood haemoglobin concentration.

then calculated:

Blood loss total = $1{,}000 \times Hb_{loss\ total} / Hb_i$

Blood loss hidden = $1{,}000 \times Hb_{loss\ hid} / Hb_i$

Blood loss drainage = $1{,}000 \times Hb_{loss\ drain} / Hb_i$

Statistics

Originally, the study was designed and powered to detect effects on prosthesis fixation as measured with radiostereometric analysis, which was taken as primary endpoint. (Data collection is continuing and the results will be presented later). In this study we present the secondary outcome variables, the clinical effects of celecoxib. These are all regarded as secondary endpoints necessitating no separate power analysis. Values are generally expressed as mean and standard deviation (SD). 95% confidence intervals (CIs) for differences between the 2 groups are also presented.

To facilitate comparisons between the groups for pain (VAS scores) and ROM, the area under the curve was measured. Thus, for each patient, an early period area (postoperative day 1 to day 28) and a late period area (day 28 to 1 year) were constructed by the trapezoid rule (VAS values day 1 + day 2 + day 3 + mean (day 4–14) × 10 days + mean (day 14–28) × 14 days. In the same way the late period area was constructed based on the time segments: 1–3 months, 3–6 months, and 6–12 months.

Results

The groups had similar characteristics before surgery (Table 1)—except for the male-to-female distribution, as there were more male patients in the placebo group. 6 patients were excluded, 5 in the control group (4 spinal anesthesia failures and conversion to general anesthesia—1 of which also suffered a gastric bleeding—and 1 tourniquet failure) and 1 in the celecoxib group (spinal anesthesia failure). We decided to exclude these patients prior to data evaluation because it is known that general anesthesia increases postoperative blood loss and also postoperative analgesics consumption compared to spinal anesthesia. Even so, we also report results for the intention-to-treat groups (ITT).

Complications

1 patient sustained a bilateral deep vein thrombosis 1 month postoperatively (placebo group) and was treated with warfarin. No wound complications and no deep infections were observed during the first year after surgery.

Perioperative blood loss (Table 2)

The total blood loss was similar in the 2 groups (0.7–0.8 L). About three-quarters of the lost blood volume remained hidden in the tissues and the rest was drained out. No patient received a blood transfusion postoperatively.

Analgesics and pain

The total ketobemidon consumption was reduced in the celecoxib group relative to that in the controls (6 (6) mg vs. 10 (7) mg, CI: –9.5 to –2.5) (ITT: 6 (6) mg vs. 12 (7) mg) and there was a lower tramadol consumption during the first 3 weeks after surgery (2.4 (1.5) g vs. 3.4 (2.5) g, CI: –3.0 to 2.2), (ITT: 2.6 (1.8) g vs. 3.6 (2.4) g). The VAS scores for pain were similar preoperatively and during hospital stay, but became lower for the celecoxib group at 14 days post surgery. They returned again to similar levels during the 1–12-month follow-up period (Figure 1). The area under the VAS curve from the first to the postoperative day 28 was smaller for patients in the celecoxib group (58 (30) VAS x days vs. 84 (40) VAS x days, CI: –47 to –5) (ITT: 59 (29) VAS x days vs. 92 (45) VAS x days). Between 1 and 12 months, no difference was noted (celecoxib 323 (299) VAS x

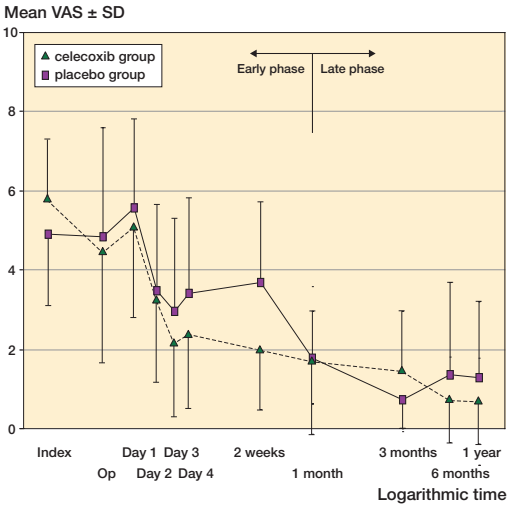

Figure 1. VAS scales.

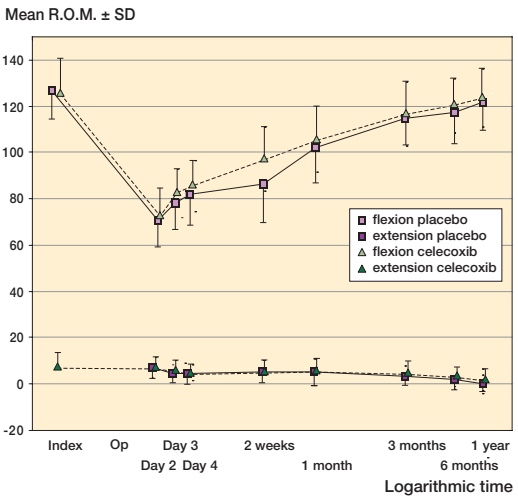

Figure 2. Range of motion.

days vs. placebo 405 (521) VAS x days, CI: –335 to 171).

Range of motion (Figure 2)

Patients in both groups had similar preoperative ROM with a slight extension deficit of 7 (6) degrees and flexion to 125 (13) degrees. During the first week, ROM was reduced by the same extent in both groups. During the 12-month follow-up period, ROM increased gradually to 122 (14) degrees without differences between the groups. There were no differences between the size of the area under the curve in the early period (1–28 days) and the late period (1–12 months).

1 patient in the control group had reduced flexion from that measured preoperatively: i.e. from 120 degrees preoperatively to 95 degrees at 2 months. He underwent knee joint mobilization under general anesthesia and achieved a final flexion of 120 degrees at the 12-month follow-up.

Subjective outcome (Figure 3)

The KOOS values increased from before operation to the 3- and 12-month follow-up without any differences between the two groups.

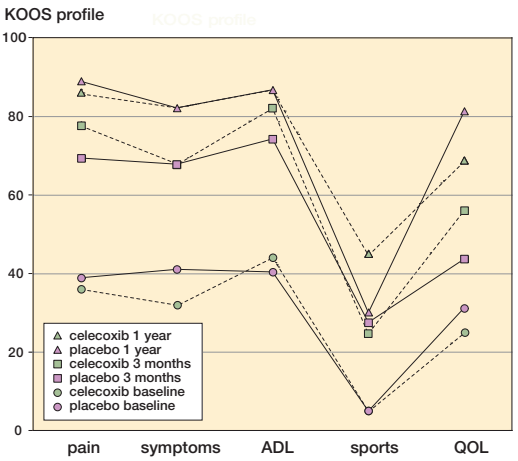

Figure 3. Knee injury and osteoarthritis outcome score (mean values).

Discussion

We found that celecoxib can be administered safely in the perioperative period to patients undergoing cemented TKR if the contraindications to the drug are respected. Blood loss was not increased, but the consumption of strong opioid (ketobemidone) and pain scores were lower in patients treated with celecoxib rather than placebo during the first postoperative month. No benefit was seen at the 12-month follow-up regarding patient satisfaction or range of motion.

In order to reveal any effect on hemostasis, celecoxib was administered 1 h before surgery—as is the case with traditional NSAIDs (Fauno et al. 1993). No difference in blood loss was found between celecoxib and placebo. This result was to

be expected, and is consistent with the results of other studies in which other selective COX-2 inhibitors were not found to increase perioperative blood loss in knee or hip joint replacement (Reuben et al. 2002, Weber et al. 2003). However, in those studies only drainage volume was measured and this underestimates the true blood loss. In our study, we used the Hb balance method to estimate the true blood loss. This estimation approximates blood volume from sex, body weight, and height (Nadler et al. 1962). We assumed that blood volume was normalized on day 4 after surgery and that an accelerated erythropoiesis would be irrelevant that early. Though to our knowledge never validated, the Hb balance method has been used in many studies prior to ours (Lisander et al. 1996, Mercuriali and Inghilleri 1996, Sehat et al. 2000, 2004, Good et al. 2003). We observed a tendency towards less perioperative blood loss in the celecoxib group, which can be explained by the unequal sex distribution (with more women in the celecoxib group). This is, however, a random effect. Women have less blood loss during TKR or total hip replacement (Cushner and Friedman 1991, Flordal and Neander 1991). Other interesting findings in our study were that only less than one-third of the total blood loss was recovered in the drains, while more than two-thirds remained intrarticular and in the soft tissue. The hidden blood loss was even higher than reported earlier (Sehat et al. 2000, 2004), but in those studies drainage Hb concentration was considered to be the same as blood Hb concentration. According to our findings, these other studies probably overestimated drainage blood loss.

Administration of celecoxib reduced ketobemidon consumption—even if the clinical relevance can be discussed, as the total consumption was low in both groups. Both pain scores and tramadol consumption were about 30% lower in the celecoxib group.

Because of the anti-inflammatory effect of COX inhibitors, there is a potential for increased ROM since postoperative stiffness and development of scar tissue after surgery might be depressed. Buvanendran et al. (2003) found increased ROM with rofecoxib during the first month after TKR. There were no similar findings in our study. Celecoxib did not increase ROM postoperatively, or at the 1-year follow-up. In both groups at 1 year, the average ROM had increased minimally compared to preoperative values. ROM was already relatively good preoperatively in both groups, which can be explained by the somewhat younger and healthier patients included in this study compared to TKR patients in general.

Celecoxib does not increase perioperative blood loss in total knee replacement. It does not have to be discontinued before surgery and can be used in postoperative pain management, provided general contraindications are respected.

We are presently investigating whether celecoxib has an effect on early prosthesis fixation.

Contributions of authors

AM: participated in the study design process, performed all data collection and evaluation, and was the principal writer of the manuscript. BL: participated in the study design process and took part in writing and revision of the manuscript. LG: was responsible for the study design and all communication with the Medical Product Agency in Sweden. He was supervisor for AM during the study, and participated in writing and revision of the manuscript.

No competing interests declared.

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