Cyclooxygenase-2 inhibitors and knee prosthesis surgery

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© Andreas Meunier 2008-08-04 Cover picture: Celecoxib bound to cyclooxygenase-2, created by TJ. O'Donnell (model and image) and R Kurumbail (crystal structure), "The coloured cylinders and strands represent the enzyme chain, and the white dotted area at lower left is its deep active site. Celecoxib (shown in blue) is bound to this active site."(Reprinted with permission from TJ O'Donell) All previously published papers were reproduced with permission from the publishers Printed by LIU-Tryck, Linköping 2008

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Abstract

Adverse effects of cyclooxygenase (COX) inhibitors on bone healing have previously been demonstrated in diaphyseal fracture models in animals. In spite of that, they are widely used as postoperative analgesics in orthopaedic surgery. After joint replacement, a bone repair process starts at the interface between bone and cement. If this process is disturbed, the prosthesis may never become rigidly fixed to the bone, leading to migration and with time loosening.

This thesis investigates the effects of a selective COX-2 inhibitor (parecoxib or celecoxib) on bone healing in metaphyseal bone in a rat model and on knee prosthesis migration after total knee replacement, as measured with radiostereometric analysis. Blood loss, postoperative recovery, and the 2-year subjective outcome, were also measured. In addition, a hemoglobin dilution method for blood loss estimation, used in this thesis, was evaluated.

In the first study, pull-out force of a screw inserted in metaphyseal bone of the tibia in rats was only marginally decreased by parecoxib after 7 days but not after 14 days. In the second and third study, celecoxib treatment resulted in less pain postoperatively in conjunction with total knee replacement (TKR), but no effects were seen on blood loss, range of motion, subjective outcome, or prosthesis migration after 2 years.

Comparing the true blood loss of blood donors with the blood loss estimated by the hemoglobin dilution method, this method was found to underestimate the true blood loss. It is therefore not suitable for calculation of the absolute blood loss volume, but may be used for a rough estimate.

In summary, celecoxib and presumably other cyclooxygenase inhibitors seems not likely to increase the risk of prosthesis loosening.

Abbreviations

ADL activity of daily living

BMP bone morphogenetic protein

BV blood volume

CI confidence interval

CN conditioning number

COX cyclooxygenase

Hb hemoglobin

KOOS knee injury and osteoarthritis outcome score

ME mean error of rigid body fitting

MTPM maximum total point motion

QOL quality of life

PG prostaglandin

ROM range of motion

RSA radiostereometric analysis, radiostereometry

SD standard deviation

TKR total knee replacement

VAS visual analogue scale

List of papers

This thesis is based upon the following papers, which will be referred to by their Roman numerals.

I. Parecoxib impairs early metaphyseal bone healing in rats Andreas Meunier, Per Aspenberg Arch Orthop Trauma Surg, 2006, 126(7): 433-6

II. Effects of celecoxib on blood loss, pain and recovery of function after total knee replacement. A randomized placebo-controlled trial Andreas Meunier, Björn Lisander, Lars Good Acta Orthop, 2007, 78(5): 661-7.

III. Celecoxib does not affect prosthesis fixation in total knee replacement. A randomized study using radiostereometry in 50 cases Andreas Meunier, Per Aspenberg, Lars Good Accepted for publication in Acta Orthop 2008 06 02

IV. Validation of a hemoglobin dilution method for estimation of blood loss Andreas Meunier, Annika Petersson, Lars Good, Gösta Berlin Accepted for publication in Vox sanguinis 2008 05 10

Thesis at a glance

Paper	Question	Material	Study design and Method	Conclusions
I	Does COX-2 inhibition impair metaphyseal bone healing?	70 rats	Randomised controlled trial, parecoxib administered via implanted minipump, pull-out force of a screw in tibial metaphysis	Yes, but only transiently
II	Does COX-2 inhibition affect clinical results after total knee replacement?	50 patients	Randomised controlled trial, placebo vs celecoxib during 3 weeks, blood loss, VAS pain, range of motion, KOOS	Early pain relief, no effects after 1 or 2 years
III	Does COX-2 inhibition affect fixation of total knee prosthesis?	50 patients	Randomised controlled trial, placebo vs celecoxib during 3 weeks, radiostereometry	No effects on prosthesis migration
IV	Is the Hb dilution method valid for estimation of perioperative blood loss?	39 blood donors	Observation study, measured blood loss vs estimated blood loss in blood donors	Low accuracy, low precision, blood volume stabilized day 6 after donation

Introduction

Cyclooxygenase, prostaglandins, and bone healing

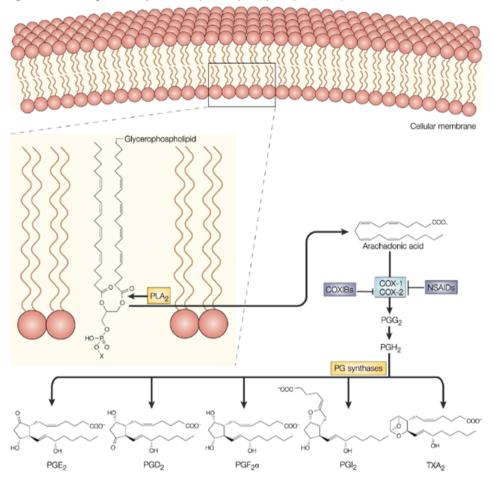
Cyclooxygenase (COX) inhibitors are a group of drugs that block enzymes which are required for the synthesis of prostaglandins. Different prostaglandins have various functions depending on their subgroup and in which cells they are synthesised. COX inhibitors reduce the synthesis of these mediators^{24,102}.

Phospholipids, for example those released from the cell membrane after tissue damage, are modified by phopholipase to form arachidonic acid. Subsequently, arachidonic acid is converted into prostaglandin H2 (PGH2)⁶⁴ by the 2 different isoenzymes of cyclooxygenase⁷⁸. Synthase enzymes then convert PGH2 into specific prostaglandins produced by that specific cell. Cycloxygenase type 1 is expressed constitutively 16 in many tissues and provides a homeostatic level of prostaglandins in specific tissues such as the mucosa¹¹² or in thrombocytes⁸ (Figure 1). Cyclooxygenase type 2 is inducible⁴⁴ which means that production of the enzyme increases by increased transcription from the gene after different stimuli, such as tissue damage⁶⁹ or other pro-inflammatory stimuli like cytokines or growth factors^{44,68,109}. Hence, cells that have mechanisms to activate COX-2 transcription, for example osteoblasts, osteoclasts, and soft tissue cells, can rapidly increase PGH2 production 16,44. PGH2 can then be converted to PGE2 and other prostaglandins. PGE2 has many effects, mainly on pain and inflammation⁷⁶, but also on bone and soft tissue healing¹³. It stimulates both bone formation and resorption by effects on growth and differentiation of osteoclasts and osteoblasts⁴⁶. Accordingly, if COX-2 is inhibited, pain is reduced, but the bone healing process may also be disturbed.

Recently, PGE2 receptor agonists have been developed as a future treatment option to stimulate local bone formation and enhance fracture healing⁵⁰. These substances work on the PGE2 receptors EP 2^{12,71} or EP 4^{56,106}, which have some specificity for bone, and illustrate the important role of PGE2 in fracture healing.

Unspecific COX inhibitors (non-steroidal anti-inflammatory drugs; NSAIDs) have been used for many years as analgesics or anti-inflammatory drugs. These older drugs inhibit both the COX-1 and COX-2 isoenzymes, resulting in perturbation of the homeostatic PG levels and thereby unwanted side effects like gastrointestinal ulceration or thrombocyte dysfunction with prolonged bleeding time. This may also necessitate discontinuation several days before major surgery^{22,105,113}. Selective COX-2 inhibitors have been designed to avoid negative effects of COX-1 inhibition on hemostasis and gastric mucosa, while maintaining analgesic and anti-inflammatory effects. In meta-analyses, COX-2 inhibitors seem as effective as traditional NSAIDs but better tolerated^{20,62,75,95}. Because of their lesser side effects compared to nonselective COX inhibitors and opioids^{12,47} and an active introduction campaign, selective COX-2 inhibitors, such as parecoxib and celecoxib, quickly became widely used in postoperative pain management.

Figure 1: Prostaglandin synthesis (PLA₂: phospholipase A2)³⁰



Nature Reviews | Cancer

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COX-2 inhibitors have also been increasingly used in orthopaedic surgery in spite of their potential negative effects on bone healing. Several authors^{4,17,23,25,117} have recommended caution in the use of COX inhibitors when bone healing is essential.

Animal studies have shown that COX inhibitors delay bone healing in diaphyseal fracture models ^{93,99,118}. Prostaglandin supplementation was shown to be essential for mesenchymal cell differentiation during skeletal repair in studies of mice homozygous for a null mutation in the COX-2 gene ^{101,118}. The histology of the fractures in the COX-2-null mice showed a persistence of undifferentiated mesenchyme and a marked reduction in osteoblastogenesis, resulting in a higher rate of non-unions.

Although many animal studies have demonstrated the negative effects of COX inhibitors on fracture healing in animals^{39,93,99,118}, studies on bone healing in humans give diverging results. COX inhibitors inhibit heterotopic bone formation after hip prosthesis surgery^{87,93,110} whereas selective COX-2 inhibitors are as effective as non-selectives⁸⁷. They also appear to delay bone healing in diaphyseal fractures^{9,26} as demonstrated in patients with concomitant acetabular fractures⁹, but no effects were found on metaphyseal distal radius fractures². Two studies have shown delayed healing after spinal fusion^{27,79}, while others did not find adverse effects^{40,54,81}.

COX inhibitors and joint replacement

The effect of selective COX-2 inhibitors on the bone healing process may also be relevant for the initial fixation of cemented or cement-less joint arthroplasties. When a joint prosthesis is implanted, a repair process starts because of bone damage ⁴⁸. This is essentially fracture repair in metaphyseal bone. It is unclear to what extent this process is influenced by COX inhibitors. If this process is disturbed, the prosthesis might never become rigidly fixed to the bone, leading to migration and, with time, aseptic loosening. Although not statistically significant, an increased number of revisions were found in a 10-year follow-up of patients who received a COX inhibitor as heterotopic bone prophylaxis in conjunction with total hip replacement ⁷⁴. On the other hand, COX inhibitors are effective analgesics, may reduce the inflammatory response to surgery, and have been shown to increase the range of motion in the early phase of rehabilitation ⁸³. Therefore COX inhibitors may also have the potential to permanently increase the objective and the subjective outcome after total knee replacement (TKR).

Safety of COX-2 inhibitors

In 2004 rofecoxib was withdrawn because of increased risk of myocardial infarction^{7,18}. Since then it has been debated whether this adverse effect is specific for rofecoxib or a class effect of COX-2 inhibitors. In a meta-analysis conducted by White¹¹⁴ from 2003, involving nearly 32,000 patients, celecoxib was associated with a lower risk of serious cardiovascular thrombotic events compared to paracetamol (relative risk 0.9). In contrast, another recent meta-analysis conducted by Caldwell¹¹, involving about 13,000 patients, showed an increased risk for myocardial infarction with celecoxib (odds ratio 2.3), but no increased composite risk for stroke, cardiovascular events, or cardiovascular death. The differences in findings between the two studies might be explained by different meta-analysis search strategies or differences in celecoxib dose. Most patients in White's analysis were assigned to 200 - 400 mg celecoxib, whereas in Caldwell's analysis they were assigned to 800 mg.

Blood loss estimation

Due to their known effects on thrombocyte function, COX inhibitors would be expected to influence blood loss at surgery. The true blood loss is underestimated if only intraoperative blood loss and drainage blood is measured, as the hidden blood loss in the tissue or joint is not taken into account ^{97,98}. Therefore, a common way to estimate perioperative blood loss is to

use a formula based on the decrease in hemoglobin (Hb) concentration by dilution ^{28,41,42,52,53,55,58,60,89,97,98}, as well as to estimate the need for transfusion in other clinical settings⁶. The dilution method is simple, inexpensive, and non-invasive. The blood volume of a patient is calculated taking sex, weight, and height into account. Different formulae can be used, for example based on the height and body mass⁶³ or based on the body surface area⁷³. It is assumed that the blood volume after an acute blood loss is rapidly restored by redistribution of extravascular fluid to the intravascular space, which leads to a dilution of Hb. Hence, the blood loss can theoretically be calculated by the decrease of Hb concentration comparing the value before and after the blood loss.

However, in order to correctly calculate blood loss, the patient must be strictly normovolemic. Several studies have demonstrated that the blood volume is not fully normalised within a few days after an acute blood loss^{1,31,111}. Yet, in most studies evaluating perioperative bleeding, the Hb concentration has been analysed on the second to fourth day after surgery. In spite of being widely used, the Hb dilution method has, to our knowledge, never been validated.

General aim of the thesis

The main purpose was to study potential positive and negative effects of COX-2 inhibitors during and after joint replacement.

Specific questions addressed in the thesis

Does parecoxib, a selective COX-2 inhibitor, affect bone healing in metaphyseal bone? (I)

Does celecoxib administration put knee prosthesis fixation at risk? (III)

Does celecoxib, given during the postoperative phase, improve long-time subjective outcome? (II, III)

Does celecoxib affect blood loss during and after TKR? (II)

Is the hemoglobin dilution method valid to estimate a moderate blood loss? (IV)

Material and methods

Assessment of metaphyseal bone healing in rats

We used an animal model (study I) applying stainless steel screws in metaphyseal bone of the proximal tibia of Sprague Dawley rats. This model is well tested to monitor bone healing processes in metafyseal bone ^{103,104,108}. A 10 mm longitudinal incision was made along the right tibia. The periosteum was reflected towards the epiphysis. A hole was drilled through one cortex into the cancellous metaphyseal bone of the proximal tibia (Figure 2).

Figure 2: stainless steel screw inserted in the metaphysis of the tibia



The screw was inserted and the skin was sutured. The rats were randomly allocated to either no treatment or continuous subcutaneous infusion of parecoxib by a mini-pump. The daily dose of parecoxib was 6.4 mg/kg body-weight. In humans, a dose of about 1mg/kg body-weight is the recommended maximum daily dose. The dose used is higher than the human dose in order to ensure a sufficient COX-2 inhibition and to compensate for the approximately 3 times higher metabolic rate in rats. The advantage of parecoxib compared to other COX-2 inhibitors is that it can be administered parenterally, which provides a more reliable dosage. After 7 or 14 days the rats were sacrificed and the tibia harvested.

The screw was tested for pull-out strength in a computerized materials testing machine (Figure 3) at a speed of 0.2 mm/s. Force at failure, stiffness, and energy at 10 % drop of the curve were recorded.

Figure 3: tibia with screw placed in the materials testing machine ready for pull-out test



We had expected to find a decrease in pull-out force following parecoxib treatment. However, our initial results showed no effect on the pull-out force of the screw after 7 days of treatment. We then learned that selective COX-2 inhibitors are metabolized more quickly in male rats compared to females⁷². As our initial study was conducted on male rats, we suspected that the dose was inadequate and decided to repeat the experiment using female rats. As we found an effect in female rats a third experiment on female rats, treated for 2 weeks, was undertaken in order to see how the effects on pull-out force developed over a longer period of time.

Patient selection

The study (II and III) was conducted from March 2004 through February 2005 at the Department of Orthopaedic Surgery, University Hospital in Linköping, Sweden. 50 patients suffering from osteoarthritis, who met the inclusion criteria below, were consecutively recruited from the waiting list for elective primary unilateral TKR. The inclusion criteria were: age 50 - 80 years, ASA I - II, and capacity to give informed consent. The exclusion criteria were: a history of coagulopathy or of a thromboembolic event, plasma creatinine > $100 \, \mu \text{mol/L}$ in women and > $115 \, \mu \text{mol/L}$ in men, acute infection, malignant disease, unstable angina, myocardial or cerebral infarction within 1 year before operation, and allergy to NSAIDs or sulphonamides. All ongoing NSAID therapy was discontinued 7 days before surgery and for 3 weeks postoperatively.

Assessment of pain

Patients were asked to rate their pain on a visual analogue scale (VAS) where 0 signifies "no pain" and 10 "worst possible pain". Rating followed the question "How much pain did you experience during the last week" for all measurements except those during hospital stay when the question "How much pain are you experiencing today?" was asked in the morning before rehabilitation exercises started.

Assessment of range of motion

Range of motion was measured after 4 repetitions of passive flexion (applied by the patient using a band around the ankle) and 4 repetitions of active extension (with the foot resting on a pad and the patient trying to reach maximum extension by quadriceps muscle activity). Measurements were conducted by one of two physiotherapists using a long handheld goniometer.

Blood loss estimation

Blood volume (BV) was estimated according to Nadler⁶³ as follows:

men: $BV(ml) = 0.0003669 \text{ x height}^3(cm) + (32.19 \text{ x body weight}(kg) + 604)$

women: $BV(ml) = 0.0003561 \text{ x height}^3(cm) + (33.08 \text{ x body weight(kg)} + 183)$

Blood loss was calculated according to the Hb dilution method⁵² as follows:

blood loss (ml) = BV x
$$(Hb_i-Hb_e)/Hb_i$$

Calculation of the expected Hb concentration after a known blood loss volume:

calculated
$$Hb_e = Hb_i - blood loss x Hb_i /BV$$

The expected decrease in Hb concentration (Hb_{decrease}) was calculated as follows:

$$Hb_{decrease} = Hb_i - Hb_e = blood loss x Hb_i /BV$$

where BV is the calculated blood volume (ml); Hb_i (g/L) = the Hb concentration before blood donation or surgery; Hb_e (g/L) = the Hb concentration at a given day after blood donation or surgery; blood loss (ml) = the estimated lost blood volume according to the Hb dilution method.

Assessment of subjective outcome

The knee injury osteoarthritis outcome score (KOOS)⁸⁸ was used to measure subjective outcome. This previously validated patient administrated score consists of in total 52 questions within 5 subscales: pain, symptoms, function in daily living (ADL), function in sport and recreation (Sport/Rec) and knee related quality of life (QOL). The last week is taken into consideration when answering the questions. Five standardised answer options are provided and each question is scored from 0 to 4. A normalised score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. The results are plotted as an outcome profile.

Radiostereometric analysis

Radiostereometric analysis is a method described by Selvik during the $70^{\circ}s^{100}$. Both the prosthesis and the bone in which it is fixed were marked with multiple tantalum balls, in our study 6 in each, thus forming 2 three dimensional rigid bodies (Figure 4). The knee was placed in a three-dimensional reference frame, which was also marked with multiple tantalum balls. Two X-rays, oriented approximately 90° from one another, were then simultaneously exposed. With help of software and computer assisted definition of the tantalum balls the technique has been improved to define movement between the two rigid bodies with a precision of about 0.05 to 0.1 mm in translation or 0.1- 0.2° in rotation planes^{5,38,65-67,70,90}. We

missed to perform double examinations^{5,32,45,67,77} to determine the precision of our RSA measurements, which may constitute a weakness in the analysis, but standard deviations of our measurements are in line with previously reported measurement precision and therefore a relevant imprecision of our measurements is improbable.

Figure 4: RSA x-ray images. Using both 0.8 mm and 1 mm tantalum balls, the markers can easily be identified in both the AP and the lateral view (balls in the tibia tray are marked with \leftarrow , reference balls in the proximal tibia are marked with *, and some of the visible balls from the reference frame round the knee are marked with +).



The index RSA x-ray was conducted on the second day after surgery, after weight bearing had been initiated. This served as a baseline for subsequent measurements of migration that were performed after 6, 12 and 24 months. The primary variable evaluated was maximum total point motion (MTPM) at 2 years. MTPM describes the vector length of the one tantalum ball in the tibial component with the largest migration, without taking the direction into account. Additionally, we measured rotation and translation of the rigid body formed by the tantalum balls in the tibial prosthesis in relationship to the reference body in the skeleton of the proximal tibia. Rotation about the x-axis denotes forward or backward tilting of the prosthesis, rotation about the y-axis denotes in- or outward rotation, and rotation about the zaxis denotes varus-valgus tilting. Accordingly, translation along the x- and z-axes denotes prosthesis movement in medio-lateral and anterior-posterior direction. Translation along the y-axis denotes subsidence or lift-off of the prosthesis. The tantalum ball position was determined using digital x-ray images processed with RSA software (UmRSA, Biomedial). If the mean error of the rigid body fitting exceeded 0.35 mm the software excluded the tantalum ball that caused the lack of rigidity in the rigid body, because this particular ball was judged not to be fixed in the rigid body anymore. Mean error for rigid body fitting in our study was 0.16 mm (SD 0.08 mm) for the proximal tibia and 0.13 mm (SD 0.06 mm) for tibial prosthesis.

The conditioning number (CN) is a gauge of measurement quality of the rigid body formed by the tantalum balls. The lower the CN the larger the volume of the rigid body formed by the balls and the better the measurement quality. If the CN exceeds 90, measurements are considered inexact and that particular x-ray is excluded from further evaluation. In our study CN for the proximal tibia was 19 (SD 3.6) and for the tibial prothesis 26 (SD 4). One patient with a CN of 135 at the 1-year RSA x-ray was excluded from evaluation.

RSA is used as a surrogate variable to estimate the risk of aseptic loosening. Ryd⁹¹ showed that prosthesis migration over 0.2 mm during the second year after TKR predicts the risk of revision. RSA has previously been used to detect improvement of initial prosthesis fixation when comparing groups with or without local or systemic treatment with biphosphonates³³⁻³⁵ in a study with similar design. Therefore this method should also be sensitive enough to detect possible effects of COX-2 inhibitors on initial prosthesis fixation.

Statistics

In study I, the groups of male and female rats were compared using a one-way ANOVA followed by Tukey's Multiple Comparison test. Because the three experiments were performed in sequence, each testing a new hypothesis, we consider it justified to analyze them separately.

In study II and III the primary endpoint was MTPM. The study was powered to detect a clinically relevant difference in MTPM of 0.2 mm, as suggested by Ryd et al. 91 . With α =5% and β =20% and the SD for MTPM from a comparable study 35 , a study size of 18 patients/group was calculated. To compensate for possible exclusion we chose to include 25 patients/group. MTPM at 24 months was analyzed using Student's t-test and the 95% CI of group differences. To avoid multiplicity-testing problems the secondary outcome variables are only reported descriptively as graphs or arithmetic means with the SD and with the 95% CI for group differences, with the exception of VAS pain where values had to be normalized by logarithmic transformation due to skewed distribution, which then showed similar means and standard deviations. In addition, Levene's-test was performed for segment motion to detect significant differences in SD. As segment motion can occur in 2 directions along the different axes, values can either be positive or negative making mean values poor measures of segment motion. SDs however are insensitive to direction; small SDs reflect small and high SDs large segment motion.

In study IV results are presented as arithmetic means with SD. For differences between calculated and measured values, a Student's t-test was performed.

Summary of results

Study I

Parecoxib impairs early metaphyseal bone healing in rats.

The aim was to investigate the effect of parecoxib on bone repair in a stable fixation model in metaphyseal bone in rats.

Pull-out force increased with about 50% during the first 1 to 2 weeks as a sign of bone healing around the screw. In male rats no significant effect on pull-out force was observed after 7 days between no treatment and parecoxib groups, possibly due to inadequate dosing because of a quicker metabolism of coxibes in male rats⁷². In female rats, however, parecoxib decreased the pull-out force by 16% at 7 days but after 14 days no significant effects were observed (Table 1).

Table 1: Pull-out force, study I

Treatment		n	Pull-out force (N)	р	95% CI for difference
Male rats 7 days	immediately tested	10	14.9 (SD2.7)	p<0.0001	12.8 to 30.1
	control	10	36.3 (SD 13.7)	ρ<0.0001	12.6 (0 30.1
	parecoxib	9	40.1 (SD 7.7)	ns	-6.3 to 15.6
Female rats 7 days	immediately tested	10	21.3 (SD 5.0)	p<0.001	12.9 to 26.4
	control	8	41.0 (SD 6.2)	·	
	parecoxib	8	33.6 (SD 6.0)	p=0.03	-14.5 to -0.2
Female rats 14 days	immediately tested	10	25.4 (SD 4.9)	p<0.001	18.8 to 45.4
	control	9	57.5 (SD 12.5)	p<0.001	
	parecoxib	10	55.1 (SD 15.9)	ns	-15.7 to 10.9

Study II and III

Celecoxib showed good effect on pain postoperatively but no effects on blood loss, recovery of function, or prosthesis fixation after total knee replacement.

The aim was to evaluate the effect of celecoxib on clinical parameters (perioperative blood loss, pain, range of motion, and subjective outcome after 1 and 2 years) and prosthesis

migration in a randomised placebo controlled study of 50 patients undergoing total knee replacement. Both groups had similar characteristics, although more males were randomly allocated to the placebo group (Table 2).

Table 2: Group characteristics of TKR patients in study II and III

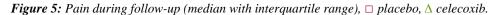
	Placebo (n=25)	Celecoxib (n=25)
Sex (Male/Female)	14/11	8/17
Age (years)(SD)	69 (8)	68 (6)
Weight (kg) (SD)	84 (12)	84 (13)
Height (cm) (SD)	173 (9)	169 (9)
Estimated blood volume (ml) (SD)	5056 (727)	4797 (752)
Time of surgery (min) (SD)	87 (11)	80 (9)

Celecoxib did not appear to increase total blood loss (placebo 810 ± 314 ml vs. celecoxib 733 \pm 316 ml, CI -264 ml to 110).

During the first month after surgery, celecoxib decreased VAS pain scores by approximately 30% and ketobemidon consumption by approximately 40% (placebo 10 ± 7 mg, vs celecoxib 6 ± 6 mg, CI -9.5 to -2.5 mg). Thereafter no effect on pain was found (Figure 5).

Independent of celecoxib, range of motion recovered rapidly in both groups during the first 3 months and then more slowly during the first but not the second year after surgery (range of motion segment defined as flexion minus extension: placebo $121 \pm 13^{\circ}$ vs celecoxib $123 \pm 13^{\circ}$, CI -6 to 10) (Figure 6).

Subjective outcome, as measured with the KOOS, increased dramatically after surgery during follow-up, independently of initial treatment with celecoxib. At 2 years postoperatively, scores increased with a factor of 2.2 for pain, 1.9 for symptoms, 1.8 for function in daily living (ADL), 3.7 for sport/recreation and 2.3 for quality of life (Figure 7 and Table 3a and b).



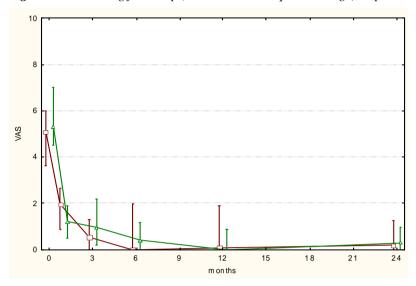


Figure 6: Development of range of motion during follow up (mean \pm SD), \square extension placebo, \square flexion placebo, \triangle extension celecoxib, \triangle flexion celecoxib.

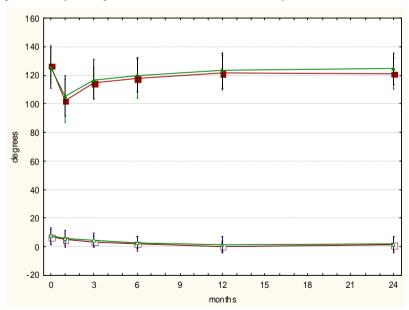


Figure 7: Mean KOOS values before and 2 years after TKR, \Box placebo baseline, \triangle celecoxib baseline, \blacksquare placebo 2 years, \triangle celecoxib 2 years.

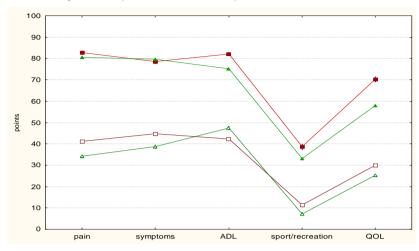


Table 3a: KOOS values before TKR

	Placebo Mean (SD)	Celecoxib Mean (SD)	difference	95% CI of difference
pain	40 (15)	35 (11)	5	-13 to 2
symtoms	44 (20)	38 (18)	5	-16 to 66
ADL	41 (17)	46 (19)	-5	-5 to 15
sport/recreation	11 (14)	7 (10)	4	-11 to 3
QOL	30 (11)	26 (10)	4	-10 to 2

Table 3b: KOOS values 2 years after TKR

	Placebo Mean (SD)	Celecoxib Mean (SD)	difference	95% CI of difference
pain	82 (21)	80 (20)	2	-14 to 9
symtoms	78 (17)	79 (16)	-2	-7 to 11
ADL	82 (17)	74 (23)	8	-19 to 4
sport/recreation	37 (31)	31 (24)	6	-22 to 10
QOL	70 (26)	57 (23)	13	-26 to 1

Celecoxib during 3 weeks after TKR did not increase prosthesis migration as measured with RSA. The MTPM at 2 years was similar in both groups (celecoxib: 0.39 mm (SD 0.16 mm), placebo: 0.39 mm (SD 0.18 mm), p=0.99, CI for group difference -0.09 to 0.1). In total 7/24 prostheses in the celecoxib group and 9/23 in the placebo group were classified as unstable (MTPM >2 mm between 1 and 2 years) with a few more outliers in the celecoxib group (Figure 8 and 9).

Differences in segment motion was negligible at 2 years (Table 4).

Figure 8: MTPM during follow-up, median (line) with interquartile range (boxes) and non – outliers range (whiskers), \square placebo, \blacksquare celecoxib, o Outliers (values 1,5-3-fold larger than the interquartile range), * Extremes (values >3-fold larger than the interquartile range).

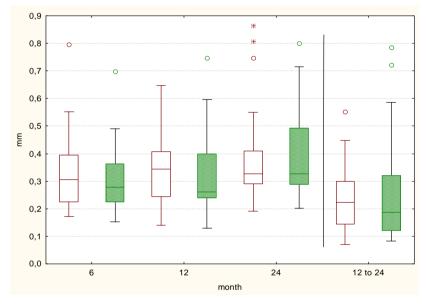


Figure 9: MTPM between 1 and 2 years, placebo, celecoxib

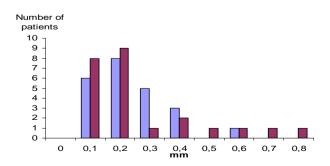


Table 4: MTPM (mm) and segment motion (rotation in degrees and translation in mm) at 2 years.

	Placebo Celecoxib		95% CI		Levene's test		
	mean	SD	mean	SD	Min	Max	р
MTPM	0.39	0.18	0.39	0.16	-0.09	0.1	0.97
Rotation x Anterior posterior tilt	-0.17	0.25	-0.17	0.17	-0.12	0.12	0.07
Rotation y Inward-outward rotation	0.15	0.24	0.19	0.19	-0.08	0.16	0.68
Rotation z Varus-valgus tilt	-0.04	0.19	-0.01	0.12	-0.06	0.12	0.16
Translation x Medial-lateral transl	0.02	0.04	0.00	0.05	-0.05	0.01	0.42
Translation y Subsidence - lift-off	0.04	0.10	0.02	0.08	-0.07	0.03	0.14
Translation z Anterior-posterior transl	0.02	0.08	0.02	0.05	-0.04	0.04	0.03

Study IV

The HB dilution method underestimates blood loss⁶¹.

The aim of this study was to validate the method of blood loss estimation used in study II. The tapped blood volume (442 ± 10 ml) of healthy blood donors was compared to the volume calculated according to the Hb dilution method using the Hb decrease at different time points after donation and the donors estimated total blood volume.

The results show that the Hb dilution method underestimates the true blood loss with at least 30% after a moderate blood loss of about 10% of total blood volume. The Hb concentration continued to decrease until day 6 after blood donation after which it increased slowly.

When the Hb concentration on day 1 was used, blood loss was calculated to be 152 ± 214 ml, an underestimation of the blood loss by more than 60% compared to the actual blood loss (p<0.00001). Using the Hb concentration on day 6, the blood loss was calculated to be 301 ± 145 ml which still is an underestimation of approximately 140 ml (32%) (p=0.0009) (Figure 11).

With an actual blood loss of 442 ml, the expected decrease in intraindividual Hb concentration was calculated to be 13.9 ± 1.8 g/l assuming full blood volume restoration. The observed decrease in intraindividual Hb concentration between day 0 and day 6 after blood donation was 9.8 ± 5.1 g/l (p=0.001, observed vs calculated value) (Figure 10).

Figure 10: Calculated Hb decrease after blood donation and observed intraindividual decrease in Hb concentration day 1-14 after blood donation. Each symbol represents mean \pm SD. \Box observed difference in Hb concentration before and after blood donation. \blacktriangle calculated decrease in Hb concentration based on blood donation volume and full volume restoration.

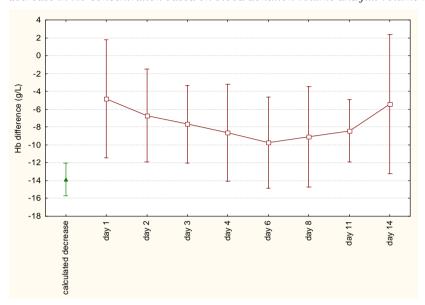
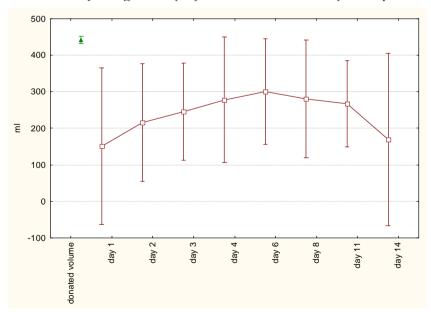


Figure 11: Actual donated blood volume (\blacktriangle) and calculated blood loss volume (\Box) using Hb concentration of the different days after blood donation. Each symbol represents mean \pm SD.



General discussion

The results of the investigations in this thesis suggest that celecoxib and presumably other COX-2 inhibitors can safely be used in knee prosthesis surgery. Modern perioperative pain management includes multimodular analgesics ^{15,80,96,116} where COX inhibitors play an important role not only in the reduction of prostaglandin stimulation of periphereal nociceptive receptors and inflammatory reactions, but also through direct analgesic effects on the spinal cord and central nervous system ^{92,116}. Similar to previous studies, our results do not suggest an increased risk of perioperative blood loss, such has been seen with non-selective COX inhibitors ^{10,49,83}. Although celecoxib might disturb bone healing at the interface between bone and cement after TKR, this does not lead to increased prosthesis migration as measured with RSA. Hence, COX inhibitors would not be expected to lead to an increased risk of future aseptic loosening.

Bone healing in metaphyseal bone

The inhibitory effect of selective COX-2 inhibitors on bone healing, demonstrated in diaphyseal fracture models in animals ^{93,99,102,118}, was only marginal and transient in our metaphyseal fixation model. The metaplastic membranous healing process that takes place in a stable fixation situation in metaphyseal bone differs from the bone healing process through endochondral bone formation in the diaphyseal fracture callus⁵⁷. In spite of that, experiments on COX-2 knock-out mice have demonstrated the essential effects of COX-2 on enchondral fracture healing as well as on metaplastic membranous bone healing in a calvaria model¹¹⁸. There are only few experimental studies dealing with the effects of COX inhibitors on metaphyseal bone healing or implant fixation. Osseointegration in a bone chamber in rabbits was reduced by rofecoxib²⁹, while the push-out interface shear strength of a titanium implant in a canine model was only reduced at 3 weeks during treatment with indometacin but not thereafter¹⁴. In humans, celecoxib has not been shown to affect osseointegration of cementless total hip stems⁵¹ nor porous-coated titanium or pure tantalum plugs that were inserted in connection with stage bilateral TKR³⁶. In summary, it appears that COX inhibitors have an inhibitory effect on bone healing, but in many situations this effect is transient and clinically irrelevant. If a stable implant fixation is achieved in surgery, the implant remains fixed to the bone during the vulnerable phase of the initially delayed bone healing process. It should be noted that the morphology of metaphyseal bone shows better healing conditions than that of diaphyseal bone. Metaphyseal bone has a large bone surface area, good blood circulation, and a higher metabolism with more osteoblasts and osteoclasts. Diaphyseal bone with its compact cortex has a lower turn-over and less blood supply. It is also well known from clinical experience that diaphyseal fractures more frequently present problems with delayed healing or non-union compared to fractures in metaphyseal bone.

Prostaglandins, particularly PGE-2, play a part in bone healing, not only by stimulating osteoblasts but also osteoclasts and bone resorption ^{18,46}, implying that COX inhibitors may also have an inhibitory effect on bone resorption ^{18,94}. This might diminish resorption of the initial bone necrosis at the interface between bone and cement that follows sawing and high temperature during cementation ⁴⁸. Therefore, the cement and the prosthesis may remain rigidly fixed to the trabecular metaphyseal bone while bone healing can advance to the

interface. Even if bone healing is reduced by COX inhibitors, it is not disrupted, and after discontinuation of treatment bone healing will progress normally^{24,101} unless non-union develops. COX-2 expression is high during the first 2 weeks after a fracture²⁵ and the PGE-2 level in normal fracture callus is high during the first week and then declines rapidly to the baseline level. Levels of PGE2 are decreased if a COX inhibitor (valdecoxib or celecoxib) is administered, but inhibition is only partial^{24,102}. Probably, regulation of COX-1 and COX-2 activity and thereby PGE-2 production is complex, involving also other enzyme systems³. In addition, prostaglandins, although important for stimulating osteoblastogenesis during the early phase of bone healing, are only one group in a myriad of different molecules important for bone healing. For example, bone morphogenetic proteins (BMPs) are a group of proteins that facilitate bone healing. Zhang 118 demonstrated in cell cultures of bone marrow cells lacking the COX-2 gene, that BMP-2 was a much more potent stimulator of osteoblastogenesis than restoration of PGE-2 levels alone. These experiments demonstrate that prostaglandins may play an important roll in the early phase of bone repair, but that other stimulating systems, for example BMPs, are more potent stimulators of continued osteoblastogenesis. In addition, pharmaceutical inhibition of COX-2 is only partial, leaving some production of prostaglandins that may be enough to maintain stimulation of osteogenesis. This may explain our findings both in rats⁵⁹, where an initial decrease in pullout force during COX inhibition disappeared at 2 weeks, and in TKR patients where a possible initial delay in bone healing following celecoxib treatment did not lead to increased prosthesis migration.

RSA and the risk of prosthesis loosening

Overall, prosthesis migration was small in this study and in line with results from other studies 35,37,38,66,67. About 30% of the prostheses in these studies and in our investigation would be classified as continuously migrating implants according to Ryd⁹¹, with a MTPM of more than 0.2 mm between 1 and 2 years. The accuracy of RSA as applied to knee arthroplasty has previously been defined to be 0.2 mm⁹⁰ while later reports demonstrate an even higher accuracy of between 0.1-0.2 mm^{37,66,67}. While most implants move somewhat during the first year, Ryd demonstrated that none of the implants that were defined as stable prostheses during the second year continued to move. Neither were they revised due to aseptic loosening later on 91. Migration of more than 0.2 mm after the first year was defined 91 to be the threshold value of increased risk of further aseptic loosening (based on the mean MTPM of the subgroup of prostheses with later revisions, minus 1 SD). This value was generated on the basis of in total 15 revised knees, of which 10 were revised within 4 years after initial surgery. In addition, the study group was heterogeneous, as it included both uni- and total knees, cemented and non-cemented prostheses, as well as several designs that are abandoned today (10 year revision rate: PCA total 4/33, Freeman-Samuelsson 10/32). Using modern prosthesis designs and cementation techniques it is not known where the crucial limit of prosthesis migration lies, which defines a higher risk of later aseptic loosening. As mentioned above, about 30% of modern knee prostheses would be defined as continuously migrating, according to current praxis, but the true 10-year total revision rate is only about 5% 85,86. Aseptic loosening is the cause of revision in only about 50% of these cases⁸⁶. Patients with a larger prosthesis migration probably do have a higher risk of late loosening, but the current cut-off level of 0.2 mm seems too low. To my knowledge the only data linking a high MTPM with definite loosening are Ryd's revision group (mean 3.3 mm at 2 years) and one case of definite

aseptic loosening from another study ⁶⁶ (9.4 mm at 7 months). In hip surgery, segment motion with a subsidence of more than 1.2 mm at 2 years was found to predict a high revision risk⁴⁵, but these data can not automatically be applied to TKR. Probably there is a relatively large group of prostheses with some migration that never become loose. In our study, there were a few more outliers with increased MTPM in the celecoxib group, but the SD of rotation and translation values were somewhat smaller than in the placebo group. Thus, all in all, our findings do not support increased prosthesis migration after celecoxib treatment. Moreover, the calculated CIs are narrow, less than the pre-specified minimal clinically relevant value of 0.2 mm. However, the study was powered to detect a difference in mean MTPM between the groups and not to detect a difference in the number of outliers. Perhaps, future mathematic techniques using frequency analysis in order to identify dichotomies will succeed in distinguishing between 2 different populations (migrators and non-migrators) to clarify where the threshold of increased migration and increased risk of loosening truly lies. Nevertheless, this requires a larger study sample than ours.

Range of motion and subjective outcome

COX inhibitors affect not only bone healing but also soft tissue healing. Based on somewhat conflicting results in previous studies, both positive and negative effects on clinical outcome following COX inhibitor treatment after TKR can be expected. Tissue culture from human tendons showed decreased cell proliferation with some COX inhibitors (naproxen and indomethacin) but no effects with others (diclofenac and aceclofenac)⁸⁴. Parecoxib impaired early tendon repair after Achilles tendon transection in rats, but improved later remodelling 115 while celecoxib decreased load at failure 2 weeks after transection of the medial collateral ligament in rats²¹. COX inhibitors have also been found to diminish intraperitoneal adhesion reformation in rats¹⁰⁷. If synovial adhesions are similarly inhibited, COX inhibitors may be beneficial in the prevention of arthrofibrosis following TKR. We expected to find a more rapid increase in range of motion in the TKR group treated with celecoxib, as was previously observed in the early phase of rehabilitation (1 month) with rofecoxib¹⁰. However, our results failed to demonstrate an increase in range of motion following celecoxib administration, both in the early phase of rehabilitation and after 2 years. We did not document pain in connection with initial rehabilitation exercises, neither did we document the use of additional COX inhibitors after the 3-week study period of treatment, nor how frequently and intensively physiotherapy was applied during follow-up. This of course is a weakness of our study and hence, it cannot be excluded that patients in the placebo group experienced more pain during rehabilitation and needed more intensive physiotherapy to achieve the same range of motion as patients in the celecoxib group.

Our findings of reduced pain scores and of a morphine sparing effect of celecoxib are consistent with previous reports on COX inhibitors as part of a multimodular postoperative pain management strategy ^{15,80,82,83,96,116}.

Blood loss estimation

Because bleeding also occurs after wound closure, blood loss is underestimated if only perioperative blood loss is measured^{28,98}. Total blood loss estimation by Hb dilution is an easy, non-invasive, and logical method.

A requirement for correct calculation of blood loss according to this method is a normalised blood volume. However, based on the findings of this study, the assumption that the blood volume is rapidly normalised after an acute blood loss, e.g. blood donation, appears to be incorrect. We found that after a moderate blood loss of 10% of the total blood volume, the true blood loss is underestimated by at least 30%. The Hb concentration in fact continued to decrease during the first 4 -6 days, but less than expected, reflecting a slow blood volume restoration. The lowest Hb concentration, caused by Hb dilution following redistribution of fluid from the extravascular to the intravascular space, was observed on day 6 after blood donation, but still at this point the measured Hb concentration was higher than that calculated from the donated blood volume. After day 6 the Hb level slowly increased, most likely due to increased erythropoiesis. Thus, compensatory erythropoiesis is likely to interfere with the estimation of blood loss by the Hb dilution method. All in all, our results suggest that a Hb decrease after surgery will never entirely reflect the true blood loss. Furthermore, the sooner after surgery the Hb analysis is made, the larger the underestimation of blood loss. We also found a relatively large SD of the difference between the true and the estimated blood loss volume. Therefore the method is not suitable for an exact calculation of individual blood loss.

A moderate blood loss of 10% of total blood volume is probably well compensated by mechanisms other than blood volume restoration, for example vasoconstriction. In TKR, blood loss is higher, about 20-30% (1000-1500 ml) of the total blood volume, and the patients are older implying that the mechanisms and extent of blood volume restoration may differ from those in our study. We prospectively followed the Hb concentration in a group of 18 TKR patients (data not presented) preoperatively until discharge from the hospital on day 4 after surgery and found the same pattern of continuously decreasing Hb values. Unfortunately we did not succeed to follow up Hb after discharge and therefore do not know when the lowest level was reached. In addition, we do not know the true blood loss or to what extent further bleeding occured in the wound postoperatively. Accordingly, it is more difficult to interpret these data than those from the well-controlled group of blood donors. The diurnal variation of blood volume of about 150 ml^{19,43} may imply that a minor blood loss (10%), such as that following blood donation, is relatively easily countered, but that a loss of 20-30% requires a larger proportion of volume compensation in order to ensure sufficient circulating volume. Thereby the underestimation of blood loss by hemodilution might be smaller after a moderate blood loss.

We conclude that the Hb dilution method is not suitable for calculation of the absolute blood loss volume, but can be used for a rough estimate. Although not suitable for individual blood loss calculation, the method may be used to compare groups of patients, assuming the degree of underestimation is the same in both groups.

Conclusions

In the rat model, we found only minor and transient effects of parecoxib on metaphyseal bone healing.

In humans, celecoxib did not show a clinically relevant effect on knee prosthesis migration as measured with RSA.

Pain was effectively reduced by celecoxib during the postoperative phase, but no effects were seen on range of motion or subjective outcome 1 and 2 years after TKR.

Celecoxib does not appear to affect blood loss during TKR.

The Hb dilution method is not suitable to estimate moderate blood loss in individuals, due to a systematic underestimation and a large interindividual variation. It may be useful when groups of patients are compared.

Although we did not observe any adverse effects on prosthesis fixation, COX inhibitors should be used with caution especially in patients with diaphyseal fractures or if other risk factors are present that may disturb fracture healing.

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