Perioperative Celecoxib Administration for Pain Management After Total Knee Arthroplasty – A Randomized, Controlled Study

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Abstract

Background
Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended for multimodal management of postoperative pain. We evaluated opioid-sparing effects and rehabilitation results after administration of perioperative celecoxib for total knee arthroplasty.

Methods
This was a prospective, randomized, observer-blind control study. Eighty patients that underwent total knee arthroplasty were randomized into two groups. The study group (n=40) received a single 400mg dose of celecoxib one hour before surgery, and 200mg celecoxib every 12 hours for five days, along with patient-controlled analgesic (PCA) morphine. The control group (n=40) received only PCA morphine for postoperative pain management. Visual analog scale (VAS) pain scores, active movement, total analgesic use and postoperative nausea/vomiting were analyzed.

Results
Groups were comparable for age, pre-operative ROM, operation duration and intraoperative blood loss. VAS pain scores significantly improved in the study group, at rest (p=0.002) or during activity (p=0.05). Active ROM also increased significantly in patients receiving celecoxib, especially in the first 72 hrs (p<0.001). Analgesic dosage decreased about 40% (p=0.03) in this group, while post-operative nausea/vomiting decreased about 15%. Celecoxib resulted in no significant increase in postoperative blood loss or the need for blood transfusion.
Conclusions

Perioperative celecoxib significantly improved pain scores, opioid consumption, and rehabilitation outcomes after total knee arthroplasty, without increasing the risk of bleeding.
Background

Pre-emptive analgesia which was introduced by Crile[1] is defined as an antinociceptive treatment which prevents pain before its onset. Preoperative analgesia is thought more effective than an equal post-operative dose. [2] Surgical trauma induces the synthesis of prostaglandins, which sensitize the peripheral nociceptors.[3] Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis both in the periphery and the spinal cord, therefore decreasing the post-operative hyperalgesic state.[4] NSAIDs have a proven 30-50% opioid-sparing effects [5, 6] and reduce postoperative nausea and vomiting (PONV) by 30%.[7]

However, the effects of perioperative administration of NSAIDs are still uncertain.[8-10] Some suggest that perioperative NSAIDs improve postoperative pain for ambulatory arthroscopic knee surgery [11] or spinal fusion surgery.[12] However, few papers have discussed perioperative NSAIDs effectiveness in pain management after total knee arthroplasty (TKA).[13, 14] Rofecoxib was chosen to be the perioperative coxib in previous studies. However, in September 2004, it was withdrawn from the market due to its thrombotic effects (especially myocardial infarction) and risks of colorectal cancer.

Celecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor and an effective analgesic for acute postoperative pain.[15] However, pre-operative NSAIDs increase the risks of bleeding.[10, 16] But celecoxib (1200mg daily) has no effects on serum thromboxane or platelet functions.[15] Celecoxib (400mg) also has similar analgesic effects in comparison with conventional NSAIDs.[17] We want to achieve less postoperative pain and better rehabilitation after TKA surgery, especially in the first week. Considering the risks and benefits, we prescribed oral celecoxib preemptively for pain management of TKA patients.
Methods

After institutional IRB approval, this study was performed (7/06 to 3/07). All total knee arthroplasty (TKA) surgery was performed by one surgeon. Under a randomized, prospective, observer-blind study design, subjects were randomized by random numbers. The study group (n=40) received 400mg oral celecoxib about 1 hr prior to surgery, and 200mg every 12 hrs, along with PCA morphine, over the first five post-operative days. The control group (n=40) received PCA morphine over the same postoperative period. All patients had spinal anesthesia and hemovac drain tubes inserted for postoperative blood loss evaluation. Patient data included gender, age, ROM, pain scores, blood loss and procedure duration. Pain scores, using VAS, were checked by the same observer at rest at 6, 12, 24, 48, 72 hrs and 7 days after surgery. We encouraged patients to ambulate 24 hrs after TKA. Pain scores at ambulation and active ROM were also analyzed. PCA morphine dose and PONV occurrence were also recorded. Exclusion criteria for this study were rheumatoid arthritis, end-stage renal disease, previous cerebral vascular accident history and peptic ulcers.

Demographics were analyzed by ANOVA or Chi-squared. Postoperative pain scores, postoperative ROM, morphine doses, blood loss, and PONV rates were analyzed by Mann-Whitney. We also used ANOVA to compare group differences in pain intensity and ROM. Significance was defined as p < 0.05.
Results

From July 2006 to March 2007, ninety-seven patients received elective TKA surgery by the senior author, in the author’s institute. Fifteen patients were excluded. Two patients suffered from epigastralgia, without tarry stool, during the study and were also excluded. This left a total of eighty patients. They were divided into two groups by random number. There were no significant differences between the groups in age, preoperative ROM, preoperative pain scores, operation duration and intraoperative blood loss (Table 1).

VAS pain scores

We noted postoperative VAS pain scores at rest (Fig 1) and during exercise (Fig 2). Figure 1 shows that the celecoxib group had less pain than controls at rest, reaching statistical significance at postoperative 48 (p=0.03) and 72 hrs (p=0.02). We encouraged patients to ambulate one day after surgery to reduce the risks of deep vein thrombosis and achieve better rehabilitation results. The celecoxib group had reduced postoperative pain at ambulation, but this was not significant when compared with controls. We used repeated ANOVA to analyze overall pain scores at rest or ambulation. The celecoxib group had significantly improved pain at rest (p=0.002) and ambulation (p=0.05).

Range of motion

Celecoxib significantly improved rehabilitation results, especially in the first three days (Day1: p=0.01, Day 2: p=0.004, Day 3: p=0.004) (Fig 3). This group also had increased active ROM of 12-15 degrees. They also had significantly improved postoperative ROM than controls (p<0.0001).
Morphine sparing effect and postoperative nausea and vomiting

The celecoxib group had significantly less demand for PCA usage (Fig 4). PCA usage during the first 24 hours was significantly lower (15.1 ± 8.7 mg vs 19.7 ± 9.6 mg; p=0.03). Total PCA morphine usage in the celecoxib group and controls were 17.6 ± 11.9 and 24.6 ± 14.6 mg, respectively (p=0.03). The celecoxib group used about 40% less morphine. Postoperative nausea and vomiting were at 28 and 43% in the celecoxib group and controls, respectively; but this did not reach significant level (p=0.57).

Bleeding

There were no significant differences in blood loss (181 vs 177ml) between the celecoxib group and controls, while hemovac was 544 vs 511 ml and blood transfusions were 3.85 vs 3.93 units, respectively.
Discussion

Perioperative administration of celecoxib, a selective COX-2 inhibitor, reduced postoperative pain intensity and morphine use while providing better rehabilitation results. It also did not differ significantly in bleeding and blood transfusion.

Previous studies have shown that preoperative NSAIDs increase bleeding risks.[16, 18] Conventional NSAIDs reversibly inhibit COX and interfere with platelet functions. Selective COX-2 inhibitors have lower antiplatelet effects than conventional NSAIDs.[19, 20] Celecoxib, in doses of 1200 mg/d, have no effect on serum thromboxane or platelet functions.[15] A single oral dose does not significantly increase intraoperative bleeding.[12] In this study, perioperative administration of 400mg of celecoxib had no significant effects on blood loss. We suggest that preoperative celecoxib is reasonably safe for TKA patients.

Coxibs are effective analgesics for post-operative pain.[21-23] To the best of our knowledge, the literature lacks a review of perioperative celecoxib for pain management in TKA patients. Perioperative coxibs reduce postoperative pain and analgesic consumption while enhancing patient satisfaction.[24] In 2000, Reuben and Connelly studied perioperative use of celecoxib (200mg) and rofecoxib (50mg) for spinal fusion surgery.[12] They concluded that both decrease morphine consumption, but that celecoxib’s effects are limited. We suggest that 400 mg of celecoxib is more optimal than 200 mg in controlling acute postoperative pain.[17, 24] We also demonstrate that perioperative celecoxib improves postoperative rehabilitation results. We encouraged our patients to perform straight leg rising exercises immediately after surgery and ambulation exercises, with walker assistance, as soon as possible. In the celecoxib group, mean knee ROM was at 92 degrees, 7 days after operation. Most patients could walk, climb stairs and rise their chairs before discharge.[25]

Less
postoperative pain and better rehabilitation results can increase patient satisfaction with TKA surgery.

NSAIDs are known to decrease opioid consumption by 30-50%. [7, 24, 26] In our study, perioperative celecoxib significantly lowered it by 40%. However, the effects of perioperative coxibs on side effects is still uncertain. [24] This study also showed reduced postoperative nausea and vomiting (28% vs 43%). However, the relationship between less opioid use and postoperative complications is still questionable. Further evaluation using a larger sample is called for.

Selective COX-2 inhibitors have less gastrointestinal toxicity than conventional NSAIDs. [27, 28] However, previous study also suggests that selective COX-2 inhibitors increase the risks of cardiovascular events, myocardial infarction, stroke and heart failure. [28, 29] White et al., demonstrated no significant increase in CV risks with celecoxib in comparison to placebo or traditional NSAIDs. [30] Moore et al., demonstrated that celecoxib had less gastrointestinal and cardiovascular risk than conventional NSAIDs and all other coxibs. [31] This study involved celecoxib for the first five postoperative days, and it did not seem to increase cardiovascular risks.

One limitation of this study is the lack of a placebo group. However, this study was prospective and randomized. The observer was blind to the results. Another limitation is the limited duration. We only recorded data for the first 7 days. We demonstrated that the better rehabilitation in the first week, but long-term efficacy is still in question. We will attempt to amend these weaknesses in the future.
Conclusions

Perioperative celecoxib, combined with opioids, is an effective and safe regimen for pain control in TKA patients. Perioperative celecoxib can significantly decrease postoperative pain and opioid use while improving rehabilitation results. Considering the costs and benefits, we suggest celecoxib for multimodal analgesia.
Competing interests

The author(s) declare that they have no competing interests.
Authors' contributions

YMH, CMW, WPL, and CCJ were responsible for the design of this study. LCH was the study evaluator and recorder. CTW provided analytical support. All authors read and approved the final manuscript.
Figures

Figure 1 - Pain scores at rest
The celecoxib group had significantly less pain on Days 2 and 3.

* : p value < 0.05, Error bar indicates standard deviation.

Figure 2 - Pain scores at ambulation
The celecoxib group had less pain than controls, but it was not significant.

Error bar indicates standard deviation.

Figure 3 – Range of Motion
The celecoxib group had significantly better active ROM, especially in the first 3 days.

* : p value < 0.05, Error bar indicates standard deviation.

Figure 4 – PCA morphine use
Mean PCA morphine use was significantly lower at each measurement for the celecoxib group.

* : p value < 0.05, Error bar indicates standard deviation.
Table 1 - Patient Demographics and Surgical Data

There were no significant differences between these groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Pre-OP ROM (degrees)</th>
<th>Pre-OP VAS (degrees)</th>
<th>Surgery Duration (mins)</th>
<th>Tourniquet Duration (mins)</th>
<th>Intra-operative blood loss (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>70 ±7</td>
<td>118 ±17</td>
<td>4.7 ±1.9</td>
<td>75 ±17</td>
<td>45 ±13</td>
<td>177 ±54</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>70 ±7</td>
<td>116 ±18</td>
<td>5.1 ±1.7</td>
<td>77 ±17</td>
<td>46 ±17</td>
<td>181 ±63</td>
</tr>
</tbody>
</table>
References


Figure 1

Mean VAS Pain Score vs. Postoperative time

- **Celecoxib**
- **Control**

![Graph showing Mean VAS Pain Score](image-url)
Figure 2

Mean VAS Pain Score vs. Postoperative days for Celecoxib and Control groups.
Figure 3

Mean Active ROM vs. Postoperative days

- Celecoxib
- Control

Significant difference indicated by asterisk (*)
Figure 4