Reviewer's report

Title: Evaluation of etoricoxib in patients undergoing total knee replacement surgery in a double-blind, randomized controlled trial

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Reviewer: Chong Bum Chang

Reviewer's report:

General comment

Although lots of studies regarding pain management after TKA have been published so far, the issue of optimal pain management after TKA is still controversial and deserves more and more studies to reach the ultimate goal. The current study focused on a COX-2 inhibitor which would be valuable as a component for TKA pain management, and its study design per se, i.e. double-blind, placebo- and active-controlled, randomized clinical trial, would be the best way to reveal the efficacy and safety of the drug. Nevertheless, several critical flaws can be found in this study, and the authors should properly address the flaws before considering acceptance of this study by the current influential journal.

1. Major Compulsory Revisions

* Methods section: Several critical flaws can be found. In addition, the method section looks redundant.

A. Patients

1) The major flaw of this study is in enrollment of patients from too many hospitals (63 sites) in about 17 different countries and consequent heterogeneous nature of the patients. Although the authors enrolled relatively a large number of patients (776 for randomization with 9.5% loss till completion of the study), due to involvement of too many sites the allocated number of patients in each site would be small, about 12 patients on average in each site. Pain perception after major surgeries can vary between the patients with different conditions including differences in gender, ethnicities, contributory diseases, surgical techniques, and health care environment in each country. Thus, to overcome these variations, the number (proportion) of patients allocated in each study group should be evenly distributed in each site. However, the number of placebo group, i.e. 98 subjects in 63 sites at the time of randomization, indicates that proper distribution of the study subjects in each site would not be made. The authors should mention the precise information on randomization method and the way of allocation of the study subjects.

2) Did the entire patients undergo TKA due to primary knee OA? If other contributory diseases, such as RA, Traumatic OA, osteonecrosis, or neuropathic joint, were included, were there any differences in the proportion of the diseases
between the groups?

B. Study design

The authors designed the study that the first dose of study medicine (oral form) was given in the recovery room. Was it possible for all study patients and accepted by all investigators involved in this study? Many patients received general anesthesia in this study. Although there is controversy, generally a considerable amount of complete fasting time is still applied to the patients undergoing TKAs under general and even spinal anesthesia. The authors need to mention the applied protocols regarding this issue.

C. Surgical procedure

1) Did the authors evaluate use of MIS technique and/or tourniquet in each site and in each group? Although controversial, these two can influence on the pain levels during the immediate postoperative period.

2) Were any other pain management methods, such as periarticular injection, not used for all patients?

D. Efficacy measurements and hypotheses ~ Safety analysis

1) I can easily expect that statistical specialists fully involved in this study and thus the statistical method seems to be perfect. However, it also seems to be complex. In particular, too many statistical analyses were performed for pain level per se. Considering the limitation of patient enrollment in this study, it would be better to simplify the statistical methods, especially for pain level analysis.

2) Due to too high power for pain level in this study, small difference in the pain levels between the groups (placebo vs. other group) may be considered as significant difference. To overcome this problem, assessment of patient satisfaction in each group would be helpful. Did the authors evaluate patient satisfaction in this study? If not, should be mentioned as a limitation of this study.

* Results section

I believe that the authors can make results section more simple and clear by adjusting the statistical analyses in this study.

2. Minor Essential Revisions

* Introduction (Background) section:

Should remove one of the duplicated periods just after the citation [6].

3. Discretionary Revisions

* Introduction (Background) section:

Information on etoricoxib and study purposes intermingled in the last paragraph of the introduction. It would be better to describe the information on the etoricoxib and the study purpose separately and more clearly for better understanding of this study by readers.

*Method section:
It would be better to move the sentence for hypothesis to end of introduction.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests