PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and Safety of Postoperative Intravenous Parecoxib Sodium Followed by Oral Celecoxib Post Total Knee Arthroplasty in Osteoarthritis Patients (PIPFORCE): Study Protocol for a Multicenter, Double Blind, Parallel-group Trial
AUTHORS	Zhuang, Qiangyu; Bian, Yanyan; Wang, Wei; Jiang, Jingmei; Feng, Bin; Sun, Tiezheng; Lin, Jianhao; Zhang, Miaofeng; Yan, Shigui; Shen, Bin; Pei, Fuxing; Weng, Xisheng

VERSION 1 - REVIEW

REVIEWER	DR DESPOINA SARRIDOU GUY'S AND ST THOMAS' NHS FOUNDATION TRUST LONDON UK
REVIEW RETURNED	12-Apr-2016

GENERAL COMMENTS	Initially it appears as a well organised in detail study. However there are multiple points that need to be clarified: 1. Are there any additional analgesics that need to be administered?? For instance acetaminophen or tramadol perhaps?? 2. What about the placebo group?? Apart from the morphine PCA what would be The additional analgesia management There are recent studies that payients were benefited by regional anaesthesia technigques such as continuous femoral block etc while in the mean time were randomised to a placebo group. Please use this kind of references and also clarify the above as there may be a strong no ethical conflict. 3. Please state clearly the exact times of the administration of iv parexoxib. Was there any loading dose of iv parexoxib given intraoperatively and at which point??? 4. Spinal anaesthesia with bupivacaine and levobupivacaine will have a different effect on the VAS score. It's appropriate to have only one LA for intrathecal use. 5. The pharmacodynamics and kinetics of parexoxib and eclecticism need to be presented more thoroughly it is the main drugs of the study. Other fields need to be reduced significantly in length. 6. Please minimise the size of paragraphs: 3.4.1 allocation to treatment 3.4.2.1 Drug preparation and administration

	3.4.4 Lifestyle guidelines- most of it totally irrelevant. 7. Recent papers suggest that parexoxib processes anxiolytic properties in patients undergoing TKA please incorporate more recent literature on the investigated drug properties 8. The anaesthetic technique is very important as it can affect VAS and poios consumption. The related paragraphe needs to be presented more thoroughly especially the use of midazolam and propofol that may have an opoios sparing effect for the first postoperative hours. 9. This is a study that has been run by Orthopaedic centres. What about the effect of a selective CO-2 inhibitor on the remodelling of the bones after TKA ?? Is this being investigated? Are there any concerns? In my experience there are surgeons that are really relactunt to use these drugs. 10. The results were not presented at all I really struggled to find tables or clear numbers or statistics in the text. Will they be presented on the article in the future?? Forgive me if I am wrong but his was not clear at all and it's probably the main weakness of the study. Please explain accordingly. 11. Please state what kind of opioids will be used post discharge from the hospital and who and how will be assessing the use and consumption by the patient. Are any other analgesics allowed post hospital discharge this are things that may be affecting again significantly the VAS, opioid consumption and ROM. 12. At which stage are the serum tests going to be performed ? Thank you

REVIEWER	Associate Professor Supranee Niruthisard, MD Department of Anesthesiology, Faculty of Medicine Chulalongkorn University King Chulalongkorn Memorial Hospital Bangkok 10330 THAILAND
REVIEW RETURNED	17-Apr-2016

GENERAL COMMENTS	1. In the abstact (Methods and Analysis) and 2.2 secondary objectives do not include the report of adverse events. 2. Trial registration number on page4 line 15 should also be presented on the footnote of the abstract. 2. Page 8: 3.4.1 Allocation to Treatment - Lackof details of surgical technics e.g., standard TKA or minimally invasive surgery. - Lack of details of anesthetic technics e.g., if failure of spinal anesthesia or inadequate duration of spinal anesthesia, patients with tourniquet pain. Technics of general anesthesia to continue the surgery? Use of opioid, ketamine, sedation, inhalation agents during (general) anesthesia? Or drop out from the protocol. - If oral tramadol even max dose could not give good rescue-pain

	control, how could you manage the pain? 3. Page 12 line 27: Antiemetics that can be confounding factors e.g. ondansetron line 36: Please clarify the PCA morphine setting: no loading dose, no background infusion? 4. Page 13 line 6: Please clarify the route of opioids used to compare the equinalgesic dose. The reference is mandatory. 5. Page 14. Each perameter should have references of reliability and validity. 6. The synovial fluid actually at this stage contains blood? 7. Page 18 line 56. Cumulative morphine use on Day14, not morphine? 8. Page 21 line 22. The current standard care for osteoarthritis is not the issue in this study. Opioids and NSAIDs play a part in the postoperative pain control after TKA. 9. Page 24. References 6 and 7 are not complete. 10. The details of limitations of this study is not well presented.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1:

We would like to thank Reviewer 1 for his/her kind encouragement, careful review and very useful comments.

Reviewer #1: Initially it appears as a well organised in detail study. However there are multiple points that need to be clarified:

Question 1(Q1): Are there any additional analgesics that need to be administered? For instance acetaminophen or tramadol perhaps?
Answer (A): We thank the reviewer for this question. In this study, except for celecoxib& parecoxib as the study drug and morphine& tramadol as drug for rescue therapy, no additional analgesic will be administered. Acetaminophen1 is not allowed to be used since it can inhibit cyclooxygenase-2 and thus influence the evaluation of inflammation-related endpoints.
References
1. Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. FASEB J. 2008 Feb;22(2):383-90.

Q2: What about the placebo group? Apart from the morphine PCA what would be the additional analgesia management? There are recent studies that patients were benefited by regional anaesthesia technigques such as continuous femoral block etc while in the mean time were randomised to a placebo group. Please use this kind of references and also clarify the above as there may be a strong no ethical conflict.
A: We thank the reviewer for this question. In placebo group, participants will be given tramadol as drug for rescue therapy. All subjects with a VAS equal to or more than 3 may take open-label oral rescue medication, tramadol 100mg each time as needed, not to exceed 400mg per day. Several previous studies1-2 have reported the results of comparison between parecoxib& celecoxib with placebo control, which demonstrated that participants in placebo group can have an acceptable pain control with morphine as the rescue treatment. In addition, our study design has gained ethics approval from the Ethics Committee, Peking Union Medical College Hospital, China.
As for continuous femoral block, although it has become an important option of multimodal analgesia strategy after TKA, it has the potentiality leading to lower extremities weakness and thus affecting knee function score evaluation. In addition, quality control of continuous femoral block procedure among different centers is also a big concern. Therefore, it was not adopted in this study.

References

1. Zhu Y, Wang S, Wu H, Wu Y. Effect of perioperative parecoxib on postoperative pain and local inflammation factors pge2 and il-6 for total knee arthroplasty: A randomized, double-blind, placebo-controlled study. European journal of orthopaedic surgery & traumatology : orthopedie traumatologie. 2014;24:395-401
2. Huang YM, Wang CM, Wang CT, Lin WP, Horng LC, Jiang CC. Perioperative celecoxib administration for pain management after total knee arthroplasty - a randomized, controlled study. BMC musculoskeletal disorders. 2008;9:77

Q3: Please state clearly the exact times of the administration of iv parexoxib. Was there any loading dose of iv parexoxib given intraoperatively and at which point???
A: We thank the reviewer for this suggestion and apologize for not making this clear. In this study, The first iv administration of parecoxib 40mg or placebo will be performed at the beginning of wound suture during the TKA surgery, followed by parecoxib 40mg or placebo every 12 hours for 3 consecutive days. (Please see line 36-39, page 10, in the 3.4.2.3. Administration part in the revised manuscript.)

Q4: Spinal anaesthesia with bupivacaine and levobupivacaine will have a different effect on the VAS score. It's appropriate to have only one LA for intrathecal use.
A: We apologize that we uploaded the early version instead of the final version at our submission, and we sincerely thank the reviewer for point it out. Our early version of study design originally planned to use spinal anesthesia, but it was changed to general anesthesia at our kick-off meeting because the anesthesiologists from 4 centers came to a consensus that GA does not exert postoperative analgesic effect while spinal anesthesia exerts prolonged analgesia. As a result, we confirmed GA as the anesthesia method in our final version protocol before the initiation of the study.
The GA protocol is as follows: Patients will be operated under general anesthesia (GA) with tracheal intubation. GA induction will be conducted with intravenous administration of 1-2 ug/kg sufentanil, 0.6-0.8mg/kg rocuronium, 0.02mg/kg midazolam, 4mg ondansetron and target-controlled infusion (TCI) of propofol at 4.0- 6.0μg/ml. GA will be maintained with propofol TCI at 3-5ug/ml and continuous infusion of sufentanil at 0.1-0.2ug/kg. Rocuronium and 1ug/kg of sufentanil will be given when necessitated. Parecoxib or placebo drug will be dripped at suture, and neostigmine plus atropine will be given as muscle relaxant reversal before extubation. Total amount of intraoperative sufentanil consumption will be documented at GA conclusion.
We have made corresponding correction in our revision according to our final version protocol. We apologized again for this fault. (Please see line 30-48, page 9, in the 3.4.1. Allocation to Treatment part in the revised manuscript.)

Q5: The pharmacodynamics and kinetics of parexoxib and eclecticism need to be presented more thoroughly it is the main drugs of the study. Other fields need to be reduced significantly in length.
A: We appreciate the reviewer for this constructive suggestion. Parecoxib (N-[[4-(5-methyl-3-phenyl-4-isoxazolyl) phenyl]sulphonyl]propanamide) is an injectable sulphonamide-based prodrug of the COX-2 inhibitor valdecoxib. It can be rapidly hydrolyzed in vivo to its active form, valdecoxib, which is approximately 28,000-fold more potent against COX-2 than COX-1. 1 Its chemical structure is shown in Figure 1. Following IV or IM injection, parecoxib is rapidly converted to valdecoxib, the pharmacologically active substance, by enzymatic hydrolysis in the liver. AUC and Cmax following twice daily administration is linear up to 50 mg IV and 20 mg IM. Following single IV and IM doses of parecoxib sodium 20 mg, Cmax of valdecoxib is achieved in approximately 30 minutes and approximately 1 hour, respectively. After IV or IM dosing of parecoxib sodium, the elimination half-life (t1/2) of valdecoxib is about 8 hours. 2
Figure 1. Chemical structure of Parecoxib
We have added the introduction and related discussion of the pharmacodynamics and kinetics of parecoxib in our revision. In addition, we also reduced the length of other parts of the protocol as the

reviewer requested. (Please see line 40-52, page20, in the 4. Discussion part of the revision.)
References
1. Parecoxib sodium for injection package insert. Approval date: May 23, 2008. Revision date Sep25, 2012.
2. Talley JJ, Brown DL, Carter JS, Graneto MJ, Koboldt CM, Masferrer JL, Perkins WE, Rogers RS, Shaffer AF, Zhang YY, Zweifel BS, Seibert K: 4-[5-Methyl- 3-phenylisoxazol-4-yl]-benzenesulfonamide, valdecoxib: A potent and selective inhibitor of COX-2. J Med Chem 2000; 43:775–7

Q6: Please minimise the size of paragraphs:
3.4.1 allocation to treatment
3.4.2.1 Drug preparation and administration
3.4.4 Lifestyle guidelines- most of it totally irrelevant.
A: We would like to thank the reviewer for this important suggestion. We feel sorry for having made these parts tedious and sometimes irrelevant. We have minimized the size of 3.4.1(Although we added details of surgical techniques and anesthesia techniques into this part, as another reviewer requested) and 3.4.2 and deleted 3.4.4 in the revision, as the reviewer suggested. (Please see the changes from line 25, page 8 to line 32, page 12 in the revised manuscript.)

Q7: Recent papers suggest that parecoxib processes anxiolytic properties in patients undergoing TKA. Please incorporate more recent literature on the investigated drug properties
A: We thank the reviewer for this insightful question. We did read several recent literatures1-2 which reported parecoxib may exert positive influence on pain and anxiety levels in patients undergoing TKA. However, our study design does not evaluate the anxiety levels as endpoints, which required further studies in the future to clarify. We have added relevant literatures of anxiolytic influence of parecoxib in the paragraph discussing the limitations of the study in the revision, as the reviewer requested. (Please see line 48-53, page 21 in the revised manuscript.)
References
1. Sarridou DG, Chalmouki G, Braoudaki M, Siafaka I, Asmatzi C, Vadalouka A.Parecoxib Possesses Anxiolytic Properties in Patients Undergoing Total Knee Arthroplasty: A Prospective, Randomized, Double-Blind, Placebo-Controlled, Clinical Study. Pain Ther. 2016 Feb 9. PMID:26861666
2. Vadalouca A, Moka E, Chatzidimitriou A, Siafaka I, Sikioti P, Argyra E. A randomized, double-blind, placebo-controlled study of preemptively administered intravenous parecoxib: effect on anxiety levels and procedural pain during epidural catheter placement for surgical operations or for chronic pain therapy.Pain Pract. 2009 May-Jun;9(3):181-94. PMID:19298364

Q8: The anaesthetic technique is very important as it can affect VAS and opoios consumption. The related paragraphe needs to be presented more thoroughly especially the use of midazolam and propofol that may have an opoios sparing effect for the first postoperative hours.
A: We apologize again for having uploading the early version instead of the final version at our submission. In fact, GA was confirmed as the anesthesia method in our final version protocol before the initiation of the study.
The GA protocol is as follows: Patients will be operated under general anesthesia (GA) with tracheal intubation. GA induction will be conducted with intravenous administration of 1-2 ug/kg sufentanil, 0.6-0.8mg/kg rocuronium, 0.02mg/kg midazolam, 4mg ondansetron and target-controlled infusion (TCI) of propofol at 4.0- 6.0μg/ml. GA will be maintained with propofol TCI at 3-5ug/ml and continuous infusion of sufentanil at 0.1-0.2ug/kg. Rocuronium and 1ug/kg of sufentanil will be given when necessitated. According to our protocol, midazolam and propofol are given only intraoperatively with no administration after the surgery, thus avoiding the potential opioid sparing effect for the postoperative hours. In addition, the 4 centers in this study will adopt the same anesthesia protocol (as presented above) and same anesthesia drugs to minimize difference among centers and ensure the comparability between the two study groups. (Please see line 30-48, page 9, in the 3.4.1. Allocation to

Treatment part and line 32-36, page 11 in the 3.4.2.6. Concomitant Medications part in the revised manuscript.)

Q9: This is a study that has been run by Orthopaedic centres. What about the effect of a selective CO-2 inhibitor on the remodelling of the bones after TKA ?? Is this being investigated? Are there any concerns? In my experience there are surgeons that are really relactunt to use these drugs.
A: We totally understand the reviewer's concern about the potential effects of selective COX-2 inhibitors on bone remodeling. However, there is no solid evidence till now to support that these drugs will inhibit bone remodeling and bone regeneration. For celecoxib, there are several studies1-3 which investigated celecoxib effects on bone remodeling and ingrowth process in short term (2 weeks) and long term (6 months) post TKA/THA, and found no overall difference with placebo. As for parecoxib, several animal studies4-6 revealed no significant effects by the drug on bone healing, though no parallel human research was conducted. Based on these evidences and our daily practice, we feel quite comfortable to use paracoxib and celecoxib. Bone remodeling issue will be recorded as AE, but not endpoint in this study.
References
1. Lionberger DR, Noble PC. Celecoxib does not affect osteointegration of cementless total hip stems. J Arthroplasty 2005;20(7):115-122.
2. Hofmann AA, Bloebaum RD, Koller KE, et al. Does celecoxib have an adverse effect on bone remodeling and ingrowth in humans? Clin Orthop Relat Res 2006;452:200-204.
3. Meunier A, Aspenberg P, Good L. Celecoxib does not appear to affect prosthesis fixation in total knee replacement: A randomized study using radiostereometry in 50 patients. Acta Orthop 2009;80(1):46−50.
4. Cai WX, Ma L, Zheng LW, Kruse-Gujer A, Stubinger S, Lang NP, et al. Influence of non-steroidal anti-inflammatory drugs (nsaids) on osseointegration of dental implants in rabbit calvaria. Clinical oral implants research. 2015;26:478-483
5. Utvag SE, Fuskevag OM, Shegarfi H, Reikeras O. Short-term treatment with cox-2 inhibitors does not impair fracture healing. Journal of investigative surgery : the official journal of the Academy of Surgical Research. 2010;23:257-261
6. Akritopoulos P, Papaioannidou P, Hatzokos I, Haritanti A, Iosifidou E, Kotoula M, et al. Parecoxib has non-significant long-term effects on bone healing in rats when administered for a short period after fracture. Archives of orthopaedic and trauma surgery. 2009;129:1427-1432

Q10: The results were not presented at all I really struggled to find tables or clear numbers or statistics in the text. Will they be presented on the article in the future?? Forgive me if I am wrong but his was not clear at all and it's probably the main weakness of the study. Please explain accordingly.
A: We feel sorry for not having made this clear enough and we truly appreciate the reviewer for pointing this out. As the title "Efficacy and Safety of Postoperative Intravenous Parecoxib Sodium Followed by Oral Celecoxib Post Total Knee Arthroplasty in Osteoarthritis Patients (PIPFORCE): Study Protocol for a Multicenter, Double Blind, Parallel-group Trial" indicated, we would like to submit our protocol first to be published as "Protocol" on BMJ-Open before the study is completed. We will present our data and statistical results as "Research" after the database is locked and clinical trial is completed. We have added explanation accordingly in our revised manuscript. (Please see line 25, page 21 in the 4. Discussion part of the revision.)

Q11: Please state what kind of opioids will be used post discharge from the hospital and who and how will be assessing the use and consumption by the patient. Are any other analgesics allowed post hospital discharge this are things that may be affecting again significantly the VAS, opioid consumption and ROM.
A: We thank the reviewer for this question. In this study, only tramadol will be used as rescue medication post discharge from the hospital. Doctor and research nurse will give the participants very thorough and clear education on how to take tramadol as rescue medication (all subjects with a VAS

equal to or more than 3 may take tramadol 100mg each time as needed, not to exceed 400mg per day), how to record on the patient diary, and how to return the left tramadol at each visit. They will also assess the use and consumption of the participants at each follow-up visit. No other analgesics will be allowed to taken by the participants post hospital discharge. (Please see line 16-26, page 12 in the 3.4.3 Rescue Therapy part in the revision.)

Q12: At which stage are the serum tests going to be performed ?
A: We thank the reviewer for this question. According to our protocol, the serum tests will be conducted at the following stages: 1. ESR and CRP at preoperative and at 72h, 2w, 4w and 6w post operation. 2. Peripheral blood cytokine (including IL-6, IL-8, IL-10 and PGE2) concentration prior to operation and at 24h, 48h,72h, 2w, 4w and 6w post operation. 3. Blood coagulation tests prior to operation and at 72h, 2w, 4w and 6w post operation. We have made the correction accordingly in the revised manuscript. (Please see line 32-42, page 13 in the 3.5. Outcome measures part in the revised manuscript)

Response to Reviewer 2:

We would like to thank Reviewer 2 for his/her careful review, useful comments and constructive suggestions.

Reviewer #2:

Q1: In the abstract (Methods and Analysis) and 2.2 secondary objectives do not include the report of adverse events.
A: We thank the reviewer for this important suggestion. Our secondary objective should include 1) To compare the effects of the sequential treatment versus placebo on pain relief, inflammation control and functional rehabilitation after TKA. 2) To investigate the safety of the sequential treatment with parecoxib and celecoxib versus placebo post TKA.
As safety endpoints in the study design, the nature, incidence, duration, and severity of adverse events; discontinuation due to adverse events; adverse events occurring during and after trial medication discontinuation; body weight, clinical safety laboratory, 12 lead ECGs, physical exams, and vital signs will be monitored.
We have made the correction accordingly in the abstract, 2.2 Secondary objective, and 3.5.3 Safety endpoints in the revision, as the reviewer requested. (Please see line 35-36, page 2; line 50-53, page 4; line 43-50 page 13 in the corresponding parts in the revised manuscript).

Q2: Trial registration number on page4 line 15 should also be presented on the footnote of the abstract.
A: We thank the reviewer for this suggestion, and we have added the Trial registration number on the footnote of the abstract as the reviewer requested. (Please see line 46, page 2 in the Abstract in the revised manuscript).

Q3: Page 8: 3.4.1 Allocation to Treatment
- Lack of details of surgical technics e.g., standard TKA or minimally invasive surgery.
A: We feel sorry that we didn't make it clear and we appreciate the reviewer for pointing it out. All the participants will undergo standard TKA on unilateral side under general anesthesia. A standard medial parapatellar approach was used through a midline skin incision, and a tourniquet was used which was inflated (280mmHg) following limb exsanguination immediately before skin preparation. Bone cuts and soft tissue balancing were done in the same sequence. The joint capsule and wound layers were closed in layers. A wool and crepe dressing was applied to the wound from mid-calf to

mid-thigh at which point the tourniquet was then released. (Please see line 21-29, page 9 in the 3.4.1. Allocation to Treatment part in the revised manuscript.)

- Lack of details of anesthetic technics e.g., if failure of spinal anesthesia or inadequate duration of spinal anesthesia, patients with tourniquet pain. Technics of general anesthesia to continue the surgery? Use of opioid, ketamine, sedation, inhalation agents during (general) anesthesia?
A: We apologize that we uploaded the early version instead of the final version at our submission, and we sincerely thank the reviewer for point it out. Our early version of study design originally planned to use spinal anesthesia, but it was changed to general anesthesia at our kick-off meeting because the anesthesiologists from 4 centers came to a consensus that GA does not exert postoperative analgesic effect while spinal anesthesia exerts prolonged analgesia. As a result, we confirmed GA as the anesthesia method in our final version protocol before the initiation of the study.
The GA protocol is as follows: Patients will be operated under general anesthesia (GA) with tracheal intubation. GA induction will be conducted with intravenous administration of 1-2 ug/kg sufentanil, 0.6-0.8mg/kg rocuronium, 0.02mg/kg midazolam, 4mg ondansetron and target-controlled infusion (TCI) of propofol at 4.0- 6.0μg/ml. GA will be maintained with propofol TCI at 3-5ug/ml and continuous infusion of sufentanil at 0.1-0.2ug/kg. Rocuronium and 1ug/kg of sufentanil will be given when necessitated. Parecoxib or placebo drug will be dripped at suture, and neostigmine plus atropine will be given as muscle relaxant reversal before extubation. Total amount of intraoperative sufentanil consumption will be documented at GA conclusion.
We have made corresponding correction in our revision according to our final version protocol, and we apologized again for this fault. (Please see line 30-49, page 9 in the 3.4.1. Allocation to Treatment part in the revised manuscript.)

Or drop out from the protocol. - If oral tramadol even max dose could not give good rescue-pain control, how could you manage the pain?
A: We thank the reviewer for the question. We will have no other choice but withdraw this patient from the study to guarantee the pain control quality and clinical safety, in case that even max dose of oral tramadol could not give good rescue-pain control. Cases who are withdrew from the study due to inadequate pain control with the study drug plus rescue drug will be recorded and later analyzed by statistician, as a parameter to evaluate the efficacy of study drug after the trial complete. (Please see line 18-22, page 8 in the 3.3.3. Withdrawal criteria part in the revision.)

3. Page 12 line 27: Antiemetics that can be confounding factors e.g. ondansetron.
A: We thank the reviewer for the question. According to our protocol, nausea, vomiting and administration of anti-emetics will be recorded as adverse effects. The dose and total number of doses of the anti-emetic treatment should be documented on the CRF and later analyzed by statistician after the study is completed. (Please see the line 43-45, page 11 in the 3.4.2.6. Concomitant Medications part in the revised manuscript.)

line 36: Please clarify the PCA morphine setting: no loading dose, no background infusion?
A: We feel sorry that we failed to present clear description of the patient control analgesia (PCA) regimen in our submitted version, which was as follows: Sixty milligrams morphine in 240ml normal saline (NS) will be prescribed for postoperative patient control analgesia (PCA). The background infusion rate of PCA is set at 4ml/hr, and 5ml bolus infusion is available with 15min lockout interval. A dosage limit of 60ml within 4hr is applied for preventing the potential adverse events. We have updated the PCA protocol in our revision. (Please see the changes from line 52, page 11 to line 5, page 12 in the 3.4.3 Rescue Therapy part in the revision.)

4. Page 13 line 6: Please clarify the route of opioids used to compare the equinalgesic dose. The reference is mandatory.
A: We thank the reviewer for this question. Intravenous (IV) PCA and oral tramadol will be used as

rescue treatment and their consumption will be calculated as morphine equivalents in statistical analysis. According to the previous literatures1-4, the converting of Tramadol to morphine equivalents is estimated as 300mg oral administered tramadol equals to 20mg of intravenous morphine. (Please see line 32, page 12 in the 3.4.3 Rescue Therapy part in the revision.)

References

1. Lee CR, McTavish D, Sorkin EM. Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. Drugs. 1993;46:313-340
2. Silvasti M, Svartling N, Pitkanen M, Rosenberg PH. Comparison of intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction. European journal of anaesthesiology. 2000;17:448-455
3. Hadi MA, Kamaruljan HS, Saedah A, Abdullah NM. A comparative study of intravenous patient-controlled analgesia morphine and tramadol in patients undergoing major operation. The Medical journal of Malaysia. 2006;61:570-576
4. Huang YG, Luo AL. Pain management drugs. ISBN-978-7-5062-8919-1. 2008.4

5. Page 14. Each parameter should have references of reliability and validity.

A: We thank the reviewer for this suggestion. All subjective parameters in 3.5 Outcome Measures (e.g. WOMAC, KSS, VAS, EQ-5D) 1-4 have been added the references of reliability and validity, as the reviewer requested. (Please see the changes from line 52, page 12 to line 19, page 13 in 3.5 Outcome Measures part in the revised manuscript.)

References

1. Symonds T, Hughes B, Liao S, Ang Q, Bellamy N. Validation of the chinese western ontario and mcmaster universities osteoarthritis index in patients from mainland china with osteoarthritis of the knee. Arthritis care & research. 2015;67:1553-1560
2. Liu D, He X, Zheng W, Zhang Y, Li D, Wang W, et al. Translation and validation of the simplified chinese new knee society scoring system. BMC musculoskeletal disorders. 2015;16:391
3. Brokelman RB, Haverkamp D, van Loon C, Hol A, van Kampen A, Veth R. The validation of the visual analogue scale for patient satisfaction after total hip arthroplasty. European orthopaedics and traumatology. 2012;3:101-105
4. Wang HM, Patrick DL, Edwards TC, Skalicky AM, Zeng HY, Gu WW. Validation of the eq-5d in a general population sample in urban china. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2012;21:155-160

6. The synovial fluid actually at this stage contains blood?

A: We thank the reviewer for this insightful question. Cytokines of synovial fluid, as one of the exploratory endpoints, will be tested in this study aiming to observe the trend of change of local inflammation. The synovial fluid tested after surgery is actually obtained from the wound drainage and indeed inevitably contains blood. However, we'll ensure that same technique is used to obtain the synovial fluid sample in both groups to guarantee the comparability. In addition, we will also observe peripheral blood cytokines as reference. We added related discussion in the paragraph discussing the limitations of the study in the revised manuscript. (Please see the changes from line 52, page 21 to line 5, page 22 in the 4. Discussion part of the revision.)

7. Page 18 line 56. Cumulative morphine use on Day 14, not morphine?

A: We feel sorry for not having made this clear enough and we truly appreciate the reviewer for pointing this out. We actually calculated the sample size based on the predicted difference of "Cumulative opioid consumption" as the primary endpoint (expressed by morphine equivalent) on Day 14 between two groups, which is used as the estimated effect size during the calculation. We have made the correction in the revised version. (Please see line 46, page 17 in 3.11. Sample Size Determination part in the revision manuscript.)

8. Page 21 line 22. The current standard care for osteoarthritis is not the issue in this study. Opioids and NSAIDs play a part in the postoperative pain control after TKA.
A: We totally agree with the reviewer's comments and apologize for not making it clear in our discussion. Actually, multimodal analgesia is currently recommended for postoperative pain control after TKA.1-4 It basically refers to the administration, via the same route or by different routes, of multiple analgesics to provide superior analgesia and limit side effects and adverse events. Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms (e.g., NSAIDs, opioids, and local anesthetics), resulting in additive or synergistic analgesia, lower total doses of analgesics, and fewer side effects.2,3 Among Multimodal analgesia modalities, NSAIDs, especially Selective cyclo-oxygenase-2 (COX-2) inhibitors play an important part in the postoperative pain control after TKA. 4 (Please see line 11-24, page 20 in the 4. Discussion part of the revision.)
References
1. Elmallah RK, Cherian JJ, Pierce TP, Jauregui JJ, Harwin SF, Mont MA. New and common perioperative pain management techniques in total knee arthroplasty. The journal of knee surgery. 2016;29:169-178
2. Baratta JL, Gandhi K, Viscusi ER. Perioperative pain management for total knee arthroplasty. Journal of surgical orthopaedic advances. 2014;23:22-36
3. Webb CA, Mariano ER. Best multimodal analgesic protocol for total knee arthroplasty. Pain management. 2015;5:185-196
4. Barrington JW, Halaszynski TM, Sinatra RS, Expert Working Group On A, Orthopaedics Critical Issues In H, Knee Replacement Arthroplasty FT. Perioperative pain management in hip and knee replacement surgery. American journal of orthopedics. 2014;43:S1-S16

9. Page 24. References 6 and 7 are not complete.
A: We thank the reviewer for pointing this out. The references 6 and 7 were just published ahead of print without page number at our first submission. These two references have been edited in the revised manuscript. (Please see line 38-46, page 23 in the References 6 and 7 in the revised manuscript).

10. The details of limitations of this study is not well presented.
A: We feel sorry for not having presenting the potential limitations of this study, and we appreciate the reviewer for pointing it out. The limitations of the PIPFORCE study are listed as follows: Firstly, Since the 4 study centers of this multicenter RCT study are all from mainland China, the future results of PIPFORCE study should be explained with this concern and require further validation studies in data sets from other institutions outside of China. Secondly, PIPFORCE study does not investigate the long-term (e.g. >3 months) effects of the sequential treatment versus placebo on pain relief, inflammation control and functional rehabilitation after TKA. Thirdly, several recent literatures reported parecoxib may exert positive influence on pain and anxiety levels in patients undergoing TKA. However, our study design does not evaluate the anxiety levels as endpoints, which required further studies in the future to clarify. Lastly, cytokines of synovial fluid, as one of the exploratory endpoints, will be tested in this study aiming to observe the trend of change of local inflammation. However, the synovial fluid tested after surgery is actually obtained from the wound drainage and inevitably contains blood, which will compromise the test accuracy. We'll ensure that same technique is used to obtain the synovial fluid sample in both groups to guarantee the comparability. In addition, we will also observe peripheral blood cytokines as reference. (Please see line 17-23, page 3 in the Strength and limitations of this study part and changes from line 41, page 21 to line 5, page 22 in the 4. Discussion part of the revision.)

VERSION 2 – REVIEW

REVIEWER	DR DESPOINA SARRIDOU GUY'S AND ST THOMAS' NHS TRUST
REVIEW RETURNED	21-Jun-2016

GENERAL COMMENTS	It needs to be clarified whether acetaminophen will be included on the rescue analgesia and at what doses. Also the addition of the most recent literature with regards to the anxiolytic effect of parexoxib should not be included on the weaknesses of the study and it would be reflected better on the properties of the drug in pharmacology section. It is not necessarily a weakness that the above study will not investigate this affect like other researchers did. Hence it should be addressed deferent lt according to my opinion. Thank you.

REVIEWER	Supranee Niruthisard MD Department of Anesthesiology Faculty of Medicine, Chulalongkorn University Bangkok 10330, Thailand
REVIEW RETURNED	05-Jun-2016

GENERAL COMMENTS	1. The VAS score described in the study is not consistent. 2. Tramadol slow released preparation used in the study should be clearly mentioned. 3. The estimated equianalgesic dose of oral tramadol 300 mg and IV morphine 20 mg cannot be found in the references. For example, Lee CR, et al. stated that IV tramadol 50-150 mg was equivalent potency to IV morphine 5-15 mg for moderately severe acute pain. Others stated the comparison of the two drugs in sense of potency ratio of the IV loading dose (8.5:1- 25:1) and PCA dose (11:1-10:1) depending on the types and pain severity of surgeries. 4. Background infusion is generally not recommended for the opioid-naive patients. It also affect the outcome comparisons between the groups. Some patients may receive overdosage of morphine and still be calculated as the seemed-to-be appropriate primary outcome. 5. The withdrawn patients from the study because of inadequately pain control following the protocol should be clearly stated of the other pain treatments received. 6. I am confused with the sequence of the names of the authors. To my knowledge, the principal investigator is the first name of all the authors.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer 1:

We would like to thank Reviewer 1 for his/her kind encouragement, careful review and very useful comments.

Reviewer #1:
Question 1(Q1): It needs to be clarified whether acetaminophen will be included on the rescue analgesia and at what doses.
Answer (A): We thank the reviewer for this question. In this study, except for celecoxib & parecoxib as

study drugs and morphine& tramadol as drugs for rescue therapy, no additional analgesic will be administered. Rescue Therapy consists of only intravenous PCA in the first 24hs post surgery and following oral tramadol (100mg each time as needed, not to exceed 400mg per day). In case that maximal dose of oral tramadol could still not provide satisfying rescue-pain control, we will withdraw the patient from the study to guarantee the pain control quality and clinical safety. These patients will be shifted to NSAIDs or acetaminophen for pain treatment, and the details of altered treatments will be documented in the study.
Acetaminophen[1] is not included in the rescue analgesia since it can inhibit cyclooxygenase-2 and thus influence the evaluation of inflammation-related endpoints. We have added explanation accordingly in our revised manuscript. (Please see line 36-38, page 47 in the 3.4.3. Rescue Therapy of the revision)
References
1. Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. FASEB J. 2008 Feb;22(2):383-90.

Q2: Also the addition of the most recent literature with regards to the anxiolytic effect of parexoxib should not be included on the weaknesses of the study and it would be reflected better on the properties of the drug in pharmacology section. It is not necessarily a weakness that the above study will not investigate this affect like other researchers did. Hence it should be addressed deferent lt according to my opinion.
A: We thank the reviewer for this constructive suggestion. The most recent literature[1-2] revealed important findings that 40 mg of intravenous, even pre-emptively administered parecoxib alleviates the anxiety during perioperative period of TKA. Consequently, this led to better satisfaction scores and overall experiences for the patients, regarding pre- and post-procedural pain, as well as pre- and post- interventional anxiety. We have deleted the discussion of the anxiolytic effect of parecoxib in the limitation part, and added relevant discussion in the pharmacology section in the revision manuscript instead, as the reviewer suggested. We'd like to thank the reviewer for this insightful suggestion again. (Please see line 19-23, page 56 in the revised manuscript.)
References
1. Sarridou DG, Chalmouki G, Braoudaki M, Siafaka I, Asmatzi C, Vadalouka A.Parecoxib Possesses Anxiolytic Properties in Patients Undergoing Total Knee Arthroplasty: A Prospective, Randomized, Double-Blind, Placebo-Controlled, Clinical Study. Pain Ther. 2016 Feb 9. PMID:26861666
2. Vadalouca A, Moka E, Chatzidimitriou A, Siafaka I, Sikioti P, Argyra E. A randomized, double-blind, placebo-controlled study of preemptively administered intravenous parecoxib: effect on anxiety levels and procedural pain during epidural catheter placement for surgical operations or for chronic pain therapy.Pain Pract. 2009 May-Jun;9(3):181-94. PMID:19298364

Response to Reviewer 2:

We would like to thank Reviewer 2 for his/her careful review, useful comments and constructive suggestions.

Reviewer #2:

Q1: The VAS score described in the study is not consistent.
A: We thank the reviewer for pointing this out and apologize for this fault. In this study, we test VAS (0-10) prior to operation and at 24h, 48h, 72h, 2w, 4w and 6w post operation, with 0 point representing no pain and 10 points representing the worst imaginable pain. We feel sorry that we

have mistakenly mentioned the 100mm VAS scale, and we would like to apologize again. We have made corresponding corrections in the revision manuscript. (Please see line 23-26, page 48 in 3.5.2.2. Other secondary endpoints part in the revised manuscript).

Q2: Tramadol slow released preparation used in the study should be clearly mentioned.
A: We appreciate the reviewer for this suggestion. In this study, we use commercial product RYZOLT™ which is tramadol hydrochloride extended-release tablets, a centrally acting analgesic composed of a dual-matrix delivery system with both immediate-release and extended-release characteristics. The median time to peak plasma concentrations of tramadol and O-demethylated metabolite (M1) after multiple-dose administration of RYZOLT™ 200 mg tablets to healthy subjects are attained at about 4 h and 5 h, respectively. We have added related information in the revised manuscript. (Please see line 17-25, page 47 in the 3.4.3. Rescue Therapy in the revised manuscript).

Q3:The estimated equianalgesic dose of oral tramadol 300 mg and IV morphine 20 mg cannot be found in the references. For example, Lee CR, et al. stated that IV tramadol 50-150 mg was equivalent potency to IV morphine 5-15 mg for moderately severe acute pain. Others stated the comparison of the two drugs in sense of potency ratio of the IV loading dose (8.5:1- 25:1) and PCA dose (11:1-10:1) depending on the types and pain severity of surgeries.
A: We feel sorry that we didn't make it clear and we appreciate the reviewer for pointing it out. As the reviewer mentioned, several literatures [1-3] have come to the consensus that the potency ratio of IV tramadol to IV morphine is around 10:1. Furthermore, the anesthesiology textbook "Pain management drugs"[4] (Chinese Version)stated that 10mg IV morphine is equivalent potency to 100mg IV tramadol (consistent with the above literatures) and to 150mg oral tramadol. Based on this textbook and other references, we finally set that the converting of tramadol to morphine equivalents is estimated as 300mg oral administered tramadol equals to 20mg of intravenous morphine. The picture of the cover page and related pages of the textbook "Pain management drugs"[4] has been uploaded as "Supplement files for reviewer 2" since picture files are not allowed to be uploaded in the text of the "Author's response to reviewers". We sincerely thank the reviewer for taking the time and trouble checking the referenced picture, and genuinely hope that this will help illustrate our presented protocol.
References
1. Lee CR, McTavish D, Sorkin EM. Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. Drugs. 1993;46:313-340
2. Silvasti M, Svartling N, Pitkanen M, Rosenberg PH. Comparison of intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction. European journal of anaesthesiology. 2000;17:448-455
3. Hadi MA, Kamaruljan HS, Saedah A, Abdullah NM. A comparative study of intravenous patient-controlled analgesia morphine and tramadol in patients undergoing major operation. The Medical journal of Malaysia. 2006;61:570-576
4. Huang YG, Luo AL. Pain management drugs. ISBN-978-7-5062-8919-1. 2008.4

Q4: Background infusion is generally not recommended for the opioid-naive patients. It also affect the outcome comparisons between the groups. Some patients may receive overdosage of morphine and still be calculated as the seemed-to-be appropriate primary outcome.
A: We really appreciate the reviewer for this excellent question. In this study, all the TKA patients enrolled are estimated to be opioid-naive patients since opioid-tolerant patients will be excluded according to our exclusion criteria. Therefore, the even distribution of opioid-naive patients and the same PCA regimen adpoted in the two groups will lead to comparability. Moreover, according to our pilot study, each TKA patient consumed averagely 25-30 bolus(1mg/bolus) of morphine except for the background infusion(1mg/h), which make the possibility of overdosage due to background infusion nearly negligible. Furthermore, based on the observations of the patients enrolled in this study till

now, no clinical symptoms or signs of morphine overdosage have ever been observed. In summary, we hope that the reviewer can understand and agree with our PCA regimen, given the fact that any modification of PCA regimen in the middle of the study will definitely compromise the comparability between two groups.

Q5: The withdrawn patients from the study because of inadequately pain control following the protocol should be clearly stated of the other pain treatments received.
A: We thank the reviewer for this constructive question. In case that even maximal dose of oral tramadol could not provide good rescue-pain control, we may withdraw the patient from the study to guarantee the pain control quality and clinical safety. These patient will be shifted to NSAIDs or acetaminophen for pain treatment, and the detail of altered treatment will be documented in the study. We have added related description in the revised manuscript. (Please see line 19-21, page 43 in the 3.3.3. Withdrawal criteria part in the revised manuscript.)

Q6: I am confused with the sequence of the names of the authors. To my knowledge, the principal investigator is the first name of all the authors.
A: We thank the reviewer for this question. In this study, the first author Qianyu Zhuang, as the sub PI, wrote the first draft of the manuscript and contributed greatly to the design of the study. He is also responsible for the entire coordination and quality control of the study. Dr. Weng (the PI & corresponding author) regarded Dr. Zhuang as the most important contributor and thus decided the sequence of authors of the protocol as submitted. In addition, we also noticed that it is not uncommon that the most important contributor of the study, instead of the PI, was set as the first author in published BMJ Open.[1-2] We therefore hope the reviewer can understand our reasons and our arrangements of the author sequences.

References

1. Shin CH, Zaremba S, Devine S, Nikolov M, Kurth T, Eikermann M. Effects of obstructive sleep apnoea risk on postoperative respiratory complications: protocol for a hospital-based registry study. BMJ Open 2016,6:e008436.
2. Robins L, Newby J, Wilhelm K, Smith J, Fletcher T, Ma T, et al. Internet-delivered cognitive behaviour therapy for depression in people with diabetes: study protocol for a randomised controlled trial. BMJ Open Diabetes Res Care 2015,3:e000144.