Author’s response to reviews

Title: The Analgesic Efficacy and Safety of Peri-articular Injection Versus Intra-articular Injection in One-stage Bilateral Total Knee Arthroplasty: A Randomized Controlled Trial

Authors:

Kai-Yuan Cheng (ckymedicine@163.com)
Bin Feng (pumcfeng@163.com)
Hui-Ming Peng (penghuiming@139.com)
Yan-Yan Bian (bianyan4@163.com)
Lin-Jie Zhang (linjie0222@qq.com)
Chang Han (hanchanglc@gmail.com)
Gui-Xing Qiu (qiuguixingpunch@gmail.com)
xisheng weng (xshweng@medmail.com.cn)

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Author’s response to reviews:

Dear Martin Kaczocha,

Thank you for reviewing the manuscript “The analgesic efficacy and safety of peri-articular injection versus intra-articular injection in one-stage bilateral total knee arthroplasty: a randomized controlled trial(BANE-D-19-00701R1)”. I also appreciate it very much that the three reviewers made an elaborate review of our study and gave us valuable and informative comments and proposals! We carefully read the comments and made point-by-point responses in the following part.

Response for Professor Karim (Reviewer 1):

1. Indeed, the drainage tubes had multiple orifices in our study and all of the orifices were inside the articular cavity. We also add this point to the revised manuscript.

2. We were supposed to provide more detail towards this issue in our manuscript. In our hospital, we routinely performed ‘WATERTIGHT TEST’ in every single joint, during which the surgeon bent the knee again and again after closing the deep fascia of the knee to check the watertight condition of the area. And if fluids were leaking in somewhere, we would make more sutures to ensure the articular cavity was watertight.
Furthermore, according to the previous study[1], the timing of IAI or PAI also contributes to the analgesic efficacy. Therefore, we choose to give IAI after closing the deep fascia instead of giving IAI before surgery to make the timing of giving IAI more similar to that of PAI.

As we have confirmed in the 1st response, all of the orifices of the drainage tube were inside the articular cavity. We placed the drainage tube in the same direction and region inside the articular cavity in every single joint. Thus, giving IAI through drainage tube would ensure the repeatability and accuracy of the IAI procedure.

3. Thank you for commenting and that is an absolutely extraordinary point! Futures studies could be performed to compare the analgesic efficacy between the low volume method and high volume method. The result would be of great value for both orthopaedic surgeons and anaesthesiologists!

Dear Professor Hamaguchi (Reviewer 2):

1. As you mentioned in the comment, our background in the Abstract was too redundant. After discussing with all of the co-authors, now we have simplified the background and added more details of the result in the Abstract.

2. I fully agree with you that it is not easy to assess the pain score of two separate body area accurately, because in some way it is really difficult to distinguish the pain feeling from one side to another and identify the source of pain. However, in our study, the assessment of pain score seemed to work out comparably smoothly, maybe due to the clear difference of feeling between one knee joint and the other. It is quite common for patients to distinguish and complain about the pain of one joint or two joints. In previous studies involving simultaneous bilateral TKA[2], the assessment procedures were described without additional explanations towards the particularity of the assessment of pain score of two separate body areas.

3. Thank you for this advice which makes the article more scientific. According to a previous cadaveric study[3], the outer capsule is more abundant of innervation such as saphenous nerve and genicular nerves, while the inner synovium and articular cavity have fewer nerve distribution. Another histologic survey of human cadaveric knees performed by Jiranek et al.[4] elucidated the distribution of free nerve endings after hematoxylin and eosin staining. High concentrations of nociceptors were found in the medial and lateral retinacula, patellar tendon, pes anserinus, and meniscofemoral ligaments. The lowest concentration was seen in the central portion of the anterior cruciate ligament. The information above would consolidate the findings of our study.

4. We have consulted some native English speakers to polish the writing style and solve grammar problems of our manuscript.
Dear Professor Estèbe (Reviewer 3),

1. Any trials have to obtain IRB agreement in the very beginning. And there is no exception for our study. I apologized for our first manuscript didn’t provide the detail of IRB agreement. Although this study was posteriorly registered in Dec 2018, the IRB agreement was obtained in Oct 2016 and the evidence (in Chinese character) was in the Appendix.

2. We performed a priori power analysis based on the results of the previous studies to determine whether our sample size had sufficient statistical power. Although the previous literature did not report any difference towards this issue, we calculated the sample size according to the clinically minimal important difference of 1.3 [5] with the standard deviation of 2.0[6], using the 2-sided hypothesis test at an alpha level of 0.05 and a power of 90%. We did not perform the preliminary study. Our hypothesis is non-inferiority. However, the result indicated the significant inferiority of IAI compared with PAI.

3. Thanks for raising this paramount question. And we make an elaboration investigation on this. We made a mistake about VAS pain score and NRS pain score. It was NRS pain score that was used in our study. However, because our data of pain score did not comply with normal distribution or equal variance simultaneously, thus we did nonparametric tests, the results of which were not influenced by the type of data, regardless of continuous data or discontinuous data.

4. That is a good point. According to the previous literature, the duration of IAI action is commonly less than 48hrs[7]. However, since the hypothesis is the non-inferiority of IAI compared with PAI, we didn’t set up the placebo control group in our study. Therefore, only the efficacy between IAI and PAI could be compared. It is difficult to determine the accurate duration of IAI action in the study, especially in this multimodal analgesic regimen, where patient-controlled analgesia, intravenous and oral medication contributed to the overall analgesic effect and improvement of NRS pain score.

5. Since pain is a subjective experience, there is no single objective measurement to best characterize the extent of the problem or to evaluate treatment outcomes. In our study, the difference of observed pain score between two groups could be underestimated or overestimated, and on account of the ceiling effect in our study, there are no objective parameters to reflect the pain score such as morphine consumption. Therefore, the trial towards this issue based on unilateral total knee arthroplasty is still under investigation. We hope the outcomes of the trial of unilateral total knee arthroplasty would substantiate the current study. On the other hand, in our study, we only came to the qualitative conclusion that PAI had better analgesic efficacy than IAI instead of making a quantitative conclusion. To determine the accurate difference between the two techniques requires further research.

6. PAI or IAI typically involves the infiltration of a “pain cocktail” into the local tissues, the effects of which depend on several factors: type of analgesic, percentage of medication, additives or adjuncts, and density of nerve fibers or vascularity of the area to be injected. Multiple effective preparations of cocktail have been described in previous studies[8, 9]. At our institution, we chose the constituents disclosed in the manuscript: ropivacaine, fentanyl, adrenaline, flurbiprofen axetil and diprospan. At present, there are no optimal constituents of cocktail and the magic bullet may vary inside a country or even a hospital. Nevertheless, the aim of our study is to compare the analgesic efficacy between two
techniques of local infiltration analgesia in patients receiving total knee arthroplasty, where two groups used the same constituents of the cocktail. The outcome of the study would not be affected by the constituents of the cocktail.

7. The setting of the placebo control group would substantiate our study and we could know the duration time and the authentically analgesic effect of PAI or IAI when compared with the placebo control group. However, there are multiple previous studies to report the efficacy of local infiltration analgesia in total knee arthroplasty[10-12]. Thus, we consider it unethical to set up placebo control groups or control groups using techniques that we know to be inferior. In addition, the aim of this study was to compare the analgesic efficacy between two techniques of LIA. Thus, we did not design the placebo control group in the study.

The manuscript has been revised and the major revision portions were marked in green highlighting. We have consulted a native speaker to review and polish our manuscript. We hope it could be comprehended more fluently. I have uploaded the supporting data and hope it would work out.

I am looking forward to receiving your decision and comments. If you have any further question, don’t hesitate to contact us.

Sincerely,

Dr Xisheng Weng

References


