Peer Review File

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Reviewer A

1)Please clarify if the pain management providers were routinely providing genicular nerve ablations to patients prior to this study or if they had been specifically trained in this intervention prior to the study only.
2) Please clarify if opioid consumption post operatively in the outpatient setting was confirmed verbally with patients or if other modality was utilized to measure opioid consumption. Prior studies have utilized picture messages from patients to verify pill counts and the way it's currently written is unclear.
3) Was there a power analysis performed prior to this study to avoid the conclusions being attributed to a type II error?

Comment 1: Please clarify if the pain management providers were routinely providing genicular nerve ablations to patients prior to this study or if they had been specifically trained in this intervention prior to the study only.

Reply 1: Thank you for the insightful comments/clarification requests. Two of the three pain management providers had previous extensive clinical experience with both the cooled and traditional RFA procedures in the knee prior to the study. The other provider had previously used primarily traditional RFA procedures for management of knee pain associated with osteoarthritis. All three participated in training from the company sponsor for this study prior to study commencement in order to standardize techniques for both t-RFA and c-RFA.

Changes in the text: We have modified our text as advised (see page 6 line 20 - page 7, line 2).

Comment 2: Please clarify if opioid consumption post operatively in the outpatient setting was confirmed verbally with patients or if other modality was utilized to measure opioid consumption. Prior studies have utilized picture messages from patients to verify pill counts and the way it's currently written is unclear.

Reply 2: Picture messages would have been an excellent means of documenting opioid usage. In this study we utilized opioid diaries that were given to patients and verified by phone interview for patients discharged prior to day 3 and at week one and week 6, and by in-office interview at weeks 2 and 6 by research staff.

Changes to the Text: We have modified our text as advised (see page 9, lines 3-5).

Comment 3: Was there a power analysis performed prior to this study to avoid the conclusions being attributed to a type II error?

Reply 3: This study was designed primarily to detect differences in hospital length of stay, opioid usage, and total days to opioid cessation, numeric pain scores, and secondarily WOMAC scores. For simplicity, we powered the study based on expected changes in pain scores. An ad hoc power analysis was performed using a commonly used nomogram (Altman DG, Practical Statistics for Medical Research, Chapman and Hall, 1991) assuming a standardized difference of 0.82 (for pain scores a clinically significant difference of 2 was assumed, and based on prior RFA studies for OA a standard deviation of 2.4 was used), a power of 0.80, and an alpha level of 0.05, we determined a sample size of 45 (n=45) to be needed for each arm.

Changes to the text: We have modified our text as advised (see page 6, lines 6-10)

Reviewer B

Congratulations on the manuscript
Interesting article. It can help in surgical practice.
This manuscript is important for medical practice, since a procedure, such as Radiofrequency ablation prior to total knee arthroplasty, can be avoided, decreasing costs and the risk of complication.

Title:
- Appropriate.

Abstract:

- Put at the end of the introduction the objective of the work equal to the abstract.

Introduction:
- Too long, I suggest reducing it.
- Put at the end of the introduction the objective of the work equal to the abstract.

Methods:
- Appropriate

Results:
- Appropriate.

Discussion:
- Start with the main finding of the study.
- Interesting to put the limitations of the study in a separate section.

Conclusion:
- Preferably, write the same as the conclusion of the abstract.

Figure and Table legends:
- Appropriate.

References:
- Appropriate.

Thank you for the helpful comments. We have made significant changes accordingly.

Comment 1: Introduction:
- Too long, I suggest reducing it.
- Put at the end of the introduction the objective of the work equal to the abstract.

Reply 1: We have deleted the paragraph referencing outpatient TKA and removed the associated reference. This shortened the introduction and removed an unnecessary paragraph.

We also made significant changes, including the objective of the work, to the final paragraph in the introduction. The objective in the final paragraph of the introduction now matches the objective of the abstract.

Changes to the Text: We have modified our text as advised (see page 5, lines 13-19)

Comment 2: Discussion:
- Start with the main finding of the study.
- Interesting to put the limitations of the study in a separate section.

Reply 2: We now start the discussion with the main finding of the study. We deleted the first sentence of the first paragraph, thereby moving the main findings to the top of the first paragraph. We have also introduced a new subsection titled "Study Limitations".

Changes to the text: We have modified our text as advised (page 11, lines 6-11 and page 12, line 16)

Comment 3: Conclusion:
- Preferably, write the same as the conclusion of the abstract.

Reply 3: We appreciate this comment and have improved consistency between the final conclusion and conclusion of the abstract by writing the same sentence in both: "Radiofrequency of the genicular nerves prior to TKA did not affect opioid use, or time to cessation, pain, or WOMAC scores following TKA." We also added the following sentence to the abstract conclusion. "Current techniques of t-RFA and c-RFA of these specific genicular nerves preoperatively are not indicated as routine interventions to improve short term recovery after TKA."

Changes to the text: We have modified our text as advised (Page 13, line 21 - Page 14, line 3)

Reviewer C

We appreciate the helpful critique offered by this reviewer. The following responses will hopefully improve the clarity of the text.

Comment 1:

The authors describe a randomized double-blind study on the effect of RF prior to TKA on pain and the outcome of TKA. This is an important and timely topic considering the high number of TKAs performed yearly. I have, however, several comments
Abstract:
- mention timeline of follow-up: eg., 6 weeks post-surgery
- what is the primary outcome, what are secondary outcomes …

Reply 1:

We have mentioned the timeline of follow-up in the abstract. We felt it prudent to follow the participant cohort for up to a year to detect any unexpected complications. Since some theoretical complications may take quite some time to present (such as avascular necrosis) we elected to follow the cohort for up to a full year.
The primary outcomes of this study were directly related to the acute recovery period post-TKA. These were pain scores, narcotic usage and time to cessation, and hospital LOS. The secondary outcome is the WOMAC questionnaire.

Changes to the text 1: We have mentioned the timeline of follow-up in the abstract. We have also included the following sentence(s) in the abstract: "Participants were followed for a year to detect any unexpected side effects." (Page 2, line 13)

We edited a sentence in the Methods section of the abstract to read: "Primary outcomes included hospital length of stay (LOS), opioid consumption and cessation, and pain scores. Secondary outcomes included Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) measures." (Page 2, lines 10-12)

Comment 2: Introduction:
- The authors mention 'We hypothesized that both t-RFA and c-RFA would reduce pain, opioid usage, and functional scores in the short term after TKA, with c-RFA having a more significant.' Please specify the timing, what is short term? The follow up of the study is actually 1 year- which is not really short term..

Response 2:

Thank you for this important clarification. This study was designed and powered to primarily detect differences in outcomes in the first three months after TKA. Since the use of RFA at the time was relatively new in knees, there were some concerns that unforeseen complications may occur. We felt that since neural and vascular structures run adjacent to one another, the nerve ablation procedure may injure adjacent vascular structures and delayed infection or avascular necrosis may be encountered later in the recovery process. In order to detect these types of problems, we felt it prudent to follow all participants for a year after surgery. Fortunately, we did not encounter delayed complications in any of the groups.

Changes to the text 2:

In order to address this point, we have edited the entire last paragraph of the introduction to read, "The purpose of this randomized clinical trial was to determine the effects of c-RFA and t-RFA on three month clinical measures after TKA. We compared c-RFA and t-RFA to one another and to a sham procedure. We hypothesized that both t-RFA and c-RFA would reduce pain, opioid usage, time to opioid cessation, and WOMAC scores in the short term (three months) after TKA, with c-RFA having a more significant impact. To detect any unexpected complications or side effects from the procedure we followed patients for a year after TKA." (Page 5, lines 13-19)

Comment 3: Methods:

- The description of the multimodal analgesia should be done in a less chaotic manner. E.g., Analgesic care during TKA was anesthesiologist dependent and consisted of x% of patients undergoing locoregional anesthesia and x% receiving general anesthesia. X% received a single shot (or + catheter) nerve block. Postoperative (opioid) analgesics were prescribed in a standard manner to all patients after the operation etc …
- Describe if there were major differences in the TKA procedure between surgeons
- what is the primary outcome, what are secondary outcomes …
- the RFA is performed under general anesthesia: is this standard practice? It is arguably overshooting
- Which nerves were blocked during RFA?
- Describe in a more detailed manner the moments when the data was gathered e.g., Pre-study intervention, after study intervention (timepoint? Was it the day of surgery? or which day did you gather the 'pre-op' WOMAC?). Please elaborate all timepoints of data gathering.

- how was the sample size calculated? Based on which primary outcome?
- What was the statistical comparison plan: first comparison of (t-RFA & c-RFA) VS sham-procedure, and then c-RFA VS t-RFA? Would each RFA procedure be compared to placebo?
- Could patients receive IV morphine? As you mention that all Oral morphine is converted to MEQ, what about IV morphine?

Results & Discussion:

- where there statistical differences in the baseline characteristics of the 3 parallel arms?
- you mention that ‘ It is unclear if significant time variation from intervention to surgery has a substantive effect on the effects of RFA in the context of TKA.’ You could address this with a post-hoc subgroup analysis.

Response 3: We found the comments and questions presented by this reviewer extremely helpful. Since there were multiple questions/suggestions we will address each one individually with this response:

3A:- The description of the multimodal analgesia should be done in a less chaotic manner. E.g., Analgesic care during TKA was anesthesiologist dependent and consisted of x% of patients undergoing locoregional anesthesia and x% receiving general anesthesia. X% received a single shot (or + catheter) nerve block. Postoperative (opioid) analgesics were prescribed in a standard manner to all patients after the operation etc …

Response 3A: We see how the description of perioperative treatment could have been confusing to the reader in the prior submitted manuscript. Per this comment, we have edited/simplified this section.

Changes to the text 3A: We rearranged the description of the anesthesia to read, ” Anesthesia care during TKA was dependant on both an anesthesiologist and surgeon preferences and consisted of 28/139(20.1%) participants receiving a spinal anesthetic and 111/139(79.8%) receiving a general anesthetic augmented by a periarticular infiltration of local anesthetic. Eighteen participants 18/139(12.9%) received a single shot (adductor canal) nerve block. Peri- and postoperative analgesics were prescribed in a standardized manner to all participants including oral and IV opioids with a pain-dependent protocol.” (Page 7, lines 17-22)

3B:- Describe if there were major differences in the TKA procedure between surgeons

Response 3B: All three surgeons performed TKA in a similar fashion. All surgeons performed both cruciate-retaining and posterior stabilized knee arthroplasties at their sole discretion, and since there is not a consensus on which implant design is superior, this was not a variable that was considered important in data collection. Two of the three surgeons preferred a cruciate retaining implant design while the other generally preferred a posterior stabilized implant design. All knees in this study underwent patella resurfacing.

Changes to the Text 3B: We added a line representing the differences in the surgeons' preferences on page 7, lines 13-16.

3C:- what is the primary outcome, what are secondary outcomes …

Response 3C:
We edited a sentence in the Methods section of the abstract to read,"Primary outcomes included hospital length of stay (LOS), opioid consumption and cessation, and pain scores. Secondary outcomes included Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) measures."

Changes to the text 3C: We have modified our text as advised (page 2 lines 10-12).

3D:- the RFA is performed under general anesthesia: is this standard practice? It is arguably overshooting
- Which nerves were blocked during RFA?

Response 3D: This was reviewed and should have read, "RFA was performed under conscious sedation", not general anesthesia.

Specific geniculate nerves targeted in this study included the superior medial, inferior medial, and middle geniculate nerves (branches of the tibial n.), and superior lateral geniculate n (branch of the femoral n.)

Changes to the Text 3D:

- **Page 7 line 4 has been changed to reflect the use of conscious sedation.**

- **Page 5 lines 9-12: changes have been made to identify the specific nerves targeted with RFA.**

3E:- Describe in a more detailed manner the moments when the data was gathered e.g., Pre-study intervention, after study intervention (timepoint? Was it the day of surgery? or which day did you gather the 'pre-op' WOMAC?). Please elaborate all timepoints of data gathering.

Response 3E: Participant baseline numeric pain scores and WOMAC Scores were initially recorded by research staff on the date of enrollment in the study, prior to scheduling the RFA procedure. The study intervention (sham, t-RFA, or c-RFA) was performed between 3 and 12 weeks prior to the scheduled arthroplasty procedure.

Pre-TKA (after study intervention but prior to TKA) pain scores and WOMAC scores were recorded at a routine pre-TKA surgeon office visit. All data was collected independently and in a blinded fashion by research staff.

All inpatient pain scores and narcotic usage (both IV and PO) was obtained by review of hospital records and converted to oral morphine equivalents (MEQ).

Follow up records of narcotic usage, pain scores, and WOMAC scores were obtained by research staff by phone interview (postoperative day 3, week 1, week 12, and month 6) and at the time of routine office visit (post operative week 2, week 6, and month 12). A standardized pain/narcotic use diary was provided to the participants and used to determine accuracy of interviews and time to cessation.

Changes to the Text 3E:

We have introduced the above paragraph (Page 8, second paragraph) and deleted the previous description for clarity. We have also updated the methods section of the abstract. (Page 2, lines 6-14)

3F:- how was the sample size calculated? Based on which primary outcome?

Response 3F: This study was designed primarily to detect differences in hospital length of stay, opioid usage, and total days to opioid cessation and numeric pain scores and secondarily WOMAC scores. For simplicity, we powered the study based on expected

changes in pain scores. An ad hoc power analysis was performed using a commonly used nomogram (Altman DG, Practical Statistics for Medical Research, Chapman and Hall, 1991) assuming a standardized difference of 0.82 (for pain scores a clinically significant difference of 2 was assumed, and based on prior RFA studies for OA a standard deviation of 2.4 was used), a power of 0.80, and an alpha level of 0.05, we determined a sample size of 45 (n=45) to be needed for each arm.

Changes to the text 3F: We have modified our text as advised (see page 6, lines 6-10)

3G:- What was the statistical comparison plan: first comparison of (t-RFA & c-RFA) VS sham-procedure, and then c-RFA VS t-RFA? Would each RFA procedure be compared to placebo?

Response 3G: The primary and secondary outcomes and other relevant measures are compared among randomized groups based on one-way ANOVA, Kruskal-Wallis, or Fisher's exact tests, as appropriate. (Page 9, lines 9-11) For this study, each group was considered independent and compared to each other and to the sham procedure.

We considered a post hoc analysis combining both treatment arms and comparing them to the sham arm, but felt that this would have little meaning since it was not included in the original study design.

3H:- Could patients receive IV morphine? As you mention that all Oral morphine is converted to MEQ, what about IV morphine?

Response to 3H: Participants were prescribed IV morphine prn as part of the post operative standard analgesia plan. The original sentence should have read "all oral and IV opioids were converted to MEQ".

Changes to the text 3H: The following changes were made: "All inpatient pain scores and narcotic usage (both IV and PO) was obtained by review of hospital records and converted to oral morphine equivalents (MEQ) (16)." (Page 8, lines 21-22)

3I: Results & Discussion:
- where there statistical differences in the baseline characteristics of the 3 parallel arms?

- you mention that ‘ It is unclear if significant time variation from intervention to surgery has a substantive effect on the effects of RFA in the context of TKA.’ You could address this with a post-hoc subgroup analysis.

Response 3I: There were no statistically significant differences in the baseline characteristics of the three parallel arms. Table 1 lists the baseline demographics of each group (age, gender, and operative side) while tables 4 and 7 compare baseline numeric pain scores and WOMAC scores with 95% confidence intervals.

There wasn’t enough data, since time from RFA to TKA was a continuous variable, to perform a meaningful post hoc analysis on the effects of time between RFA and TKA to the measured outcomes. However, there has been evidence published since the inception of this project that indicated that the effects of RFA are more durable than previously thought (Lyman J, et al, 2022). It's likely that we could have avoided excluding participants who had delays in having TKA more than 12 weeks after RFA/sham.

Changes to the text 3I: We have modified the text as advised (Page 9, lines 19-20).