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OPEN PEER REVIEW

Comparison of Effectiveness and Safety of Oxycodone Hydrochloride and Fentanyl for Post-operative Pain Following Total Hip Arthroplasty: A Randomized Triple-Blind Trial

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1 Original submission

4 comments · 23 Dec 2023 – 29 Dec 2023

Referee 1 Reviewer

MINOR REVISION 23 Dec 2023

Dear Authors
Please fully describe the randomization and blinding procedure.
Preferably, the references should be from the last 5 years.
Explain the novelty of this manuscript.

Referee 2 Reviewer

MAJOR REVISION 27 Dec 2023

Dear AE,
- The manuscript mentions a triple-blind study design but lacks a detailed explanation of how blinding was maintained throughout the study, especially during the administration and assessment phases. This is vital to ensure the reliability of the results.

- The use of the VAS (Visual Analog Scale) is mentioned for pain assessment, but the manuscript should ensure that this assessment was consistently applied across all participants at all time points. This is crucial for the validity of the pain scores obtained.

- The rationale behind the chosen doses of oxycodone and fentanyl should be explained. The manuscript needs to clarify why these specific doses were selected and how they compare to standard dosages used in clinical practice.

- The design of the control group needs to be clear. For instance, if the fentanyl group is considered the control group, the manuscript should discuss why this is an appropriate comparator.
- The impact of comorbidities and the use of concomitant medications on pain management and drug efficacy should be addressed. This information is crucial to understand the study's applicability to patients with varying medical backgrounds.
- More detailed data on the use of rescue analgesia (if any) and its impact on the study's outcomes should be provided. This is important for understanding the overall effectiveness of the pain management strategy.

Addressing these additional aspects would further enhance the quality and comprehensiveness of the study, providing a clearer understanding of its implications in the field of pain management after total hip arthroplasty.

Associate Editor

MAJOR REVISION 29 Dec 2023

Dear EIC,
I thank the authors and express my appreciation to the researchers. The manuscript presents valuable research. But some revisions are needed. The authors should revise it based on the comments. Also, minor changes should be made to the abstract:
ABSTRACT:
The study design should be mentioned in the first line of the method section of the ABSTRACT.

Editor-in-Chief MAJOR REVISION 29 Dec 2023

Dear Author,
Thank you for submitting the article. It needs some revision. Please revise it based on the reviewers' and AE's comments.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear reviewers, Thanks for your instructive comments. the following are point by point reply to your comments:

Reviewer 1:
Dear Authors
Please fully describe the randomization and blinding procedure.

Randomization and blindness

Utilizing computer generated randomization numbers, patients were randomly assigned equally into two groups. Group fentanyl (n=36): patients received 50 ug of fentanyl. Group oxycodone (n=36): patients received 4 mg of oxycodone. Drugs were received 20 min prior to the end of the operation. Patients, observers, and the outcome evaluators were unaware of the trial pharmaceuticals. *Drugs were prepared by an additional pharmacist who did not join in the remaining phases of trial.* All containers were *sealed by aluminum foil* identical in appearance.

Preferably, the references should be related to the last 5 years.

Done as possible as there are studies in the discussion section cannot be updated.
-Explain a novelty in this manuscript?

A recent systematic review and metanalysis by Raff et al.**(Raff et al., 2019)** concluded that oxycodone has more analgesic efficiency compared to fentanyl with fewer side effects, such as sedation but the included studies were limited to abdominal surgeries. Kim et al. evaluated oxycodone and fentanyl for postoperative pain management in orthopaedic surgery patients but their studied was limited by small sample size and they recommended generalization through large-scale research **(Kim et al., 2018)**. Consequently, this randomized trial was designed to examine the efficacy of oxycodone and fentanyl for postoperative pain management following THR.

Reviewer 2:
Dear AE,
-The manuscript mentions a triple-blind study design but lacks a detailed explanation of how blinding was maintained throughout the study, especially during the administration and assessment phases. This is vital to ensure the reliability of the results.

Drugs were received 20 min prior to the end of the operation. Patients, observers, and the outcome evaluators were unaware of the trial pharmaceuticals. *Drugs were prepared by an additional pharmacist who did not join in the remaining phases of trial.* All containers were *sealed by aluminum foil* identical in appearance.

A triple-blind administration occurred 20 minutes prior to the surgery termination: 50 ug of fentanyl was administered to the fentanyl group, and 4 mg of oxycodone were administered to the oxycodone group. *Surgery was done under general anesthesia*

- The use of VAS (Visual Analogue Scale) is mentioned for pain assessment, but the manuscript should ensure that this assessment was consistently applied across all participants at all time points. This is crucial for the validity of the pain scores obtained.

We mentioned that during the preoperative appointment, patients were instructed on the use of the visual analogue scale (VAS) (0, no discomfort and no pain; 10 extreme discomfort and maximal pain). And then pain was assessed using VAS at different time intervals post-surgery as reflection for analgesic effect.

-The rationale behind the chosen doses of oxycodone and fentanyl should be explained. The manuscript needs to clarify why these specific doses were selected and how they compare to standard dosages used in clinical practice.

Added in the discussion section.

A dose of 50mg fentanyl and 4mg oxycodone was administered 20 minutes before the end of surgery, guided by established potency ratios. To assess the analgesic effects of these drugs, equivalent doses were necessary. In a study following laparoscopic cholecystectomy, intravenous fentanyl (100mg) was compared to oxycodone (10mg), revealing lower pain scores for oxycodone but a higher incidence of side effects, particularly severe nausea and vomiting **(Koch et al., 2008)**. This study was pivotal in establishing equivalent doses for oxycodone and fentanyl, with subsequent investigations exploring lower oxycodone doses. Intravenous oxycodone is recognized as having an equivalent or 3:4 ratio to morphine. Comparisons with morphine and fentanyl suggested varying potency ratios, such as 1:100 and 1:75 for fentanyl to oxycodone **(Kim et al., 2018)**. Given concerns about side effects, a ratio of 1:80 was utilized in the mentioned study **(Koch et al., 2008)**.

-The design of the control group needs to be clear. For instance, if the fentanyl group is considered as the control group, the manuscript should discuss why this is an appropriate comparator.

Fentanyl group is the control one. Oxycodone has a longer duration of action than fentanyl and hence, may have a more sustained analgesic effect after a single bolus injection than fentanyl at the end of the surgery. So, we conducted this trial to confirm that as these two drugs are the most common and available in management of pain after THR.

-The impact of comorbidities and the use of concomitant medications on pain management and drug efficacy should be addressed. This information is crucial to understand the study's applicability to patients with varying medical backgrounds.

We excluded all patients with comorbid conditions to avoid the effect of any factor on the study outcomes.

Exclusion criteria were history of medication allergies, drug addiction, mental or emotional concerns, chronic kidney and liver impairment.

-More detailed data on the use of rescue analgesia (if any) and its impact on the study's outcomes should be provided. This is important for understanding the overall effectiveness of the pain management strategy.

When the VAS was > 4 in the PACU, fentanyl bolus dose of (50ug) was administered for patient as rescue analgesia regardless of his assigned group. In addition, in the ward a similar IV dose of fentanyl (as in PACU) was administered for severe pain (VAS score > 4).

Fentanyl consumption (ug) in 1st 12h, 24h and 48h postoperative was significantly lower in oxycodone group than fentanyl group (P value <0.001). Figure 3

Addressing these additional aspects would further enhance the quality and comprehensiveness of the study, providing a clearer understanding of its implications in the field of pain management after total hip arthroplasty.

Associate Editor's Comments:

Associate Editor 1:
Dear EIC,
Thanks to the authors and appreciation to the researchers. The manuscript is a valuable research. But some revisions are needed. Authors should revise it based on comments. Also minor changes should be done in abstract:
ABSTRACT:
Study design should be mentioned in first line of method section of ABSTRACT

Done

Methods: Seventy-two cases scheduled for elective THR were included in this randomized, triple-blind trial.

2 Revision 1

4 comments · 11 Jan 2024 – 16 Jan 2024

Referee 1 Reviewer — ACCEPT 11 Jan 2024

Dear Authors
The points were corrected and your design is acceptable.

Referee 2 Reviewer — ACCEPT 16 Jan 2024

Dear AE.
Previous errors have been corrected, and there are no further recommendations.

Associate Editor — ACCEPT 16 Jan 2024

Dear EIC.
The great effort in improving the manuscript is highly appreciated.
The authors have addressed all the comments. Now, it is acceptable.

Editor-in-Chief — ACCEPT 16 Jan 2024

Dear authors.
Thanks for your valuable efforts in carefully revising the manuscript.