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OPEN PEER REVIEW

Perioperative Use of Pregabalin vs. Duloxetine for Pain Management of Knee Fracture Surgery: A Double-Blind Randomized Clinical Trial

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Contents

1 **Original submission** Ardeshir Tajbakhsh, Referee 1, Referee 2 2
2 **Revision 1** 5
Authors' reply to reviewers 6
Reviewer and editor comments 18

1 Original submission

3 comments · 15 Dec 2024 – 31 Dec 2024

Ardeshir Tajbakhsh Reviewer

ACCEPT 15 Dec 2024

Title
The title is appropriate and reflects the content without any abbreviations. The title is novel and of interest in anesthesiology.
Abstract

The abstract is well organized and well described. I recommend listing the keywords in alphabetical order.

Introduction
The introduction is relevant and justifies the aims of the study. However, it is advised to mention adverse effects of duloxetine, such as insomnia.

Materials And Methods
The selection of patients is described. However, some of the exclusion criteria should be restated as inclusion criteria specifying their absence (e.g., no chronic use of duloxetine). Statistical analysis is appropriate. Ethical considerations are explained. Although mentioning the name of the hospital (Sina) is not necessary, you can state that it is a referral or tertiary hospital, if applicable.

Results

This section follows a logical sequence and is well organized.

Discussion
This section explains the results.

References
References are written in Vancouver style.

Referee 1 Reviewer

MAJOR REVISION 16 Dec 2024

The manuscript investigates the efficacy of pregabalin versus duloxetine in managing perioperative pain in knee surgery patients. Utilizing a double-blind randomized controlled trial (RCT) design, the study aims to compare these two medications in terms of pain relief and opioid-sparing effects. Key findings indicate differences in the onset of action and overall effectiveness between the two drugs.
Strengths:
The manuscript is notable for its rigorous methodology, employing a double-blind RCT approach, which enhances the reliability of the findings. The study provides a clear and detailed description of interventions and outcomes, and it includes comprehensive demographic and clinical variables for comparison.
Major Concerns:
1. The blinding method needs further clarification, as it appears more complex than described as simply double-blind.
2. The rationale for prescribing rescue therapy at an NRS score of 6 should be reconsidered, as it is typically recommended at a lower threshold.
3. The small sample size and short follow-up period limit the generalizability and depth of the findings, and these limitations should be discussed more thoroughly in terms of potential biases.
4. The conclusion's claim that duloxetine is a "superior alternative" should be tempered given the nuanced

results and small sample size.
Minor Concerns:
1. The title could be refined for clarity and brevity.
2. The introduction would benefit from explicitly stated hypotheses to provide a more focused narrative.
3. The methodology should justify the choice of drug doses with references to prior research.
4. The results section should include effect sizes to enhance the robustness of the interpretation.
5. The discussion could be expanded to explore the clinical implications of duloxetine's delayed onset of action.
6. Consideration of cost-effectiveness and practical application of findings in clinical practice would strengthen the discussion.
Recommendation:
Major revisions are required. The manuscript's methodological rigor and detailed descriptions are commendable, but addressing the major concerns, particularly regarding the blinding method, sample size, and interpretation of results, is essential for improving the manuscript's clarity and impact.

Referee 2 Reviewer

MAJOR REVISION 31 Dec 2024

This is an interesting article that compares the efficacy of pregabalin with duloxetine in perioperative pain management in patients undergoing knee fracture surgery. On October 10th, 2024, the FDA announced a Class II recall for duloxetine delayed-release capsules, which may affect the authors' valuable work. Several issues also need to be addressed.
1. The major concern about this paper is that opioid use was overlooked when interpreting the results presented in Table 2. The authors indicated that "the duloxetine group received higher doses of morphine on the first day compared to the pregabalin group." Hence, the observed significant mean difference in NRS scores from any time point to 48 hours may be related to the difference in opioid use. To reduce the bias, it is recommended to adjust the results based on the opioid dose.
2. In the discussion section, it is mentioned that the significant difference in pain scores in the delayed phase after surgery at 48 hours in the duloxetine group may be attributed to differences between the two drugs in the time taken to reach the peak. To confirm this statement, the authors cited the article in which duloxetine was compared with placebo. However, the time to reach peak plasma concentration is approximately 6 hours for duloxetine and 1.5 to 3 hours for immediate-release pregabalin. Therefore, the results in the delayed phase may not be attributed to the pharmacokinetic differences since the time to peak for both drugs is within 6 hours. Opioids delay gastric emptying, which in turn may alter the pharmacokinetics of both drugs. This issue should also be mentioned in the interpretation of the results.
3. As noted in the CONSORT flow diagram, nine patients in the duloxetine group and five patients in the pregabalin group were lost to follow-up, which may increase the risk of bias due to missing outcome data. Since the authors evaluated the safety of each drug, it should be mentioned whether "not adherence" is related to adverse effects or other reasons.
Minor comments:
1. Line 53: change "opioid sparing effects" to opioid-sparing effects.
2. Use a comma after however throughout the text.
3. Line 94: change "informed consent obtained" to informed consent was obtained.
4. Line 170: change "reduction at the 48-hour mark from any given time point" to reduction at the 48-hour from any time point.
5. Line 176: change "each period assessed" to each period assessment.
6. Line 186: change "one patient of pregabalin group" to one patient in the pregabalin group.
7. Line 98: change "Inclusion criteria for enrollment was knee fracture including distal femur, proximal tibial

and patellar fractures, consent to participate and age between 18-80 years with exclusion criteria was history of chronic or recent use duloxetine…" to Inclusion criteria for enrollment were knee fracture including distal femur, proximal tibial, and patellar fractures, consent to participate and age between 18-80 years. The exclusion criteria of the study were the history of chronic or recent use of duloxetine,…

8. Line 102: change "renal clearance" to creatinine clearance. Also, mention the calculation method (Cockcroft-Gault or CKD-EPI equation).

9. Line 240: change "no increase need" to no increased need.

10. Line 246: change "Short post-operative follow-up which prevents us from evaluating the difference on more 247 prolonged period." to Short post-operative follow-up prevents us from evaluating the difference over a more prolonged period.

2

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.

Manuscript ID: 157958

Manuscript title: Comparison of the Efficacy of Pregabalin with Duloxetine in Perioperative Pain Management for Knee Fracture Surgery: A Double-Blind Randomized Clinical Trial

Dear Editor-in-chief, Dr Elham Rezaee

Our team appreciates the editor and the reviewers for their observations and helpful comments on the manuscript. We have fulfilled their comments and suggestions and wish to submit a revised version of the manuscript for further consideration in the journal. We provide a point-by-point response explaining how we have addressed each of the reviewer and editors' comments. Changes in the revised version of the manuscript are highlighted in separated colors.

Yours sincerely,

F. N

Reviewer	Suggestion, question, or Comment from the editor	Response	Address in new manuscript file
1	I recommend mentioning keywords in alphabetic order.	Thank you for all of your helpful comments. Keywords changed in alphabetic order.	Line 45 and 46
1	The introduction is relevant and justifies the aims of the study. However, it is advised to mention adverse effects of duloxetine, such as insomnia.	The side effects of duloxetine have been added to the introduction.	Line 73 to 75
1	Some of the exclusion criteria should be stated as not having them in inclusion criteria (like having chronic use of duloxetine, etc..).	The sentence addressing: no history of chronic or recent use of duloxetine, gabapentin, and pregabalin within two weeks before enrollment was moved to inclusion criteria.	Line 104 and 105
1	mentioning the name of the hospital (Sina) is not necessary, you can state	Done	Line 98

	referral or tertiary if applicable.		
2	1. The blinding method needs further clarification, as it appears more complex than described as simply double-blind.	We sincerely appreciate all of your valuable comments and your meticulous attention to detail. When patients were assigned to a group, a unique code was opened based on randomization list, and a pocket containing 8 capsules corresponding to that code was delivered to the orthopedic ward by the pharmacy and then the nurses administered the capsules to patients every 12 hour according to study protocol. Using this method, the blinding process ensures that all patients, prescribers, administrators, pharmacists responsible for pain assessment, and final analyzers are unaware of the patients' allocation; only the researcher who prepared drug envelopes and attached the codes to the medication envelopes was informed. This researcher was not involved in pain assessment and final analysis. A summary of this procedure was added to the methods.	Line 122 to 130
2	2. The rationale for prescribing rescue therapy at an NRS score of 6 should be reconsidered, as it is typically recommended at a lower threshold.	We employed a multimodal approach, utilizing, acetaminophen, celecoxib and duloxetine/pregabalin, all of which have demonstrated a significant effect on pain improvement compared to placebo. In addition to these, according to the routine practice of the orthopedic physicians and orthopedic ward, we used opioids as rescue medication for severe pain. (NRS 6 and more).	Line 150 and 151
2	3. The small sample size	Limitation changed according to	Line 262 and

	and short follow-up period limit the generalizability and depth of the findings, and these limitations should be discussed more thoroughly in terms of potential biases.	your advice: Short post-operative follow-up prevents us from evaluating the difference over a more prolonged period. The assessment of multiple factors (e.g., age, sex, mechanism of trauma, etc.) on the pain reduction difference among the groups was not performed due to the small sample size. The small sample size and short follow-up period limit the generalizability and depth of the findings. We suggest further studies to evaluate more prolonged periods of acute post-operative pain and the effects on more chronic outcomes.	263
2	4. The conclusion's claim that duloxetine is a "superior alternative" should be tempered given the nuanced results and small sample size.	Done	Line 42 and 269
2	1. The title could be refined for clarity and brevity.	Title changed to: Perioperative use of Pregabalin vs. Duloxetine for Pain Management of Knee Fracture Surgery: A Double-Blind Randomized Clinical Trial	Line 1 and 2
2	2. The introduction would benefit from explicitly stated hypotheses to provide a more focused narrative.	Hypothesis added to introduction: We hypothesized that the pain score changes from the baseline of patients in the pregabalin and duloxetine groups may demonstrate a significant difference at 6, 12, 24, and 48 hours postoperatively. In addition, the cumulative opioid usage within 48 hours postoperatively and may shows a significant difference between the pregabalin and duloxetine groups.	Line 82 to 85
2	3. The methodology should justify the choice of drug doses with	We selected doses of 60 mg duloxetine daily and 75 mg pregabalin twice daily based on	Line 133 to 137

	references to prior research.	previous studies and the mentioned references. According to the study design, we decided to divide the administration into every 12 hours for both test drugs. In method section, we mentioned it with references: These dose schedules were selected due to proposed perioperative dosing of duloxetine and pregabalin in previous studies, and duloxetine 30 mg every 12 hours was considered equivalent for 60 mg per day to synchronize the schedule of interventions and to protect the blinding strategy of the trial (20, 21) 20.Pregabalin in acute and chronic pain. 2011;27(3):307-14. 21. Duloxetine for the treatment acute postoperative pain in adult patients: a systematic review with meta-analysis. 2020	
2	4. The results section should include effect sizes to enhance the robustness of the interpretation.	The effect size of more than 1 score was considered clinically significant (reference 23). The reduction in pain in the duloxetine group was -3.64 ± 3.30 from 6h to 48h, while in the pregabalin group it was -1.65 ± 2.63. The mean difference of pain reduction was -1.99. In addition, if we consider the pain reduction from 24 to 48 hours, independent of the opioids received on the first day, in the duloxetine group it was -1.80 ± 2.47, while in the pregabalin group it was -0.07 ± 1.87, with a mean difference of -1.73. We calculated Cohen's d of approximately -0.67 (using	Line 185 to 187

		Difference between NRS score from 6 to 48 h). A Cohen's d of approximately -0.67 indicates a medium effect size according to conventional thresholds. These results suggests that there is a meaningful difference in pain reduction between the two groups, with group duloxetine experiencing significantly greater pain reduction compared to Group pregabalin.	
2	5. The discussion could be expanded to explore the clinical implications of duloxetine's delayed onset of action.	Thank you very much for your insightful comment. Since our study focused on the acute phase, we discussed the delayed phase less extensively. We briefly mentioned that there may be potential for better pain control in the delayed phase for duloxetine.	-
2	6. Consideration of cost-effectiveness and practical application of findings in clinical practice	Both of these drugs have their generic versions available and do not seem to impose high costs. Additionally, to assess cost-effectiveness, we need a very large effect size, and it is essential to investigate what costs are reasonable for achieving this effect.	-
3	1. The major concern about this paper is overlooking opioid use in interpreting the results indicated in Table 2. The authors indicated that "the duloxetine group received higher doses of morphine on the first day compared to the pregabalin group." Hence, the observed significant mean	We sincerely appreciate all of your valuable comments and your meticulous attention to detail. Although morphine use on the first day was higher in duloxetine group; however, opioid rescue in the second day was not required in any patient in duloxetine group, while three patients in pregabalin group received rescue therapy. Pain reduction from 24 to 48 was significantly more in duloxetine group despite no opioid requirement in any patient.	Result section

	difference in NRS scores from any time point to 48 hours may be related to the difference in opioid use. To reduce the bias, it is recommended to adjust the results based on the opioid dose.	Thereupon it demonstrated that patients who received duloxetine experienced less pain despite using fewer opioids and the pain in this period is independent of the opioids consumed on the first day. Indeed, instead of adjusting in statistical method, we addressed this concern through time stratification.	
3	2. In the discussion section, it is mentioned that the significant difference in pain scores in the delayed phase after surgery at 48 hours in the duloxetine group may be attributed to differences between the two drugs in the time taken to reach the peak. To confirm this statement the authors cited the article in which duloxetine was compared with placebo. However, the time to reach peak plasma concentration is approximately 6 hours for duloxetine and 1.5 to 3 hours for immediate-release pregabalin. Therefore, the results in the delayed phase may not be attributed to the pharmacokinetic differences since the time to peak for both drugs is within 6 hours. Opioids delay gastric emptying, which in turn	Previous studies describing time to peak of each drug was done comparing to placebo; however, when we compare the two drugs together, we observe that duloxetine likely has a delayed peak effect compared to pregabalin. this observation maybe linked to unknown mechanism of delayed pharmacodynamic effect of duloxetine which could be study in further trial. Although delaying the gastric effect of opioids may alter the pharmacokinetics of both drugs, starting the medication at least 24 hours before the operation likely means they are in a steady-state phase. In addition, this situation was similar in both groups according to the randomization.	Discussion section

	may alter the pharmacokinetics of both drugs. This issue should also be mentioned in the interpretation of the results.		
3	3. As noted in the CONSORT flow diagram, nine patients in the duloxetine group and five patients in the pregabalin group were lost to follow-up, which may increase the risk of bias due to missing outcome data. Since the authors evaluated the safety of each drug, it should be mentioned whether “not adherence” is related to adverse effects or other reasons.	In total, 9 patients and 5 patients from the two groups were lost to follow-up due to mentioned reasons (Personal consent and discharge, ICU admission and etc.). One patient from each group was lost to follow-up due to “not adherence” (reason was self-administering analgesics in the form of suppositories without informing the nurse).	Figure 1
3	1. Line 53: change “opioid sparing effects” to opioid-sparing effects.	Done	Line 52
3	2. Use a comma after however throughout the text.	Done	-
3	3. Line 94: change “informed consent obtained” to informed consent was obtained.	Done	Line 98
3	4. Lin 170: change “reduction at the 48-hour mark from any given time point” to reduction at the 48-hour from any time point.	Done	Line 181 and 182
3	5. Line 176: change	Done	Line 189

	“each period assessed” to each period assessment.		
3	6. Line 186: change “one patient of pregabalin group” to one patient in the pregabalin group.	Done	Line 199
3	7. Line 98: change “Inclusion criteria for enrollment was knee fracture including distal femur, proximal tibial and patellar fractures, consent to participate and age between 18-80 years with exclusion criteria was history of chronic or recent use duloxetine…” to Inclusion criteria for enrollment were knee fracture including distal femur, proximal tibial, and patellar fractures, consent to participate and age between 18-80 years. The exclusion criteria of the study were the history of chronic or recent use of duloxetine…	Done	Line 102 to 107
3	8. Line 102: change “renal clearance” to creatinine clearance. Also, mention the calculation method (Cockcroft-Gault or CKD-EPI equation).	Done	Line 107
3	9. Line 240: change “no increase need” to no	Done	Line 253

	increased need.		
3	10. Line 246: change “Short post-operative follow-up which prevents us from evaluating the difference on more 247 prolonged period.” to Short post-operative follow-up prevents us from evaluating the difference over a more prolonged period.	Done	Line 259 and 260
Reviewer Assistant Comments and AI	The inclusion criteria (patients undergoing knee fracture surgery) are mentioned, but details on exclusion criteria and recruitment process are not provided.	Thank you for all of your helpful comments. The exclusion criteria mentioned in method and changed further in response to reviewer comment as follow: the history of chronic or recent use of duloxetine, gabapentin, and pregabalin within two weeks before enrollment, the history of hypersensitivity to the study drugs, creatinine clearance less than 30 ml/min according to Cockcroft-Gault equation, severe hepatic impairment as determined by liver enzymes levels greater than five times the upper limit of normal or by Child-Pugh class C, severe or moderate opioid dependence based on diagnostic and statistical manual of mental disorders, fifth edition (DSM V) criteria, recent opioids use within 24 hours of study enrollment, body mass index (BMI) ≥ 40 kg/m2, American society of anesthesiologists physical status IV/V, epidural or generalized anesthesia in surgery, pregnancy or lactation, intolerance to oral	Method section

		medication, active peptic ulcer, high risk of bleeding pre- or post-surgery, concomitant participation in another clinical trial, concomitant or recent use of medications with high potential for drug interactions (St. John's Wort, monoamine oxidase inhibitors, tricyclic antidepressants and SNRIs) within two weeks, hemodynamic instability, undergoing surgery within less than 24 hours after admission and any communication barrier that would hinder the evaluation of patients.	
Reviewer Assistant Comments and AI	The sample size of 54 patients is mentioned, but there is no discussion on how this number was determined or any power calculations.	It is mentioned in method as follow: the standard deviation of NRS change was considered 1.2 (22) and the effect size of more than 1 score was considered clinically significant (23). With two-tailed test $\alpha = 0.05$ and a **power of 0.80,** a sample size of 24 patients in each study arm was calculated. Allowing for a near 30% drop-out rate, 34 patients were recruited in each group.	Line 158
Reviewer Assistant Comments and AI	The method of randomization is not detailed in the provided text.	It is mentioned in method: an online block randomization program divided the patients into two groups and produced code which was assigned to medication envelopes.	Line 122 to 130
Reviewer Assistant Comments and AI	The study is described as double-blind, but the text does not specify how blinding was achieved or maintained.	It is changed further in response to reviewer comment: Patients were assigned to groups using a randomization list, with each patients assigned a unique code. The hospital inpatient pharmacy prepared identical capsules containing either duloxetine or pregabalin from a similar source brand and then delivered a pocket of eight capsules	Line 122 to 130

		that matched this code to the orthopedic ward and then nurses administered the capsules. This blinding process ensured that patients, prescribers, nurses, pharmacists involved in pain assessment, and those performing the final analysis remained unaware of the patients' group assignments. Only the researcher who prepared the drug envelopes knew the allocations and was not involved in pain assessment or analysis. hospital inpatient pharmacy prepared identical capsules containing either duloxetine or pregabalin from a similar source brand	
Reviewer Assistant Comments and AI	The text does not include a flow diagram or detailed information on participant flow through the study.	It is mentioned in figure 1	Figure 1
Reviewer Assistant Comments and AI	There is no mention of any subgroup or additional analyses.	Because of limited sample size subgroup analyses was not applicable.	-
Reviewer Assistant Comments and AI	The text does not mention any limitations of the study, which is an important aspect of the discussion.	It is mentioned in discussion and changed further in response to reviewer comment as follow: Short post-operative follow-up prevents us from evaluating the difference over a more prolonged period. The assessment of multiple factors (e.g., age, sex, mechanism of trauma, etc.) on the pain reduction difference among the groups was not performed due to the small sample size. The small sample size and short follow-up period limit the generalizability and depth of the findings.	Line 258 to 264

Reviewer Assistant Comments and AI	There is no information on funding sources or potential conflicts of interest.	We have no funding source and conflict of idea.	-

2 Revision 1

0 comments

No public comments in this round.