

Reply to editorial comments:

Reviewer 1

The article titled Topical Use of Tranexamic Acid. Are There Concerns for Cytotoxicity? Explores the cytotoxicity of tranexamic acid when used topically and concludes that there is a safe dose but it still needs to be determined with various factors such as age taken into consideration. For the article to be considered for publication, the following minor corrections need to be made. Most importantly, the grammar and language need to be revised. I suggested that the services of a language editor be sought. Define ACL in abstract. Check grammar and do additional language editing e.g. Sentence on line 46 "... seems to strongly inhibit the activation..." doesn't make sense. This sentence on line 157 is also not clear. In S-phase (or Synthesis) takes part the duplication of the... Use of the word raise in line 164. What do the authors mean? Should it be increase or are they referring to the cells swelling? The word "furtherly" on line 170 doesn't sound right as an English word or in its usage. Rather than say "old" patients.. on line 194, rather say in the "elderly" patients. Line 288. Instead of "...check the suggestion that .. rather say confirm the possibility that...." Line 293, instead of more data about TXA molecular mechanism should be clarified... rather say .. more data is needed to clarify the molecular mechanism of TXA. Line 313 many studies came into the conclusion should read, many studies came to the conclusion. These are just some examples and this makes reading difficult.

- Thank you for the comment. We took your comments into consideration and we performed a grammar and language revision on our manuscript. We made all the necessary corrections on the lines that you suggested and we also polished the whole manuscript so that it can be easier to read.

Reviewer 2

This is a review of Submission ID 75682 entitled "Topical Use of Tranexamic Acid. Are There Concerns for Cytotoxicity?". This study is a review article that narratively reviews recent evidence on the effect of topical administration of Tranexamic acid (TXA) and its cytotoxicity. This is an interesting article that reviews the concern-cytotoxic effect of, a well-known currently standard pharmacologic to reduce perioperative blood loss, TXA in orthopaedic surgery. However, there are several issues that need to be clarified. 1. Line 51 "After a mean TXA dose of 10 mg/kg on healthy individuals ...": Which is the route of this TXA administration?

- Thank you for the comment. We clarified that the route of this TXA administration was intravenous.

2. Line 58 "...chondrocytes and surrounding soft tissue, as stated in numerous studies. ": Please give a reference.

- Thank you for the comment. We gave references for this statement.

3. From line 64-84: To not be bias about the efficacy of TXA, please give evidence that shown a comparable result between TXA and no-TXA in orthopaedic surgery.

- Thank you for the comment. We cited a study that concluded that there are no significant differences in blood loss and transfusion rates between TXA and placebo. We also suggested that the number of studies supporting this conclusion is very limited.

4. In section "TXA Administration and Safe Levels" (line 98-148), please describe (or show an evidence) about effect of topical TXA and its various technics of topical application, such as periarticular injection, pouring and wash out, pouring and clamp drain (to increase tissue contact time). Moreover, please discuss about combine route of administration (IA+IV) of TXA.

- Thank you for the comment. We discussed the combined route of TXA administration and its possible benefits. We also described the various technics that TXA can be administered topically with.

5. Line 139 "... were administered for both long-term and brief time of...": please give an exact duration of these long-term and brief time.

- Thank you for the comment. We gave the exact duration of "long-term" and "brief time".

6. Line 197 "' ... 2D and 3D cultures...": please give a short detail about these 2D/3D.

- Thank you for the comment. We gave more details concerning the nature of 2D and 3D cultures.

7. In section "TXA effects depending on patient's age" (line 269): please give an exact number of these "young donors" and "older patients".

- Thank you for the comment. We gave the exact age of young donors (between 14 and 40 years-of-age) but the exact age of older patients was not given in our reference, thus we could not provide a specific number for these patients.

8. Table 1, 2: please show the year of publication of each study.

- Thank you for the comment. We updated the tables with the year of publication of each study.

9. Reference: None of your cited study is beyond 2020. Please update your article with more recent study such as - Bolam SM, O'Regan-Brown A, Paul Monk A, Musson DS, Cornish J, Munro JT. Toxicity of tranexamic acid (TXA) to intra-articular tissue in orthopaedic surgery: a scoping review. *Knee Surg Sports Traumatol Arthrosc.* 2021 Jun;29(6):1862-1871. doi: 10.1007/s00167-020-06219-7. Epub 2020 Aug 29. PMID: 32860523. - Wang F, Wang SG, Yang Q, Nan LP, Cai TC, Wu DS, Zhang L. Cytotoxicity and Effect of Topical Application of Tranexamic Acid on Human Fibroblast in Spine Surgery. *World Neurosurg.* 2021 Sep;153:e380-e391. doi: 10.1016/j.wneu.2021.06.125. Epub 2021 Jul 2. PMID: 34224885. - Eikebrokk TA, Vassmyr BS, Ausen K, Gravastrand C, Spigset O, Pukstad B. Cytotoxicity and effect on wound re-epithelialization after topical administration of tranexamic acid. *BJS Open.* 2019 Sep 26;3(6):840-851. doi: 10.1002/bjs5.50192. PMID: 31832591; PMCID: PMC6887721. - Xu JW, Qiang H, Li TL, Wang Y, Wei XX, Li F. Efficacy of topical vs intravenous

tranexamic acid in reducing blood loss and promoting wound healing in bone surgery: A systematic review and meta-analysis. World J Clin Cases. 2021 Jun 16;9(17):4210-4220. doi: 10.12998/wjcc.v9.i17.4210. PMID: 34141783; PMCID: PMC8173404.

- Thank you for the comment. We updated our manuscript with more recent studies.

In my opinion, this manuscript needs some minor revision before considering for publication in World Journal of Orthopedics.

- Thank you for the comment. We revised our manuscript according to your comments.

Science editor

This review summarized and discussed recent evidence on the toxicity of topical TXA to chondrocytes and articular cartilage. This is an interesting article. However, the manuscript still has some minor problems that can be further improved: 1. The number of total references is few and a bit outdated, maybe a few more related references could also be cited.

- Thank you for the comment. We updated our manuscript with more recent studies, thus raising the number of our references.

2. The form of the table in the article should adopt the form of three-line table and at the same time, some information are needed to make the tables more complete as reviewer said.

- Thank you for the comment. We updated the formation of the tables according to Journal's instructions and added all the additional information that were needed.

3. The grammar and language needs to be revised.

- Thank you for the comment. We performed a thorough revision of the manuscript, concerning the language and grammar.

4. please provide documents following the requirements in the journal's Guidelines for manuscript type and related ethics: Copyright License Agreement.

- Thank you for the comment. All author provided the required Copyright License Agreement.

5. The certificate certifying that a native English speaker has reviewed the paper is not formal.

- Thank you for the comment. We contacted the Vice General Manager of the Journal and he confirmed that we could skip the certificate certifying that a native English speaker has reviewed the paper or the language certificate from an editing company, provided that we would perform a thorough revision of the manuscript, concerning the language and grammar. The majority of the authors have worked in English-speaking countries and have excellent knowledge of the English language. Thus, they have revised the language of the manuscript.

Company editor-in-chief

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Orthopedics, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. However, the quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

- Thank you for the comment. We contacted the Vice General Manager of the Journal and he confirmed that we could skip the certificate certifying that a native English speaker has reviewed the paper or the language certificate from an editing company, provided that we would perform a thorough revision of the manuscript, concerning the language and grammar. The majority of the authors have worked in English-speaking countries and have excellent knowledge of the English language. Thus, they have revised the language of the manuscript.

The author(s) must include the keyword "orthopedic surgery" or "total joint arthroplasty" in the manuscript title.

- Thank you for the comment. We updated the keywords of our manuscript.

Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

- Thank you for the comment. We updated the formation of the tables according to Journal's instructions and added all the additional information that were needed.