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PEER-REVIEW REPORT

Name of journal: *World Journal of Orthopedics*

Manuscript NO: 75682

Title: Topical Use of Tranexamic Acid. Are There Concerns for Cytotoxicity?

Provenance and peer review: Unsolicited manuscript; externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03676447
Position: Editorial Board
Academic degree: MD
Professional title: Associate Professor, Director, Lecturer, Surgeon
Reviewer's Country/Territory: Thailand
Author's Country/Territory: Greece

Manuscript submission date: 2022-02-10
Reviewer chosen by: AI Technique
Reviewer accepted review: 2022-02-15 13:13
Reviewer performed review: 2022-02-28 15:59
Review time: 13 Days and 2 Hours

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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 review recent evidence on the effect of topical administration of Tranexamic acid (TXA) and its cytotoxicity. This is an interesting article that review 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? 2. Line 58 "…chondrocytes and surrounding soft tissue, as stated in numerous studies. ": Please give a reference. 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. 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. 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. 6. Line 197 "" … 2D and 3D cultures…": please give a short detail about these 2D/3D. 7. In section "TXA effects depending on patient's age" (line 269): please give an exact number of these "young donors" and "older patients". 8. Table 1, 2: please show 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

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

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Peer-review model: Single blind

Reviewer's code: 04092906
Position: Peer Reviewer
Academic degree: BSc, MSc, PhD
Professional title: Senior Researcher
Reviewer's Country/Territory: South Africa
Author's Country/Territory: Greece

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Review time: 11 Days and 16 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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SPECIFIC COMMENTS TO AUTHORS

The article titled Topical Use of Tranexamic Acid. Are There Concerns for Cytotoxicity? Explores the cytotoxicity of tranexamic accid when use topically and concludes that there is a safe dose but it still needs to be determine with various factors such as age taken into consideration. For the article to be considered for publication, the follow minor corrections need to be made. Most importantly, the grammar and language needs to be revised. I suggested that the services of a language editor is sought. Define ACL in abstract Check grammar and do additional language editing e.g. Sentence on line 46 …. seems to stronger inhibit the activation… doesn't make sense This sentence 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" line 170 doesn't sound right as an English word or in its usage. Rather than say "old" patients.. 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 cam to the conclusion. These are just some examples and this makes reading difficult.