ABS ANNALS OF BREAST SURGERY
AN OPEN ACCESS JOURNAL TO BRIDGE BREAST SURGEONS ACROSS THE WORLD

Peer Review File

Article information: http://dx.doi.org/10.21037/abs-20-126

Reviewer A

The authors are complimented on their very thorough literature review to investigate use of tranexamic acid in breast surgery. Use of tranexamic acid in surgery is experiencing a major renaissance and the topic is very relevant.

However, I do not think the current material should be presented as a full meta-analysis. This is a systematic review but the low number of papers and the questionable quality (see later) of some of them does not justify a meta-analysis.
A systematic review will be interesting, but the meta-analysis presented adheres stringently to Revman Review manager and squeezes a lot of statistics out of a very heterogenous material. A meta-analysis of this sort seems to me as pseudo-science while the interesting issues can still be addressed as a systematic/narrative review only, with statistics performed only on main findings. I suggest removing the meta-analysis part of the article, and to simplify the findings of the literature, stressing the trends but not attempting full statistical analyses of all sub-stratifications.

The article needs a major revision and should be significantly shortened, preferably down to close to 3000 words.

1.The literature search: This has been usually thorough, which has resulted in studies found in unusual search engines. The abstract states that databases searched included Embase, Medline and Pubmed. These databases encompass peer-reviewed high quality journals. However, in the manuscript itself, the authors list additional databases such as OpenGrey, Greylit and Mednar. Whether these databases include journals with lower standards regarding peer-review and screening routines regarding plagiarism is unclear. As the thorough literature search yielded 11 articles for inclusion in the review, the authors should have read all full text. It should then become apparent that the article by Pathak 2016 is to a large extent a copy, with cut-and-paste paragraphs, from Ausen 2015. Also, major sections of Introduction, patients and methods in Eldesouky 2019 is also copy-paste from Ausen 2015, but neither Pathak nor Eldesouky reference Ausen 2015. The authors may have corresponded with Pathak and Eldesouky; plagiarism does

not necessarily mean that the data reported is not valid or honest but were these articles found through the less reputable databases? Such uncertainties should be addressed.

Reply 1: where articles located included page 7 line 164

2. Choice of end points: With the relatively few publications on use of tranexamic acid in breast surgery, the aims of the review are ambitious: The authors want to determine whether tranexamic acid increases thromboembolic events in oncological breast surgical and reconstructive procedures, whether it effects haematoma or seroma rates, what dose or route of administration is most effective, and whether tranexamic acid affects infection rates, length of surgery or pain scores. Even adding up total numbers will not yield sufficient power to answer many of these questions.

Postoperative hematoma is an interesting end point. One cannot however exclude from analyses studies which have reported on hematomas but not had any. This will leave a material with a higher incidence of hematoma than breast surgery may represent.

Most studies on tranexamic acid report "postoperative bleeding". This article introduces the variable "seroma first 24 h". This refers to the drain production the first 24 h, and should therefore be called "drain production" and not seroma. For all the referred articles, this drain production has been the surrogate measure for postoperative bleeding. Also, until drain removal, I suggest calling the end point "drain production" and not seroma. Save the term "seroma" for the late aspirations - after drain removals.

End points such as operation time, intraoperative blood loss, pain score and long term outcome should be excluded. There are too few studies to say anything interesting about this. Similarly, end points with little relevance and stratification with little relevance can be omitted. E.g stratifying according to type of surgery and putting breast reconstructions with implants vs autologous tissue in the same group may be questionable, as autologous reconstruction yields a donor site with an additional risk of bleeding.

Commenting these variables in discussion can similarly be omitted, and other variables simplified.

Reply 2:
End points such as operation time, intraoperative blood loss, pain score and long term outcomes should be excluded. Seroma output changed to drain output. Non-RCTs excluded from analysis as suggested by reviewer 2.

3. Legend to figures are lacking?

Reply 3: corrected

4. Statistics for major findings: For main endpoints, such as incidence of hematoma, a statistical analysis/meta-analysis may be valid and interesting. However, remember to include all studies that have actually reported the end point- even when it was zero in both groups. Also check numbers – e.g significance for the hematoma variable says p=0.006 in results and 0.0006 in discussion.

Also, when referring the bilateral studies- use the term "breasts", not "patients" (as the patient is represented in both the case and control-group).

Reply 4: updated meta-analysis, patients and breasts changed as appropriate

5. Old references; recent references missing?
The authors should review recent literature and update/adjust references. The researchers should refer to recent meta-analyses on both topical and systemic use - e.g reference no 28 in discussion could be replaced by the recent meta-analysis by Heyns et al in Annals of Surgery.

Also, line 323: There have been two major meta-analyses of topical TXA since Ker 2013 (ref 8); both Teoh 2020 and Montroy 2018.

Line 395, reference 29: This review which reviews risk of thromboembolism in breast reconstruction actually did not find any articles addressing use of TXA in breast reconstruction….

Line 402: Regarding thromboembolic risks: More recent studies should be referenced. Be particularly aware of the recent HALT-IT study and Myers 2019
M

Reply 5: update with newer references

6. Re-structuring of discussion
The current discussion presents statements based on very fragile statistics. Instead of attempting to present findings for a variety of subgroups within breast surgery, the larger concepts should be formulated and concluded, acknowledging the heterogeneity of doses, administration form and surgeries.

A long section in discussion addresses how TXA might reduce seroma formation. You have found little evidence in sum from the articles that TXA reduces seroma - the results are not uniform. This should be downplayed/deleted- some suggest a reduction, some

suggest an increase in seroma. But you refer to the drain production- which is in other articles a measure of postoperative bleeding- as seroma? This becomes confusing.

In conclusions, adjust the main points when refraining from all the statistics of a meta-analysis? - I would also not call the drain production “postoperative seroma” as it may be mixed with late seroma. Call it drain production?

Reply 6 – discussion re-written

7. Check reference list – some are incomplete, e.g ref 29, and the structure of the references vary a great deal? Check journal format.

Reply 7 – references changed

Reviewer B

Authors performed a systematic review and meta-analysis evaluating TXA use in breast surgery. They concluded:

-The overall rate of thromboembolic and infective complications after TXA administration is not increased compared to standard treatment.
-Haematoma rates are reduced overall for all procedures and routes of administration of TXA combined, however for individual procedures significance is lost.
-Post-operative seroma fluid drainage is reduced and the length of time with drains is shortened, however late seroma requiring intervention is unaffected.
-The best route of administration of TXA is still to be determined, however topical administration seemed to have a greater effect compared to IV on haematoma formation.
-Long-term effects of TXA administration are unknown

The abstract is very disconnected from the manuscript text.

1) Abstract Methods: Line 9: “Databases searched included Embase, Medline and Pubmed” Only two databases were used (Medline and Embase). Pubmed is indexed through Medline. In the methods of the manuscript there were more databases used.

Manuscript Methods: Embase, Medline, Pubmed, the Cochrane Central Register of Controlled Trials, Scopus, OpenGrey, Greylit, Mednar and google scholar

Reply 1 : abstract has been changed, databases with 0 results not included in write up.

2) 95%CI should be consistently reported in the abstract. Haematoma rate 95% CI=0.19-0.76 while seroma volume 95% CI=-292.21 to -57.72.

Reply: re-written to be consistent

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane guidelines should be followed for all systematic reviews.

Introduction
The aim of the study is clear.

3) Eligibility
Conference abstracts, posters and commentaries are gray literature that should not be included in the review. It is difficult to properly assess the methodology of these studies.

Reply 3 – excluded from paper

4) Patient selection
Line 72: Inclusion only consisted of females greater than or equal to 18 years of age? Did women have any breast disease? What about cosmetic breast surgery? What about breast reduction?

Reply 4- page 3 line 67 changed to procedure types for patient selection, age removed.

5) Line 78: Interventions were TXA, not breast surgeries. Were these compared to placebo? Active-comparators?

Reply 5 – changed to TXA as interventions line 76 page 4

6) Line 81: Specify routes of administration. Do not simply say all were considered because not everyone may know what routes are available.

Reply 6- changed line 77 page 4
7) Appendix A. What database was this search for? How many results came from each database search?

Reply 7 appendix A – medline page 4 line 91
Search results page 7 line 152

8) Line 118: Although it is not the only risk of bias tool. Cochrane Risk of Bias is the Gold Standard for Randomized controlled trials. This is endorsed by PRISMA and The Cochrane Handbook for Systematic Reviews of Interventions.

Reply 8 – changed to ROB tool

9) Lines 143-147: What is the reference for this heterogeneity assessment? Why was a cutoff of I2 40% used? This is not the primary indication to use the random versus the fixed effects model. Please refer to the The Cochrane Handbook for Systematic Reviews of Interventions. If high heterogeneity is present, studies should be evaluated for bias contributing to the high heterogeneity.

Reply 9 – excluded and used random effects for all due to heterogeneity of trials.

10) Authors need to include a summary of findings table. See The Cochrane Handbook for Systematic Reviews of Interventions.

Reply 10 – included table 5

11) Results: Grade certainty evidence should be used for recommendations based on bias and strength of findings. GRADE pro GDT is free and very helpful. Certainty of evidence for each recommendation should consider study design, risk of bias, inconsistency, indirectness, imprecision, effect size and plausible confounding

Reply 11 – grade wording used page 15 line 341-348

12) RCT's should not be analyzed with non-RCT studies if enough RCT's exist. There were 5 RCT's. Line 449-450: "The overall quality of RCT's in this study were good." This may be one reason why the heterogeneity is high.

Reply 12 – excluded non-RCT's from analysis

13) Conclusions
These should be worded based upon GRADE certainty evidence.

Reply 13 - rade wording used page 15 line 341-348, conclusion reworded

If the authors can address the comments and use The Cochrane Handbook for Systematic Reviews of Interventions along with the PRISMA guidelines, it may be considered for publication. In its current state, it is not acceptable. Gray literature should not be included in the review. Risk of bias for randomized controlled trials should be assessed with the Cochrane Risk of Bias Tool. A Summary of Findings Table should be included. GRADE certainty-evidence wording should be used. The GRADE pro GDT software is available online for free. I attached an example from Cochrane of GRADE wording for recommendations based on certainty of evidence.