

Peer Review File

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Reviewer A

I find the article interesting because more studies on this topic are needed.

It is true that there is limited recent literature on MPH, and studies often involve a small number of cases with a very small sample size, hence offering limited validity.

However, I have several comments and questions regarding the manuscript:

Comment 1: The abstract contains some expression issues that should be addressed.

- Line 40: "A previous..."

- Lines 41-43: The sentence is not clear. It would be better for example: "Therefore, we evaluated the effectiveness of MPH in breast cancer surgery in a larger cohort as a retrospective study."

- Line 54: "seroma with puncture" would be better as "seroma requiring puncture."

Reply: We have revised the text. (see Page 3, line 41-42 and Page 3, line 52)

Comment 2: Line 91-96: I would appreciate the addition of a bibliographic citation.

Reply: We added two references in the manuscript. (see Page 6, line 95)

Comment 3: Line 116: The authors should clarify whether the coagulation method used in both groups is equivalent, as it can influence seroma production.

Reply: The energy devices were selected according to surgeon preference, but a detailed data acquisition of all cases was not possible. We added that point to the methods and limitation.

(see Page 7, line 111-112 and Page 11, line 185-187)

Comment 4: Lines 117-119: In cases where axillary lymphadenectomy is not performed, is 1 gram of MPH administered only in the chest wall or also in the axilla? This point should be clarified.

Reply: For cases without lymphadenectomy, we administered MPH for the small deficient regions after SNB. We have revised the text as follows; One gram of MPH (Arista™ AH, C. R. Bard, Inc. – Davol, Warwick, RI, U.S.) was applied to the chest wall and axillary region (slightly deficient axillary area at SNB) before wound closure.

Comment 5: Line 131: It is noted that in the MPH-treated group, there are significantly fewer cases of patients with axillary dissection (94/24). I think there are too few cases in the MPH-treated group, and the results would be more conclusive with a larger group of patients, even if the results are statistically significant.

Reply: Your comments are completely correct and a prospective study with a larger number of cases is needed in the future. It was difficult to analyze a large number of cases at our institution.

Comment 6: Lines 137-144: The authors study patients without any axillary surgical intervention and the ones treated with sentinel node dissection in the same group. They should be studied separately, as this could have implications for the results.

Reply: Your comments are completely correct. We excluded one patient with mastectomy only and analyzed again.

Comment 7: Line 193: It would be helpful to indicate the cost of the product and the increase in surgical time required for the MPH procedure, even if there is no comparison between groups. This data would be interesting.

Reply: We appreciate your helpful comment. One gram of MPH costs 12700 yen, which is \$85 in US dollars (150 yen = 1 US dollar). Intraoperative use takes less than one minute. We added sentences in discussion part. (see Page 11, line 176-177)

Comment 8: There are few recent articles that analyze MPH with a significant number of cases. However, there are numerous articles, some of them very recent, that analyze and compare different hemostatic agents in breast surgery. I miss in this article the mention and comparison of MPH with other similar techniques. For example:

Bloom JA, Foroutanjazi S, Erlichman Z, Beqiraj Z, Jonczyk MM, Persing SM, Chatterjee A. The Use of Hemostatic Agents to Decrease Bleeding Complications in Breast Cancer Surgery. *Am Surg.* 2023 Mar;89(3):395-400. doi: 10.1177/00031348211029866. Epub 2021 Jun 27. PMID: 34176297.

Falcone V, Krotka P, Deutschmann C, Danzinger S, Reischer T, Pfeiler G, Singer C, Koch M. Use of polysaccharide hemostatic agent (HaemoCer™) in breast cancer surgery to reduce postoperative complications: A randomised controlled trial. *Int Wound J.* 2023 Apr;20(4):925-934. doi: 10.1111/iwj.13939. Epub 2022 Nov 29. PMID: 36448255; PMCID: PMC10031209.

Conversano A, Mazouni C, Thomin A, Gaudin A, Fournier M, Rimareix F, Bonastre J. Use of Low-Thrombin Fibrin Sealant Glue After Axillary Lymphadenectomy for Breast Cancer to Reduce Hospital Length and Seroma. Clin Breast Cancer. 2017 Jul;17(4):293-297. doi:10.1016/j.clbc.2016.12.013. Epub 2017 Jan 10. PMID: 28161131.

Reply: We appreciate your important comment. We have not noted other hemostatic agents in breast cancer surgery. Many studies showed no positive effect of hemostatic agents in breast cancer surgery, but one systemic review showed positive effect of fibrin glue in breast cancer surgery. Because there are some problems with the number of cases and the setting of conditions, the efficacy of hemostatic agents remains controversial. We added sentences and several references, including references provided by the reviewer. (see Page 10, line 171-175)

Reviewer B

The authors have investigated an important matter, as seroma formation after mastectomy is burdensome for the patients and the health care system. Means to decrease seroma formation are important to find. The subject has been studied before, but we still don't have definite answer to the question, whether the use of MPH truly decreases the amount of seroma formation after mastectomy, so the results have some scientific relevance. However, due to the limitations of the study and relatively small difference (in sense of clinical significance) this study still does not yield convincing results in the matter.

The patient enrollment and analysis of the results is straightforward and there are no apparent flaws, although the shape of the curve in Figure I is peculiar – I suppose the authors present a correct explanation for this in the article. The number of patients is sufficient for the analysis.

The language of the article is understandable, but there are a few grammatical errors and I recommend a thorough language review if the article is considered for publication.

Reply: We appreciate your comments. We analyzed all patients at a given time period, excluding those who met the exclusion criteria. We did not create a flow, but we revised the manuscript in the method part. (see Page 6, line 104) And we did English editing again.

Major notifications:

The authors should recognize that operating control group and treatment group in different years may affect the results for several reasons, as the operating surgeons may have changed, may have become more experienced or the surgical techniques and/or equipment may have become better. This should be discussed in limitations section.

Reply: Your comment is completely correct. Throughout the period in this study, the surgeries are performed by the same team, but the members and surgeons are slightly different. Although the procedures are intended to be uniform, the experiences and proficiency level might vary. We added sentences in discussion part as a limitation. (see Page 11, line 185-187)

As the study regards only patients undergoing mastectomy, this should be stated in the Title instead of “breast cancer surgery” as this study does not consider patients undergoing breast conserving surgery or breast reconstruction.

Reply: We appreciate your comment. We changed title as follows; “Clinical Effectiveness of Microporous Polysaccharide Hemospheres in Mastectomy for Patients with Breast Cancer.”

Minor notifications:

There are several grammatical errors which require thorough reviewing.

line 114 - > “Bt” is unfamiliar abbreviation -> I recommend the authors to use established terminology and abbreviations, such as “TM” for “total mastectomy”, and for example SLNB/SNB/ALND for axillary surgery.

line 199 -> the authors should conclude that use of MPH in mastectomy (not breast cancer surgery) was associated with...

The authors should define how the complications were diagnosed and present statistics for each complication separately, as the rate of postoperative complications is rather high.

Reply: According to the reviewer's comments, we have revised the text. (see Page 7, line 118-122)

Reviewer C

The article addresses the use of microporous polysaccharide hemospheres (MPH) in breast cancer surgery by retrospectively reviewing patients receiving this treatment. With a large study population, such a review can be of great interest. I do however feel that more detailed information could be extracted from this material and quite a few aspects need to be clarified. I encourage the authors to work

through the material again to improve the paper. More details below.

General:

Co-authorship: As this is a retrospective paper, the Vancouver criteria for co-authorship is not fulfilled for authors who treated patients that were later reviewed in retrospect. I would suggest removing the surgeons who did not actively participate in planning or performing the review from the author list.

Reply: We appreciate your helpful comment. We removed some co-authors. (see Page 1, line 5-6)

The authors state that MPH are expected to reduce the incidence of seroma, while their mode of action (being a scaffold for the creation of fibrin) suggests they rather address postoperative bleeding. The initial experimental study by Egeli did not place drains, but evaluated seroma formation after 10 days. The randomized controlled study to which the authors refer also does not claim to assess seroma formation, but rather “the duration and amount of fluid drainage”. The authors may consider changing their end point to match this last version? Or you could differentiate between drain production for the first 1-2 days, which would be mainly bleeding? And then add up total drain production for the remaining drain period- to represent an assumed serous component? You could probably use your material to evaluate the effect of MPH both as a hemostat and its effect on seroma formation. But regarding seroma, one must also count the numbers of aspirations needed after drain removal.

Reply: In almost of all patients, the drain is not bloody, and it is difficult to determine if the drainage during the first day or two is blood or serous component. Following previous studies, we set outcomes as the incidence of complications such as seroma, the amount of drain drainage, and the duration of drainage. The number of punctures after drain removal was added as a new table after collecting data again. (see Table 4)

Seroma after mastectomy may be two different things – after axillary clearance, the seroma may contain a significant lymph fraction (and lymph contains no fibrogen, so it cannot clot), while in surgical cavities elsewhere, the seroma may be mainly exudate. It is logical to divide the patient population according to axillary dissection as the authors have done, but the abstract does not present this stratification.

Reply: We revised the sentences in abstract. (see Page 3, line 48-51)

This is a new mode of treatment. Focus should then be on potential adverse effects, and all postoperative complications should be reported and differentiated.

Reply: MPH is made of starch, so there is no risk of allergy. No other complications were observed in our experience. We added sentences in discussion part. (see Page 11, line 177-178)

Abstract: The abstract presents effectiveness of MPH in the overall population while only stratified data is presented in the article itself. Differentiating between axillary node dissection and the others is logical but the article should also present the total numbers (or the abstract state that the analyses were stratified).

The authors state that age was significantly older in the MPH group “due to selection bias”- is it an established practice within the clinic that older patients are more often given active interventions such as MPH? As the intervention was given to all patient between December 2020 and April 2023, while controls are from 2015 to 2020 when MPH was not used, then there should be no room for selection bias?

Reply: Your comment is completely correct. We did not show the data of drainage amount and period in total cohort. And as you mentioned, dividing the patient population according to axillary manipulation is important. So we changed sentences in result part in the abstract. (see Page 3, line 48-51)

We used MPH for all consecutive patients in a certain period of time. So we use MPH for elderly patients.

We use the term “selection bias” to mean that we did not randomize the patients because it was a retrospective study.

Methods:

The sentence “Postoperative bleeding, wound infection, skin necrosis, and postoperative seroma requiring puncture drainage were recognized as intraoperative complications”. I assume the authors mean postoperative complications.

Reply: We were so sorry, as you mentioned, it was a mistyping and we corrected. (see Page 7, line 118)

These complications are important as they are evaluating a new intervention. They should better define what is regarded a complication – e.g is postoperative bleeding a certain volume on the drain, or a condition needing intervention such as re-operation/aspiration/other? What defines an infection? Should wound dehiscence be included? As they are addressing seroma, the need for aspiration of

seroma after the removal of the drains would also be an interesting variable in this article (numbers and volumes of aspirations after drain removal).

Reply: According to your comment, we added definition of postoperative complications in patients and methods part. (see Page 7, line 118-122) And we collected the number of punctures after drain removal and added a new table (see Table 4).

You state that you separated the axillary dissection group (BtAx) from the groups with regular mastectomy or with sentinel node. That division seems logical, particularly since you use a special instrument for axillary dissection (but not for sentinel node?) But in Table 1, you have stated that the sentinel nodes are in the group with the axillary dissections? Which are correct? And does this affect how you have calculated the results?

Reply: We are sorry for the misleading description. We had included one case of mastectomy without any axillary manipulation in our analysis, but we revised and excluded that case. The division is done by SNB or ALND.

Results:

You state that for the axillary dissection group, total drain volume is significantly less in the MPH group but this is not correct as $p=0.064$. This could be explained by this group having a much larger volume fraction of lymph – without fibrogen? I would like to see you differentiate between early (bleeding) and late (seroma) drain production.

Reply: Your comment is completely correct. It was our mistake. In ALND group, only drain placement period was significant. We corrected the manuscript. (see Page 8, line 142) As you mentioned, it could be for a much larger volume fraction of lymph fluid without fibrogen, but we could not discuss about that using our data. And we could not differentiate between early (bleeding) and late (seroma), so we collected total amount of drainage volume in this study.

Generally for the tables: You must state what the numbers mean - what is in parentheses - is it range or SD? And what does 39/43 mean when it comes to complications in 94 patients..? (example taken from table 3) (but then I see you explained it in table 2 – but the numbers of present or absent does not add up to the number of patients).

Reply: Again, your comment is completely correct. We revised tables. For postoperative complications, there were some missing data because some patients were transferred to other hospitals after discharge. We added the number of

missing data as NA in tables. (see Table 4)

I would rather like to see a more differentiated analysis of the postoperative complications with a separate analysis for each type, as complications are very important when introducing a new mode of treatment. There also seem to be a high number of complications. And as mentioned – if focus on seroma, count the late punctures for seroma aspirations.

Reply: We made new table describing details of postoperative complications. (see Table 4)

In patients without axillary dissection, some patients have removed 11-15 lymph nodes. This must surely qualify as axillary dissection?

Reply: As you mentioned, there were patients with SNB that many lymph nodes were removed as a result. In this study, patients were not classified by the number of nodes removed, but by the procedure performed by the surgeon. The number of such patients is small and it does not affect the results.

Figures: It should be more clearly defined what the numbers at the bottom represent. I assume it is number of patients still with drains at the respective postoperative days.

Reply: We appreciate your helpful comment. We revised figure legends. (see Page 22-23, line 302-311)

Discussion:

You should in line 160-61 state that the other (positive) studies are retrospective. In line 165, you might want to add that Suarez-Kelly does not stratify between axillary clearance or not. This may also hide an effect in a small material.

Reply: We added sentences in discussion part. (see Page 9, line 156)

167-170: Your complications are a variety of things, and cannot be compared to post-operative seroma incidence. You must define much more clearly what you mean by “postoperative seroma” and also all the other complications.

Reply: We added sentences in discussion part. (see Page 7, line 118-122)

171: Again, how did you divide the subgroups- table 1 versus text? And the sentence “When we divided...” suggests you also analyzed the total material without dividing. I think you should present the overall material as well. It may particularly be interesting with regards to complications.

Reply: As you and other reviewers mentioned, it is logical to analyze dividing SNB and ALND, so we showed results and discussed dividing SNB and ALND.

176: Maybe the curves as you show may be not the optimal for showing the trend? Maybe just show curves for the first days when they all have drains? Maybe use the variable "days to drain removal" as an end point instead of following a curve (with few final participants) all the way to day 14?

Reply: Because it is arbitrary to set the cut off day, we have shown all data up to the period until drains were removed in almost all patients. We agree that the data for the later days is less meaningful. Therefore, we have included the numbers at the bottom to indicate only small number of patients who continue to have drainage tubes. (see Page 22-23, line 302-311)

178: And again, we need the data for each type of complication

Reply: We added sentences and table for each type of complications. (see Table 4)