Peer Review File

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Reviewer A

Thank you so much for this interesting paper. I think there are some issues that need to be addressed to increase the benefit for the readers.

Comment 1: The introduction is too long and needs to be tightened to only justify the questions asked in the study. Details of how ADMs work etc do not really add much to the quality of introduction.

Reply 1: According to the reviewer's advice the introduction has been cut down to mentioning the primary and secondary endpoint. Initially, the intention was to provide the reader with an overview of the historical use of ADM and an overview regarding the function of the products.

Changes in the text:
Originally submitted manus line 48-105: Introduction
Breast reconstructive techniques is constantly evolving aiming to offer the patients an aesthetically pleasing result and minimize short- and long-term complications. The overall goal is to relieve the psychosocial consequences following breast oncologic surgery and thereby contribute to improved quality of life (QoL). The trend in the western world is that an increasing part of breast reconstructive procedures being performed in an increasingly younger population (1,2) and this leads to an awareness of improving the psychosocial and functional result and reduce the resource utilization as more women will live for a longer time with the consequences of breast cancer treatment.
The introduction of acellular dermal matrix (ADM) to obtain a one-stage immediate breast reconstruction (BR) (3,4) provided the patients with a breast reconstructive trajectory with a minimum of discomfort and outpatient visits and an excellent aesthetic result. Historically, ADM was first introduced for the treatment of full-thickness burns in 1995 (5) and in 2001 the first use in breast surgery for reducing visible rippling of breast implants was published by Duncan (6). In 2005/2006 Breuing and Salzberg were the first to publish the use of ADM for immediate implant-based breast reconstruction following skin-sparing mastectomy (3,4) and in 2007 Bindingnavele et al. introduced the use of ADM in tissue expander breast reconstruction proposing that this would decrease the postoperative pain and allow a faster expansion course (7). The advantages of using ADM in breast reconstruction are improved control of the inframammary fold position (8) and better lower pole

projection (9) compared to the traditional expander-to-implant technique. Furthermore, studies indicate that implant-based breast reconstruction with ADM results in a lower rate of development of capsular contracture, even when the patient has to undergo radiation therapy (10,11). Seroma has, on the other hand, been associated with the use of biological meshes (12,13).

A whole range of acellular dermal matrices are available. They are derived from either human cadaveric dermis or animal dermis. These products undergo processes that eliminates all cellular elements and antigenic components from the tissue leaving only the intact extracellular matrix. Biointegration of the ADM is a consequence of remodelling, including angiogenesis, host cell infiltration, mitogenesis, and deposition and organization of new host extracellular matrix. Component growth factors as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGF-β) are released during scaffold degradation and exert their biologic effects as they are dissociated from their binding proteins and activated (14). Thus the matrix provides a scaffold, promoting integration of the connective tissue thus being revascularized and repopulated by the patient's own cells. The biological response after implantation of a biological mesh may vary depending of the processing techniques used for production (15). Comparing different meshes in regard to breast reconstructive outcomes can be difficult and possibly more associated to factors as publication frequency, surgical variance, different methodology and measurement tools and to a lesser degree to differences between matrices (16). Furthermore, new ADM products are being introduced all the time and choice of material is to a high degree depending on the surgeons preference. This makes comparison of outcomes very challenging (17).

Limited health resources necessitate careful consideration of the implementation of a given treatment modality. ADM products are expensive but may potentially be cost effective, due to the possibility of reducing expenses as i.e. fewer surgeries and shorter hospital stay, compared to the traditional two-stage expander-implant technique. The literature regarding this subject shows conflicting results. Some suggest that the use of ADM for immediate BR is cost advantageous compared with the two-stage approach and furthermore, that the use of ADM has clinical benefit for patients by allowing a one-stage procedure rather than two separate operations and results in fewer outpatient visits (18,19). Another study has reported that the direct costs of one-stage implant-based BR with ADM were higher than those of two-stage BR, and that health outcomes did not differ between the groups(20).

The patient's subjective assessment of the aesthetic outcome and the physical and psychosocial effects of BR is extremely important as the overall objective by offering BR is to improve the patients QoL.

To contribute to knowledge on the subject, the present study aims at comparing immediate implant-based BR using the one-stage approach with ADM with the two-stage expander-to-implant approach regarding resource utilization and patient reported outcomes (PROs).

We present the following article in accordance with the STROBE reporting checklist.

Resubmitted manus line 47-76: Introduction

In the western world an increasing part of breast reconstructive procedures is being performed in an increasingly younger population (1,2). This leads to an awareness of improving the psychosocial and functional result and reduce the resource utilization as more women will live for a longer time with the consequences of breast cancer treatment.

In 2005/2006 Breuing and Salzberg were the first to publish the use of ADM for immediate implant-based breast reconstruction following skin-sparing mastectomy (3,4) and in 2007 Bindingnavele et al. introduced the use of ADM in tissue expander breast reconstruction proposing that this would decrease the postoperative pain and allow a faster expansion course (5).

Limited health resources necessitate careful consideration of the implementation of a given treatment modality. ADM products are expensive but may potentially be cost effective, due to the possibility of reducing expenses as i.e. fewer surgeries and shorter hospital stay, compared to the traditional two-stage expander-implant technique. The literature regarding this subject shows conflicting results. Some suggest that the use of ADM for immediate BR is cost advantageous compared with the two-stage approach and furthermore, that the use of ADM has clinical benefit for patients by allowing a one-stage procedure rather than two separate operations and results in fewer outpatient visits (6,7). Another study has reported that the direct costs of one-stage implant-based BR with ADM were higher than those of two-stage BR, and that health outcomes did not differ between the groups (8).

The advantages of using ADM in breast reconstruction are improved control of the inframammary fold position (9) and better lower pole projection (10) compared to the traditional expander-to-implant technique. Furthermore, studies indicate that implant-based breast reconstruction with ADM results in a lower rate of development of capsular contracture, even when the patient has to undergo radiation therapy (11,12). Seroma has, on the other hand, been associated with the use of biological meshes (13,14). The patient's subjective assessment of the aesthetic outcome and the physical and psychosocial effects of BR is extremely important as the overall objective by offering BR is to improve the patients QoL.

To contribute to knowledge on the subject, we present a study where the aim was to compare immediate implant-based BR using the one-stage approach with ADM with the two-stage expander-to-implant approach regarding resource utilization and patient reported outcomes (PROs).

We present the following article in accordance with the STROBE reporting checklist.

Comment 2: The statstics are over complicated for a very small sample size. Furthermore, there is no mention of distribution testing and using parametric tests

without distribution testing is unlikely to be reliable in this situation. Furthermore using regression with so many variables is unreliable. Regression models generally work better if there are at least 10 patients per variable in question. Below that number the regression has significant limitations. Therefore, in my view this is not a reliable way of statistical assessment.

Reply 2: Statistical considerations and statistical analyzes were performed in collaboration with the Biostatistical Advisory Service, Faculty of Health at Aarhus University. To the best of our knowledge, the data in this study were analyzed, applying the statistical state of the art, in order to present the results in view of the current research question.

Changes in the text: No changes regarding statistical analysis were made.

Comment 3: There is a lot of missing data for a relatively small series. This feeds into my previous point about statistics.

Reply 3: We agree that there is a lot of missing data for this relatively small study. The data has, though, been presented in a transparent way, and we are doing our utmost to provide the reader with an honest overview of the data.

Changes in the text: No changes regarding statistical analysis were made. But an amendment was made to the "result" section line 243-246 as described in reply for comment 4.

Comment 4: I would recommend arranging the results and methods a bit better with clear primary and secondary outcomes identified and results presented accordingly.

Reply 4: In the "outcomes" paragraph line 130-163 the primary and secondary outcomes are described in details according to the STROBE guidelines. Thus, the presented primary and secondary outcomes are provided in the original text as precise as possible.
In the "result" section a modification has been made to make it clearer, what the primary and secondary endpoints are. Furthermore, the title of table 2, 3 and 4 is modified.

Changes in the text:
Originally submitted manus line 240:

“Materials for a one-stage BR (silicone implant, Strattice™, sizer) was 2.6 times more…..”

Resubmitted manus line 212-214:
“Regarding the primary endpoint “resource utilization” associated with the two different methods for breast reconstruction the materials for a one-stage BR (silicone implant, Strattice™, sizer) was 2.6 times more….”

Originally submitted manus line 270:
“Regarding pain located to the breast region there was no significant difference…”

Resubmitted manus line 243-246:
“Results concerning the secondary endpoint PRO are described as follows. Attention is drawn to the proportion of missing data especially at 12 months follow-up in the two-stage group and results are provided for 24-months follow-up (Table 3). Regarding pain located to the breast region there was no significant difference…”

Originally submitted manus:
Title table 2: Costs reported per patient for unilateral and bilateral breast
Title table 3: PROMs reported at breast level. Pain, sensation disturbance, lymphoedema and arm function.
Title table 4: PROMs reported at patient level.

Resubmitted manus:
Title table 2: Resource utilization reported per patient for unilateral and bilateral breast.
Title table 3: Secondary endpoint PROMs reported at breast level. Pain, sensation disturbance, lymphoedema and arm function.
Title table 4: Secondary endpoint PROMs reported at patient level.

Comment 5: The discussion is far too long at this point and some of the inferred conclusions are not really accounted for as the sample size calculation does not take into account any of the secondary outcomes. Therefore, in my view, the results and discussion need to be modified to make it clear that the study may not be able to identify any differences because of sample size limitation.

Reply 5: We agree, that the sample size calculation was not based on secondary endpoints and therefor conclusions regarding these data must be taken with caution. This has been emphasized in the text (please see changes below).
Furthermore, the text in the discussion has been shortened according to the reviewer´s recommendation.

Changes in the text:
Resubmitted manus line 303-319: Rearranging of text and minor modifications as follows:
"Sample size of this study was determined upon an expected decrease in duration of surgery on 60 minutes when using the one-stage approach. However, the reduction was 47 minutes in the unilateral group and 22 minutes in the bilateral group and the assumptions made before study start was thereby not met. This leads to concerns whether it is possible to identify any differences between study groups because of sample size limitations. The conclusions to be drawn from the present study may also be limited by the retrospective inclusion of the two-stage group as no baseline measurements of PROs were obtained. Furthermore, the majority of patients in the two-stage group did not complete 12-month follow-up visit but only 24-month follow-up visit leading to a large proportion of missing data. Several additional variables would have been preferred in the resource utilization analysis. For example, total number of outpatient visits for both treatment groups, duration of surgery for additional surgeries due to complications and aesthetic outcome, prize setting of operation time etc. Furthermore, this study did not take into consideration the additional cost for another BR in the case of complications leading to implant loss. At the time of study start no validated Danish questionnaire, as BREAST-Q, for use in patients undergoing breast reconstructive procedures was available. Therefore, a study specific questionnaire was used including questions previously used at our institution (18). With these limitations in mind, the following overall thoughts about the outcome was proposed".

Resubmitted manus line 323: The following sentences have been deleted: **"**Several methods for calculating health care cost exist. A simple analysis of resource utilization is presented and result discussed from the patient and the hospital's point of view as the available data in this study did not allow for a cost benefit- or a cost-utility analysis".

Resubmitted manus line 338: The following sentences have been deleted: "In this study, no difference in hospitalization or sick leave was observed between the two treatment groups. Others report shorter length of stay at the hospital (6,8,20) and this may have changed to a shorter hospitalization period at our institution since this study was conducted".

Resubmitted manus line 373: The following sentences have been deleted: "All patients in the one-stage group and the far majority of patients in the two-stage group

reported a good current overall health at both follow-up visits. This was the dichotomized outcome of the choices: “excellent, very good and good” on a five-point scale with “bad” consisting of the choices: less well and bad. Results were comparable with other studies reporting very good health states after immediate BR with the techniques used in this study (8,29)”.

Resubmitted manus line 380: The following sentence has been deleted: “In the present study more patients reported improved QoL compared to the time before BR at 24-month follow-up (73% and 53%) than previously reported for immediate BR at our institution with a mean follow-up time at 3.8 years (38.5%) (26)”.

Resubmitted manus line 381-382: Adding the phrase with the following: “Despite limitations of this study it is strengthened by the fact that the same team of three plastic surgeons and four breast oncology surgeons ….”

Resubmitted manus line 318: The following sentences have been deleted: “In 2018 Negenborn et al investigated patient satisfaction in a randomized controlled trial (RCT) comparing ADM assisted one-stage BR with submuscular two-stage expander-to implant BR. The authors concluded, that there was no significant difference between the two groups regarding satisfaction with the breast or the overall outcome (31). This result corresponds well with our own results regarding satisfaction with the aesthetic outcome in the same study population presented in another publication (15)”.

Resubmitted manus line 397: The following sentences have been deleted: “Recently the prepectoral placement of an implant fully covered by ADM has gained popularity. This approach was described in 2015 by Reitsamer and Peintinger for immediate BR (37) and is suitable for patients with well-vascularized skin envelopes of sufficient thickness. This approach eliminates the need to elevate the pectoralis major muscle thereby potentially results in decreased postoperative pain and animation deformity and a superior shoulder function compared to the direct to implant subpectoral technique. But also, potentially, this approach leads to an increased risk of rippling. Furthermore, it entails the use of a larger piece of ADM and thereby increase the direct costs for materials related to the BR. Comparison of results after either prepectoral or subpectoral ADM assisted BR have been evaluated in recent studies. Baker et al. compared the two techniques in a prospective study and found no difference in pain during the first postoperative week and no difference in patient satisfaction with breasts and outcome after three months (38)”.

Resubmitted manus line 400: The following sentences have been deleted: “The need for randomized trials is emphasized and the results of a multicenter RCT are awaited with interest (40)”.

Resubmitted manus line 401-406: Rearranging of text and minor modifications as follows: “In summary, the one-stage approach carries a shorter duration of surgery and in addition reduces the need for outpatient visits (for in average 6 times of expansion) and expander to implant exchange. In favor of the two-stage approach was reduced cost of materials due to the use of ADM in the one-stage group and fewer interventions to address the aesthetic outcome. However, pain, sensory disturbances, physical limitations, health status, QoL and body image were equally favorable between the two groups at two-year follow-up.”.

Originally submitted manus line 38-41 (abstract) + 467-470 (manuscript):
“Considering the equally good results in the two treatment groups regarding patient reported outcomes the one-stage approach **should** be preferred if the patient is deemed suitable and is well informed of the potential need for additional interventions to obtain an aesthetically satisfying result”.
Resubmitted manus line 37-40 (abstract) + 413-416 (manuscript):
“Considering the equally good results in the two treatment groups regarding patient reported outcomes the one-stage approach **may** be preferred if the patient is deemed suitable and is well informed of the potential need for additional interventions to obtain an aesthetically satisfying result”.

Reviewer B

Good study with small numbers