Two-stage implant-based breast reconstruction compared with immediate one-stage implant-based breast reconstruction augmented with an acellular dermal matrix: an open-label, phase 4, multicentre, randomised, controlled trial

Rieky E G Dikmans, Vera L Negenborn, Mark-Bram Bouman, Hay A H Winters, Jos W R Twisk, P Quinten Ruhé, Marc A M Mureau, Jan Maerten Smit, Stefania Tuinder, Yassir Eltahir, Nicole A Posch, Josephina M van Steveninck-Barends, Marleen A Meesters-Caberg, René R W J van der Hulst, Marco J P F Ritt, Margriet G Mullender

Summary

Background **The evidence justifying the use of acellular dermal matrices (ADMs) in implant-based breast reconstruction (IBBR) is limited. We did a prospective randomised trial to compare the safety of IBBR with an ADM immediately after mastectomy with that of two-stage IBBR.**

Methods **We did an open-label, randomised, controlled trial in eight hospitals in the Netherlands. Eligible women were older than 18 years with breast carcinoma or a gene mutation linked with breast cancer who intended to undergo skin-sparing mastectomy and immediate IBBR. Randomisation was done electronically, stratified per centre and in blocks of ten to achieve roughly balanced groups. Women were assigned to undergo one-stage IBBR with ADM (Strattice, LifeCell, Branchburg, NJ, USA) or two-stage IBBR. The primary endpoint was quality of life and safety was assessed by the occurrence of adverse outcomes. Analyses were done per protocol with logistic regression and generalised estimating equations. This study is registered at Nederlands Trial Register, number NTR5446.**

Findings **142 women were enrolled between April 14, 2013, and May 29, 2015, of whom 59 (91 breasts) in the one-stage IBBR with ADM group and 62 (92 breasts) in the two-stage IBBR group were included in analyses. One-stage IBBR with ADM was associated with significantly higher risk per breast of surgical complications (crude odds ratio 3·81, 95% CI 2·67–5·43, p<0·001), reoperation (3·38, 2·10–5·45, p<0·001), and removal of implant, ADM, or both (8·80, 8·24–9·40, p<0·001) than two-stage IBBR. Severe (grade 3) adverse events occurred in 26 (29%) of 91 breasts in the one-stage IBBR with ADM group and in five (5%) of 92 in the two-stage IBBR group. The frequency of mild to moderate adverse events was similar in the two groups.**

Interpretation **Immediate one-stage IBBR with ADM was associated with adverse events and should be considered very carefully. Understanding of selection of patients, risk factors, and surgical and postsurgical procedures needs to be improved.**

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Department of Plastic, Reconstructive, and Hand Surgery (R E G Dikmans MD, V L Negenborn MD, M-B Bouman PhD, H A H Winters PhD, J M Smit MD, Prof M J P F Ritt MD, M G Mullender PhD) **and Department of Epidemiology and Biostatistics** (Prof J W R Twisk PhD), **VU University Medical Centre, Amsterdam, Netherlands; EMGO Institute for Health and Care Research Amsterdam, Amsterdam, Netherlands** (R E G Dikmans, V L Negenborn, M-B Bouman, H A H Winters, M G Mullender); **Alexander Monro Breast Cancer Hospital, Bilthoven, Netherlands** (M-B Bouman, H A H Winters, J M Smit); **Department of Plastic, Reconstructive, and Hand Surgery, Meander Medical Centre, Amersfoort, Netherlands** (P Q Ruhé MD); **Department of Plastic, Reconstructive, and Hand Surgery, Erasmus MC Cancer Institute, University Medical Centre Rotterdam, Rotterdam, Netherlands** (M A M Mureau PhD); **Department of Plastic, Reconstructive, and Hand Surgery, Maastricht University Medical Centre, Maastricht, Netherlands** (S Tuinder PhD, Prof R R W J van der Hulst MD); **Department of Plastic, Reconstructive, and Hand Surgery, University Medical Centre Groningen, Groningen,**

Introduction

Breast cancer is the most common malignant disease in women, with an incidence of 1·8 million cases worldwide per year.[1] Survival has increased in high-income countries, meaning long-term clinical care to improve the quality of life of women who survive breast cancer has become ever more important. Mastectomy is indicated in most women with breast cancer, and the loss of a breast can intensely affect a woman's quality of life. In high-income countries, breast reconstructive surgery has become an important part of breast cancer treatment.[2,3] Additionally, increasing numbers of women with genetic predisposition for breast cancer are choosing prophylactic mastectomy followed by immediate reconstruction.[4] In many countries, immediate breast reconstruction, performed during the same session as mastectomy, is routinely offered to women without contraindications.

Several surgical techniques are available for breast reconstruction, and these fall into two main categories: implant-based breast reconstruction (IBBR) and reconstruction with autologous tissue.[5] IBBR accounts for most breast reconstruction procedures, and may be achieved in one stage (direct-to-implant reconstruction) or two stages (temporary implantation of a tissue expander followed by definite implant reconstruction). Many surgeons prefer two-stage IBBR despite the need for an additional operation, multiple visits for tissue expansion, the associated burden on the patient (time and number of procedures), and health-care costs. Generally, the subpectoral pocket left after mastectomy is assumed to be too small to accommodate an implant, which can lead to poor coverage of the lower part of the prosthesis.[6] The use of acellular dermal matrices (ADMs) to augment the subpectoral pocket and allow immediate implantation of a larger-volume implant or tissue expander has

Netherlands (Y Eltahir MD); **Department of Plastic, Reconstructive, and Hand Surgery, Haga Ziekenhuis, Den Haag, Netherlands** (N A Posch MD, J M van Steveninck-Barends); **and Department of Plastic, Reconstructive, and Hand Surgery, Orbis Medisch Centrum, Sittard, Netherlands** (M A Meesters-Caberg MD)

Correspondence to: Dr M G Mullender, Department of Plastic, Reconstructive, and Hand Surgery, VU University Medical Centre, PO Box 7057, 1007 MB Amsterdam, Netherlands
m.mullender@vumc.nl

Research in context

Evidence before this study

The use of acellular dermal matrices (ADMs) in implant-based breast reconstruction (IBBR) has increased substantially over the past decade. Although early reports were overwhelmingly promising, evidence on the safety of ADMs in breast reconstructive surgery has since been ambiguous. We searched MEDLINE and Embase for papers reporting studies done to assess safety outcomes of ADM-assisted breast reconstruction, according to the the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and published before April, 2016. We used the search term ("Acellular Dermis"[Mesh] OR acellular dermis[tiab] OR acellular dermal matri*[tiab] OR acellular tissue matri*[tiab] OR collagen matri*[tiab] OR adm[tiab] OR strattice[tiab] OR alloderm[tiab] OR veritas[tiab]) AND ("Mammaplasty"[Mesh] OR mammaplast*[tiab] OR (breast[tiab] AND reconstruct*[tiab]) OR mammoplast*[tiab] OR (mamma[tiab] AND reconstruct*[tiab])). After screening, we found 99 studies that were suitable to include in a meta-analysis. Most were retrospective. Reported incidences of complications varied substantially between studies. Meta-analyses of the incidences of complications revealed that study heterogeneity was significant for almost all safety outcomes. The overall proportion of events was 18·7% (95% CI 0·159–0.219). Which factors underlie the variation in outcomes, however, was unclear. Additionally, comparison of ADM-assisted techniques with conventional breast reconstructive techniques was lacking. Prospective studies are needed to investigate whether the use of ADM is beneficial in IBBR compared with conventional breast reconstructive surgery.

Added value of this study

The Breast Reconstruction in One Stage (BRIOS) randomised study prospectively assessed conventional two-stage IBBR with the newer one-stage direct-to-implant technique with ADM.

Implications of all the available evidence

The evidence before this study did not show whether the proposed advantages of ADM in breast reconstruction were realised in practice. We found far more early postoperative complications after one-stage IBBR with ADM than after two-stage IBBR, particularly wound healing problems, such as wound dehiscence, skin necrosis, and wound infection, that led to reoperation and, often, removal of the implant. Our results suggest that use of one-stage IBBR with ADM should be considered carefully. This outcome will have direct implications for all women undergoing IBBR, and understanding of selection of patients, risk factors, and surgical and postsurgical procedures will need to be improved.

See Online for appendix

increased over the past decade.[7] This change has made one-stage IBBR feasible, which could lessen the burden on patients and decrease health-care costs. The cosmetic outcome with one-stage ADM-assisted IBBR is also thought to achieve a more natural-looking breast than can be created with two-stage IBBR.[8–11] Although early reports of one-stage IBBR with ADM were overwhelmingly promising, there is little high-level evidence showing that the potential advantages are realised in practice. Outcomes of studies of IBBR with ADM vary widely,[12] and studies that directly compare IBBR techniques with and without the use of ADMs are scarce.

To our knowledge, the Breast Reconstruction in One Stage (BRIOS) study is the first prospective randomised study assessing clinical and patient-reported outcomes of immediate one-stage IBBR with ADM compared with those of two-stage IBBR. Due to worries about safety, just after the final patient was enrolled but before seven women had undergone surgery, the Dutch Health Care Inspectorate requested a preliminary safety analysis. The study ethics board decided to suspend surgery for these seven women and, therefore, here we report the early safety outcomes for the remaining enrolled women. The quality of life data analysis is continuing and will be published in the future.

Methods

Study design and patients

The BRIOS study is a prospective, multicentre, randomised controlled outcome study. Patients were enrolled at eight hospitals in the Netherlands (appendix), which were selected on the basis of having established surgical experience with two-stage IBBR. Women were eligible to participate if they had confirmed breast cancer or genetic predisposition to breast cancer (ie, mutation in *BRCA1* or *BRCA2*), were aged 18 years or older, and intended to undergo a skin-sparing mastectomy followed by IBBR. Exclusion criteria were body-mass index greater than 30 kg/m², breast size larger than C cup, request for a polyurethane implant, smoking 2 weeks before surgery, evidence of misuse of alcohol, drugs, or both, anticipated need for postoperative radiotherapy, pregnancy (current or planned during the study period), severe psychiatric illness or mental disability, inability to complete the study questionnaires, local or general infection that could affect the surgical objective, extensive local inflammatory reactions, proven or suspected hypersensitivity to surgical materials, and immunosuppressive disorders. The protocol was approved by the institutional review board at each study centre. All patients provided written informed consent.

Randomisation and masking

The randomisation schedule was generated by the coordinating researcher (REGD) with ALEA version 2.2, and was stratified by study centre and type of surgery (oncological or prophylactic). Patients were randomised in fixed blocks of ten to achieve roughly balanced groups. The study was open label, and surgeons and patients

were informed about the allocated treatment at least 3 days before surgery.

Procedures

All patients underwent skin-sparing mastectomy performed by oncological surgeons. This procedure was followed by either immediate one-stage IBBR, in which a definitive implant was placed in combination with a Strattice ADM (LifeCell, Branchburg, NJ, USA), or two-stage IBBR, which involved immediate total submuscular placement of a tissue expander that was later exchanged for a definite implant, all performed by plastic surgeons experienced in IBBR. During surgery, all rules for hygienic prosthetic surgery were followed meticulously to decrease the risk of infection (eg, one touch [change of gloves before handling the implant] and a closed-door policy). All patients received Allergan implants (Allergan, Marlow, Buckinghamshire, UK). In accordance with national infection prevention guidelines, all patients received one prophylactic dose of an antibiotic (cefazolin) 30 min before incision, and two doses in the 24 h after surgery. After surgery, all patients were instructed to wear a good-fitting sports bra for at least 2 weeks.

The technique for one-stage IBBR with ADM was to release the inferior origin of the pectoralis major muscle and create a subpectoral pocket. The procedure was continued only after viability of the skin flaps was deemed to be sufficient. If skin flaps were not deemed sufficient, the surgeon could do two-stage IBBR. At the level of the inframammary fold, the ADM sheet was fixed to the chest wall. If needed, a temporary sizer was used to determine the correct dimensions of the ADM sheet, with adjustment to fit the skin envelope made if necessary. Next, the wound bed was rinsed with antibiotic solution (1000 mg cefazolin, 40 mg gentamicin, and povidone-iodine). Two drains were placed at the exit of the inframammary fold (not in the axilla), one between the implant and the ADM and one between the ADM and the skin flap. Finally, the implant was placed and the pocket was completely closed by fixing the ADM to the inferior border of the pectoralis major muscle. The drains remained in place for at least 7 days until output was less than 30 mL in 24 h.

The two-stage IBBR procedure involved creating a complete submuscular pocket underneath the pectoralis major and serratus anterior muscles. The pectoral muscle was opened between its muscle fibres and lifted from the chest wall, which also elevated the serratus anterior muscle and the rectus abdominis fascia at the level of the inframammary fold. The wound bed was rinsed with 1000 mg cefazolin, 40 mg gentamicin, and povidone-iodine solution and a tissue expander was placed beneath the muscle. Two drains were placed at the exit of the inframammary fold (not in the axilla), one in the submuscular pocket and the other subcutaneously. Drains remained in place until output was less than 30 mL in 24 h. Tissue expansion was done in the outpatient clinic by an attending plasctic surgeon as per standard practice. The second-stage surgery for placement of the definite implant was performed at least 3 months after the final filling of the tissue expander.

Patients could be removed from the study because of death before surgery, refusal to participate, and not undergoing surgery before operations were suspended by the ethics committee.

Outcomes

The primary endpoint of the study was quality of life at 1 year after placement of the permanent prosthesis, measured by the BREAST-Q[13] and EuroQol Five-Dimensions questionnaires. Secondary outcomes were the incidence of perioperative and postoperative complications (safety), aesthetic outcome (which will be assessed by an independent panel of plastic surgeons, based on standardised photographs taken 1 year after surgery), pain, and burden on the patients in terms of number of procedures and time invested. In this Article, we report the early safety outcomes, that is, the incidence of postsurgical complications. All adverse events were recorded for 1 year after placement of the definite implant, using terms in the Common Terminology Criteria for Adverse Events (version 4.0). If a reoperation resulted in removal of the implant, ADM, or both, the patient's data were included in the analyses of adverse events and reoperations. Adverse events occurring after reoperations that did not involve removal of the implant or ADM were included in the analyses. Reoperations for aesthetic reasons were analysed separately. We also recorded data on the course and nature of the interventions, demographics, and relevant medical data for all patients, but not performance status.

Statistical analysis

We based our calculation of sample size on the expected health-related quality of life assessed with BREAST-Q in the two-stage IBBR group. BREAST-Q renders scores from 0 to 100 points. We expected a mean satisfaction score of 60 points (SD 20) in the two-stage IBBR group[13,14] and took a difference of 10 points between groups to be clinically relevant. We estimated that a group size of 65 women in each group would provide 80% power to detect at least a 10-point difference with Student's t test (α=0·05). Anticipating a dropout rate of 8%, we therefore aimed to enrol 70 women per group.

We tested the hypothesis that one-stage IBBR with ADM would result in a better quality of life, cosmetic results, and cost-effectiveness than two-stage IBBR. Descriptive statistics were used for patients' demographics, treatment-related and disease-related variables, and clinical outcomes. We assessed the effect of the surgical method on outcomes per patient (logistic regression) and per breast (logistic generalised estimating equations),[15] and results are expressed as odds

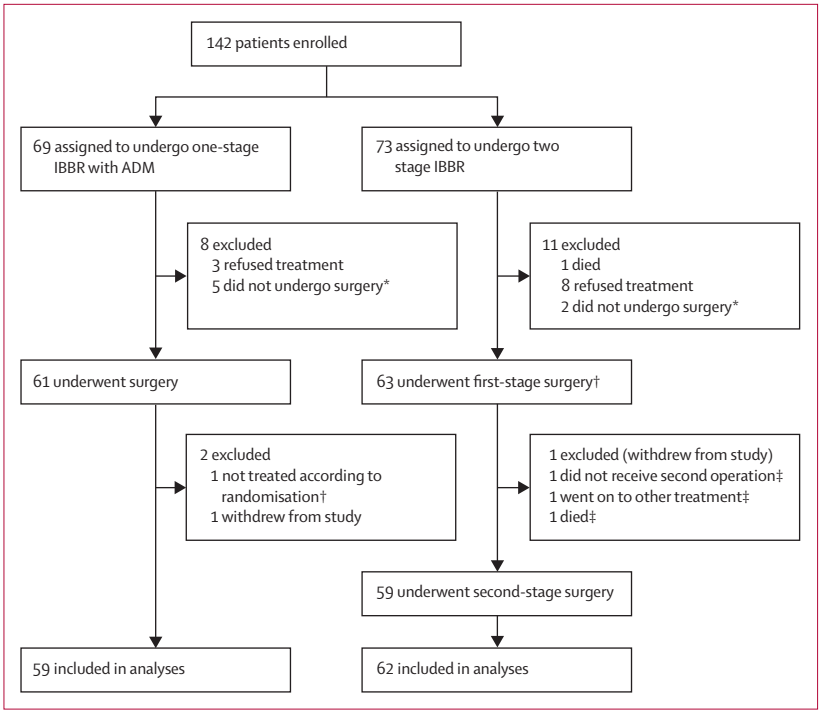

***Figure*: Trial profile**
IBBR=implant-based breast reconstruction. ADM=acellular dermal matrix. *The ethics committee put surgery on hold before these operations. †Treatment was two-stage IBBR because of the surgeon's decision during surgery, and the patient was analysed as part of the two-stage IBBR group. ‡Included in final analysis.

ratios with 95% CIs. Data were analysed per protocol for surgical complications, reoperation for medical reasons, and removal of the implant, ADM, or both, for medical reasons. In addition to a crude analysis, age, body-mass index, diabetes mellitus status, smoking, preoperative chemotherapy, postoperative chemotherapy, hormone therapy, and targeted therapy were added to the model as covariates. We did all analyses with SPSS version 22.0. This study is registered at Nederlands Trial Register, number NTR5446.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to sut for publication.

Results

Between April 14, 2013, and May 29, 2015, 142 women were enrolled and randomly assigned to undergo one-stage IBBR with ADM (n=69) or two-stage IBBR (n=73). 21 women were excluded from the analyses (figure). Those who refused treatment or withdrew from the study stated preferences for the other method or treatment in another hospital. Other exclusions were the seven women who had not yet undergone any surgery before the ethics committee suspended further operations and one patient in the two-stage IBBR group died before the first operation due to progression of breast carcinoma, including metastases in her lungs, pelvis, and axilla. One patient in the one-stage IBBR with ADM group who did not receive the allocated surgical procedure based on the perioperative decision of the surgeon and one woman in the two-stage IBBR group who died from metastatic breast cancer after undergoing the first-stage operation were included in the analyses. Thus, 59 patients (91 breasts) in the one-stage IBBR with ADM group and 62 patients (92 breasts) in the two-stage IBBR group were included in the final analyses (figure).

Patients' baseline characteristics were similar in the two groups (table 1). The overall median time of follow-up after mastectomy and first reconstructive surgery was 24·0 months (IQR 30·0–18·0), mean age was 45·5 years (SD 12·0) and the median was 47·0 years (IQR 35·0–53·5), and mean body-mass index was 23·1 kg/m² (SD 2·7). 20 patients had a history of smoking (mean pack-years 12·9 [SD 9·7]). The operations were therapeutic (ie, to remove a tumour) in 77 (64%) of 121 women and prophylactic in 44 (36%). Among the women undergoing prophylactic surgery, most operations were done because of gene mutations (table 1).

27 (46%) of 59 patients in the one-stage IBBR with ADM group had surgical complications, compared with 11 (18%) of 62 in the two-stage IBBR group (odds ratio 3·47, 95% CI 1·39–8·61, p=0·008). No events were classified as grade 4 and no deaths were associated with surgery. Severe (grade 3) adverse events occurred in 26 (29%) of 91 breasts in the one-stage IBBR and ADM group, including skin necrosis, wound dehiscence, and wound infection (table 2). By contrast, severe adverse events occurred in five (5%) of 92 breasts in the two-stage IBBR group (table 2). One case of incomplete resection was reported in each group. 11 (19%) patients in the one-stage surgery group and nine (15%) in the two-stage surgery group were considered to have cosmetically unsatisfactory results.

Reoperations for medical reasons were done in 22 (37%) women (19 [32%] of 91 breasts) in the one-stage IBBR with ADM group, compared with nine (15%) women (11 [12%] of 92 breasts) in the two-stage IBBR group (odds ratio 3·7, 95% CI 1·31–10·42, p=0·014; table 3). In the one-stage IBBR with ADM group, among six (10%) patients who needed implants removed, three had one implant removed (after which one patient had unilateral reconstruction) and three had two removed. In ten (17%) patients the implants and (part of the) ADM were removed (one breast in seven patients, of which five had had unilateral surgery, both breasts in two patients, and the implant and ADM on one side and only the implant on the other side in one patient). In one (2%) patient, only the ADM was partly removed in both breasts. In the two-stage IBBR group, only one implant had to be removed and the remaining removals were of tissue expanders (table 3). All removal surgeries except two were

	One-stage IBBR with ADM group (n=59)	Two-stage IBBR group (n=62)
Age (years)		
Mean	43·5 (11·7)	47·3 (12·1)
Median (IQR)	44·0 (52·0–32·0)	49·0 (56·0–38·0)
Body-mass index (kg/m²)	23·4 (2·9)	22·9 (2·5)
Indication for surgery		
Prophylactic	21 (36%)	23 (37%)
Gene mutation	19 (32%)	22 (36%)
Familial breast cancer	2 (3%)	1 (2%)
Therapeutic	38 (64%)	39 (63%)
Ductal (adeno) carcinoma	33 (56%)	29 (47%)
DCIS	4 (7%)	8 (13%)
Carcinoma and DCIS	0	1 (2%)
Lobular carcinoma in situ	0	1 (2%)
Paget's disease of the breast	1 (2%)	0
Unilateral treatment	27 (46%)	32 (52%)
Bilateral treatment	32 (54%)	30 (48%)
No axillary surgery		
Right	24 (26%)	27 (29%)
Left	26 (29%)	27 (29%)
Sentinel node		
Right	18 (19%)	15 (16%)
Left	17 (19%)	20 (22%)
Axillary resection*		
Right	3 (3%)	1 (1%)
Left	3 (3%)	2 (2%)
Nipple sparing		
Yes		
Right	18 (20%)	14 (15%)
Left	17 (19%)	19 (21%)
No		
Right	27 (30%)	29 (32%)
Left	29 (32%)	30 (33%)
(Table 1 continues in next column)		
(Continued from previous column)		
Mastectomy weight (g)		
Right	382·7 (152·5; n=44)	366·49 (134·0; n=35)
Left	361·7 (134·0; n=43)	353·1 (126·7; n=48)
Filling volume (mL)		
Right	N/A	431·0 (142·7; n=35)
Left	N/A	398·2 (125·2; n=47)
Implant volume (mL)		
Right	392·1 (93·5; n=45)	416·2 (132·5; n=34)
Left	394·6 (95·5; n=45)	399·8 (116·7; n=43)
Median (IQR) follow-up after implantation (months)		
First surgery	25·0 (31·0–19·0)	24·0 (29·0–17.0)
Second surgery	N/A	17·0 (22·0–10·0)
Current smoker†	12 (20%)	8 (13%)
Pack-years	11·3 (8·3)	16·0 (11·8)
Diabetes mellitus	2 (3%)	0
Chemotherapy		
Before surgery	7 (12%)	4 (7%)
After surgery	15 (25%)	17 (27%)
Radiotherapy (adjuvant)	5 (9%)	6 (10%)
Hormonal therapy	19 (32%)	17 (27%)
Targeted therapy	3 (5%)	4 (7%)

Data are mean (SD) or number (%) unless otherwise stated. IBBR=implant-based breast reconstruction. ADM=acellular dermal matrix. DCIS=ductal carcinoma in situ. N/A=not applicable. *Reported if axillary resection followed sentinel node biopsy. †These patients were advised to quit smoking 2 weeks before surgery.

***Table 1*: Baseline characteristics**

done because of wound healing problems (necrosis, wound dehiscence, and wound infection). The other two removals were in the two-stage IBBR group and were due to suspected perforation).

Nine (15%) patients in the one-stage IBBR and ADM group and 11 (18%) patients in the two-stage IBBR group without surgical complications reported dissatisfaction with the cosmetic outcome, affecting 12 (13%) and 17 (19%) breasts, respectively. Of these, seven women received autologous fat grafting (four in the one-stage IBBR with ADM group and three in the two-stage IBBR group), four received corrective surgery (two in each group), four had one or both implants removed or replaced (two in each group), and six (one in the one-stage IBBR with ADM group and five in the two-stage IBBR group) had no intervention. The interventions for cosmetic reasons per breast are shown in table 3.

The adjusted risks of surgical complication, need for reoperation, and removal of the implant, ADM, or both were all significantly higher in the one-stage IBBR with ADM group than in the two-stage IBBR group (table 4). The risk remained significant whether compared per patient or per breast.

Discussion

The BRIOS study is a prospective randomised controlled trial to assess the clinical outcomes of immediate one-stage IBBR with ADM versus the conventional approach of two-stage IBBR. In this Article we present the early safety data for IBBR, which is a secondary endpoint of the BRIOS study. One-stage IBBR with ADM was associated with higher odds ratios for surgical complications, reoperation, and removal of the implant, ADM, or both, compared with two-stage IBBR. The number of interventions for cosmetic reasons was

	One-stage IBBR with ADM group (n=91)		Two-stage IBBR group (n=92)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Haematoma	3 (3%)	0	2 (2%)	0
Seroma	0	0	2 (2%)	0
Burn wound	0	0	1 (1%)	0
Blister	0	0	1 (1%)	0
Redness without signs of infection	5 (6%)	0	1 (1%)	0
Wound infection	0	7 (8%)	0	2 (2%)
Skin necrosis	0	11 (12%)	0	1 (1%)
Wound dehiscence exposure				
ADM	0	5 (6%)	0	N/A
ADM and implant	0	2 (2%)	0	N/A
Unknown	0	1 (1%)	0	0
Suspected perforation	0	0	0	2 (2%)

IBBR=implant-based breast reconstruction. ADM=acellular dermal matrix. N/A=not applicable.

***Table 2*: Adverse events per breast**

	One-stage IBBR with ADM group (n=91)	Two-stage IBBR group (n=92)
Reoperation for surgical reasons		
Haematoma evacuation	3 (3%)	4 (4%)
Excision of burn wound	0	1 (1%)
Botox injection	1 (1%)	0
Necrosectomy	1 (1%)	1 (1%)
Removal		
Tissue expander	N/A	3 (3%)
Implant	10 (11%)	1 (1%)
ADM	2 (2%)	N/A
ADM and implant	12 (13%)	N/A
Re-excision after mastectomy with positive margins	0	1 (1%)
Reoperation for cosmetic reasons		
Autologous fat grafting	5 (6%)	3 (3%)
Dog-ear correction	1 (1%)	4 (4%)
Autologous fat grafting and dog-ear correction	1 (1%)	2 (2%)
Autologous fat grafting and lowering of NAC	0	1 (1%)
Excision of rest of border NAC	1 (1%)	0
Implant removal or replacement	3 (3%)	2 (2%)

IBBR=implant-based breast reconstruction. ADM=acellular dermal matrix. N/A=not applicable. NAC=nipple–areolar complex.

***Table 3*: Reoperations per breast**

similar in the two groups. Potential confounding factors were distributed evenly across groups, and adjustment for these factors only marginally affected odds ratios.

Although one-stage IBBR with ADM led to significantly worse safety outcomes than two-stage IBBR, the incidences of surgical complication and implant removal with the one-stage procedure were very similar to those reported in a prospective study of one-stage IBBR without ADM.[16] In that study, involving 309 women, 121 (39%) had complications and 63 (20%) needed implants removed after surgery. We suggest that the increased risk associated with one-stage IBBR is due to the increased pressure on the skin flaps and the possibility of misjudging the appropriate implant size without the possibility of adjusting implant volume. Performing nipple-sparing mastectomy involves an additional risk because nipple removal might be necessary in a second operation due to positive margins. The resulting lack of skin often necessitates replacement of the implant with a smaller one. Multiple retrospective and prospective cohort studies, most of which used human-derived ADMs and only a few used porcine-derived ADMs, have reported widely varying proportions of patients with complications, from 5%[10,17] to 46%.[18,19] A systematic review revealed that a median of 18% (range 6–64) of women who underwent one-stage IBBR with ADM had complications, compared with 14% (5–14) who underwent two-stage IBBR with ADM.[12] In Europe, human-derived ADMs are not available, thus we used a porcine-derived ADM in this study. Whether the incidence of surgical complications is affected by the type of ADM used is unclear.

Most adverse events in our one-stage IBBR with ADM group were related to wound healing problems, such as skin necrosis, wound dehiscence, and wound infection. These problems frequently progressed and, ultimately, necessitated removal of the implant, the ADM, or both. Red-breast syndrome, which potentially indicates a reaction to the ADM, was seen in five patients (five breasts) in the one-stage IBBR with ADM group and redness was also seen in one patient (one breast) in the two-stage IBBR group. Redness resolved in all patients, some after treatment with a non-steroidal anti-inflammatory drug. Because we compared two different techniques, we were unable to assess the independent effect of the ADM. However, we noted no indications of adverse reactions to the ADM as a material, but we can neither confirm nor exclude that the added complexity of the ADM-assisted procedure had a causative role in the increased incidence of complications. In a randomised trial that compared two-stage IBBR with and without Alloderm ADMs (LifeCell), the number of complications did not differ between groups (six [17%] of 36 *vs* five [15%] of 33).[20] This finding suggests that the use of ADM did not lead to additional adverse reactions when applied in a two-stage IBBR.

Radiotherapy is a known risk factor for complications after breast reconstructive surgery.[6] In this study, 11 (9%) of 121 patients received adjuvant radiotherapy, with numbers being similar in the two groups. Radiotherapy cannot, therefore, explain the difference in outcomes between groups. It is possible that radiotherapy in combination with the direct-to-implant technique used in one-stage IBBR with ADM might have amplified the

risk of adverse events, but this study was not designed to assess such an effect, and the numbers are too small to establish any interaction.

To find out which factors are predictive of an adverse outcome, one-stage IBBR should be assessed in more depth. The factors most associated with risk[21] were already exclusion criteria in this study, including breast size larger than C cup, high body-mass index, and smoking in the 2 weeks before surgery. Clear evidence about the roles of such risk factors, however, is lacking.

This study had several limitations. First, we analysed the adverse events before follow-up of all patients was completed. The time of follow-up after the first surgery ranged from 10 to 38 months, whereas after the second surgery in the two-stage group, it ranged from 1 to 33 months. Although most surgery-related complications occur soon after the surgery, events might have occurred in the remaining follow-up period. In the two-stage IBBR group, however, most complications were associated with the first surgery, with seven occurring after the first and four after the second surgery. Events and reoperations related to cosmetic outcomes are probably underestimated in our analyses, as some additional interventions for cosmetic reasons are likely to be performed in the future. Surgeons and patients were aware of the type of procedure given. As expectations are known to play a part in the patient's satisfaction after a procedure,[22] we cannot rule out a placebo effect on degree of satisfaction with cosmetic results.

Second, a learning curve for one-stage IBBR with ADM could have influenced the results. All surgeons performing IBBR were experienced plastic surgeons. However, although they were trained in the use of ADMs in one-stage procedures, experience of performing the specific procedure used in this study was limited. Specific experience with the use of ADM might be an important factor in determining the risk of complications.

Third, we did not systematically assess skin flap quality, nor did we take into account the experience of the oncological surgeon. Thin or poorly vascularised skin flaps are viewed as risk factors for complications.[23–25] Skin flap quality, however, was likely to be similarly distributed in the two treatment groups and, as such, unlikely to confound the results in this study. No validated measurement of flap viability is currently available. We did not use imaging techniques to assess flap viability and, therefore, it was judged subjectively by the operating plastic surgeon. Surgeons were instructed to perform one-stage IBBR if the flap was deemed viable, and in only one case did a surgeon decide to change the technique to two-stage IBBR because of poor skin flap quality. In the one-stage IBBR with ADM group, skin flap quality was probably of more consequence than in the two-stage IBBR group, because the wound and skin are placed under much higher tension after wound closure owing to the larger initial implant volume. In addition, neovascularisation of the skin flap originating from the well vascularised pectoral muscle might not reach the lower pole, where it directly overlies the ADM. If vascular ingrowth into the ADM is delayed, survival of the skin flap is jeopardised. Flap viability might, therefore, be one of the most important factors, or could even be the crucial factor, when deciding for or against one-stage IBBR.

	Surgical complication		Reoperation		Removal of implant	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Per patient						
Crude	3·76 (1·64–8·63)	0·002	3·74 (1·50–9·36)	0·005	11·40 (2·49–52·13)	0·002
Adjusted*	3·46 (1·39–8·61)	0·008	3·69 (1·31–10·42)	0·014	16·82 (2·44–115·94	0·004
Per breast						
Crude	3·81 (2·67–5·43)	<0·001	3·38 (2·10–5·45)	<0·001	8·80 (8·24–9·40)	<0·001
Adjusted*	3·42 (2·28–5·12)	<0·001	2·91 (1·34–6·34)	0·007	8·28 (5·22–13·14)	<0·001

Cosmetic outcomes are excluded. *Adjusted for age, body-mass index, smoking, diabetes mellitus, chemotherapy (before and after surgery), radiotherapy (postoperative), hormone therapy, and targeted therapy.

***Table 4*: Risk of medical complications, reoperation for medical reasons, and removal of implants**

To our knowledge, this is the first prospective randomised controlled trial to compare one-stage ADM-assisted IBBR with two-stage IBBR. Far more early postoperative complications occurred after one-stage IBBR with ADM than after two-stage IBBR. The one-stage technique was associated with a marked increase in wound healing problems, such as wound dehiscence, skin necrosis, and wound infection, necessitating reoperation and, frequently, removal of the implant. We found no evidence of adverse tissue reactions to the ADM itself. Our results suggest that use of one-stage IBBR with ADM should be considered carefully.

Contributors

REGD, M-BB, HAHW, PQR, MAMM, JMS, ST, YE, NAP, JMvS-B, MAM-C, MJPFR, and MGM designed the study. REGD supervised the study. VLN, M-BB, HAHW, PQR, MAMM, JMS, ST YE, NAP, JMvSB, MAM-C, RRWJvdH, MJPFR, and MGM collected the data, and analyses were done by VLN and JWRT. Data interpretation was done by REGD, VLN, and JWRT. REGD, VLN, and MGM wrote the paper. and all authors provided critical revision, gave final approval, and agreed to be accountable for the work.

Declaration of interests

We declare no competing interests.

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