Title

The Increased Risk Of Adverse Outcomes in Bilateral Deep Inferior Epigastric Artery Perforator Flap Breast Reconstruction Compared To Unilateral Reconstruction: A Systematic Review and Meta-Analysis

Category

Systematic Review and Meta-Analysis

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None declared.

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Abstract

Background: The rate of bilateral mastectomy and bilateral breast reconstruction is increasing. The deep inferior epigastric artery perforator (DIEP) flap is an ideal method of breast reconstruction. The difference in risk of adverse outcomes between unilateral and bilateral DIEP flap breast reconstruction is unclear. The aim of this review is to investigate this relationship.

Methods: Authors searched Ovid EMBASE and MEDLINE from database inception to March 2012, for reports of DIEP flap breast reconstruction studies. After screening, data were extracted on flap-related, donor-site and systemic adverse events. Descriptive statistics were generated for all pooled data. We performed meta-analysis of direct comparisons to generate relative risk (RR) ratios with 95% confidence intervals (CI) using a random-effects model.

Results: Overall, 17 case-series of 2398 women were included. Compared with unilateral DIEP flap breast reconstruction, bilateral reconstruction was associated with a significantly higher risk of total flap failure (RR 3.31 [95% CI 1.50-7.28]; p=0.003) and breast seroma (RR 7.15 [95% CI 1.21-42.36]; p=0.03). Differences between other outcomes were non-significant, although descriptive analysis appeared to favour unilateral reconstruction.

Conclusions: The current literature related to DIEP flap breast reconstruction appears to be of low quality. However, our results indicate that bilateral DIEP flap breast reconstruction is associated with a significantly higher risk of total flap failure compared to unilateral reconstruction. This review will allow clinicians to better inform patients of the risks of adverse outcomes in DIEP flap breast reconstruction. This review also highlights the need for higher quality research in this area.

Words = 249

Introduction

Advances in breast cancer screening and the early detection of women at high risk of malignancy has led to an increase in the number of bilateral mastectomy procedures and an increased demand for bilateral breast reconstruction.[1-6] The common indications for bilateral breast reconstruction include: primary prophylactic (risk reducing) bilateral mastectomy for women at high risk of cancer (e.g. BRCA1/2 carriers or strong family histories), unilateral mastectomy with contralateral prophylactic mastectomy for women with similarly high risk of malignancy, anxiety related illness, implant failure, synchronous or non-synchronous bilateral mastectomy for cancers and bilateral mastectomy for significantly distorted breasts from breast conserving surgery.[7-12]

Bilateral autologous tissue breast reconstruction seems to offer the highest level of patient satisfaction and the DIEP flap is evolving as an ideal method due to reduced donor site morbidity, fewer days in hospital, less post-operative pain and superior aesthetic outcomes.[13-14] Whilst bilateral DIEP flap breast reconstruction is generally considered to be a more complex operation with higher risks of complications, compared to unilateral reconstruction, the literature available on adverse outcomes is controversial with limited series reporting variable rates of complications.[15-19]

Rationale

Given the increasing demand for bilateral breast reconstruction and the complexity of bilateral DIEP flap breast reconstruction, there is a need for a comprehensive evaluation of the risks of bilateral versus unilateral DIEP flap breast reconstruction, in order to allow patients to be better informed and comprehensively consented.[20]

Methods

The objective of this review was to assess the literature on DIEP flap breast reconstruction, with a focus on identifying, evaluating and comparing the complications rates of unilateral and bilateral procedures in accordance with the Meta-analysis of Observational Studies guidance and using methodology described in the Cochrane Handbook of Systematic Reviews of Interventions where applicable.[21, 22]

Search methods

All authors individually carried out a full systematic literature search of all records in Ovid MEDLINE and Ovid EMBASE from 1994, when DIEP flap breast reconstruction was first described, until March 2012.[23] Both 'free-text term' and 'MeSH term' searches were completed, using variations of the keywords 'breast reconstruction', 'mammaplasty', 'DIEP', 'deep inferior epigastric artery perforator flap', 'free flap', 'unilateral', 'single', 'one-sided', 'bilateral' and 'two-sided' and were combined using Boolean operators.[22] Only English language articles were considered. The archives of three major plastic surgery journals were hand searched for recent/in-press articles that may have been missed by electronic searching. Each author's search results were merged and duplicate citations were discarded. Titles and abstracts were screened and studies unrelated to the research objective were discarded. The full text of the relevant papers were retrieved and examined by each author independently for consideration for inclusion/exclusion. The final list of the included studies was compared and discussed between all authors. The reference lists of the included papers and previous reviews were examined to ensure relevant studies had been considered. Any disparities regarding inclusion of articles were discussed between the authors and a joint decision was made based on the inclusion criteria. The published data from included studies was scrutinised for reporting of outcomes. If some relevant data was not available for extraction then the authors of the study were contacted by email with a specific data request. If there was no reply, a reminder email was sent after 2 weeks. If we received no response

then we sent a further email and waited for 8 weeks for reply. If we still received no response then the study was excluded and the authors were notified.

Criteria for selecting studies

Study selection criteria were determined in advance during the protocol stage. Two authors used a bespoke inclusion/exclusion form to independently assess eligibility of studies (Appendix 1). We only included studies if they reported a minimum of 100 patients with unilateral DIEP flap breast reconstruction or a minimum of 50 patients with bilateral DIEP flap breast reconstruction. This inclusion criterion was decided upon in the protocol stage to ensure that the sample size of included series would have minimal impact on the reliability of our results.[22, 24] Case reports were excluded. Study participants were women over 18 years old undergoing unilateral or bilateral DIEP flap breast reconstruction. Studies were included if they report any adverse outcomes for DIEP flap breast reconstruction including flap related, donor-site or systemic complications (Appendix 1).

Data collection

Data collection and analysis were performed in accordance with the Meta-analysis of Observational Studies guidance and the Cochrane Handbook of Systematic Reviews of Interventions where applicable.[21, 22] Data were extracted onto a pre-defined electronic data extraction form and included location of study, study design, recruitment period, sample size, timing of reconstruction (immediate or delayed), age of participants, BMI, active smokers, obesity, medical comorbidity (i.e. diabetes, hypertension and ischaemic heart disease), neo-adjuvant or adjuvant therapies, previous abdominal scarring and length of post-operative follow-up. Demographics were only extracted from papers reporting DIEP flap breast reconstruction patients only (i.e. demographics from papers including other free flaps were not extracted). Outcome data were extracted on flap-related complications, donor-site complications and systemic complications. Our primary outcome was total flap failure. One author (JCRW) extracted the data and the others (RGW and AF) independently checked the

accuracy of extracted data. In order to reduce the heterogeneity of the outcome reporting, we grouped all complications related to vascular compromise of the flap (venous congestion/thrombosis, arterial ischaemia/thrombosis) under the term 'vascular complications'. The data were then separated by intervention (unilateral versus bilateral DIEP flap breast reconstruction).

Statistical Analysis

The unit of investigation for our review was the patient rather than the flap. For the majority of the published literature in DIEP breast reconstruction the unit of investigation is 'the flap' instead. We believe that when considering adverse outcomes, comparing unilateral and bilateral procedures, it is not appropriate to analyse results by 'flap' as the patient will suffer the impact of the complication, especially in bilateral DIEP breast reconstruction, where the flaps are 'two' but the patient is 'one'. Equally, analysing by 'flap' will underestimate the clinical impact of the adverse outcomes. If three or more studies reported the same outcome then the data from the single studies were pooled for comparative analysis. If an outcome was reported in less than three studies then this outcome was excluded from the pooled analysis. The number of adverse events were expressed as percentages for comparative descriptive analysis.

If a study reported outcomes of both unilateral and bilateral DIEP flap breast reconstruction then we performed direct comparison meta-analysis with RevMan5 to calculate relative risk ratios with 95% confidence intervals using the Cochran-Mantel-Haenszel test.[25] We used a random-effects model due to study heterogeneity.[22] No subgroup analysis was undertaken. No indirect comparison meta-analysis was performed due to the quality of the original data and the high risk of bias.[26] Statistical heterogeneity was quantified for all direct comparisons using the I^2 statistic.[27] Significance was set at the 5% level. Meta-analysis results are displayed in forest plots with a funnel plot to assess publication bias in our primary outcome.[28]

Results

Forty-three studies were eligible for inclusion: 14 studies were eligible for immediate data extraction.[29-42] The other 29 studies were missing outcome data. Following data request emails, three authors provided the required data.[43-45] This created a total of 17 papers included in our systematic review.[29-45] Ten authors of the 29 studies with missing data replied to the email request but were unable to provide additional data.[46-55] No response was received from the remaining 16 authors.[56-71]

Characteristics of Studies

Included studies were all case series. No randomised controlled trials or cohort studies were available. There were 13 consecutive case series and 4 series described as non-consecutive. The mean recruitment period was 5.7 years (range 1 to 10.5 years). The mean sample size was 141 (range 54 to 407). Follow-up period was available from seven studies with a mean follow-up being 26 months (range 14.6 to 40 months). Eight studies reported on both unilateral and bilateral DIEP flap breast reconstruction. Five studies contained unilateral DIEP flap breast reconstruction cases only.[38-40, 43, 47] Three studies contained only bilateral DIEP flap breast reconstruction cases.[29, 33, 42] Two studies reported on the same patient database but analysis of different outcomes was performed and thus they were not excluded from the review (Table 1). Overall, 17 studies with a total of 2398 patients were included. Patient characteristics are summarised in Table 2, and were similar between studies and groups where reported.

Flap related adverse outcomes

Flap related outcomes are summarised in Table 3. Total flap failure was more common in bilateral DIEP flap breast reconstruction (3.3% vs. 2.2%). Direct comparison meta-analysis of the four studies reporting total flap failure (n=762) showed a significantly increased relative risk of total flap failure in bilateral reconstruction (RR 3.31 [95% CI 1.50-7.28]; p=0.003) (Figure 4). Although the

absolute risk of this complication is very low, there is a three-fold increase in relative risk of total flap failure for those undergoing bilateral procedures.

There were no significant difference in the incidence of partial flap failure between groups, but it was apparently higher for unilateral DIEP flap breast reconstruction (4.6% vs. 3.1%, Figure 5). There was no significant difference in the occurrence of post-operative breast haematomas between groups (bilateral 5.3% vs. unilateral 3.5%, Figure 6). The incidence of post-operative breast seroma was higher for bilateral DIEP flap breast reconstruction (4.5% vs. 0.8%) with a corresponding significantly higher relative risk (RR 7.15 [95% CI 1.21-42.36]; p=0.03) (Figure 7). The incidence of fat necrosis was apparently higher for unilateral reconstruction, but this was not statistically significant (16.9% vs. 14.9%, Figure 8). Vascular complications were more frequent in unilateral reconstruction but this was not statistically significant (6.2% vs. 4.5%, Figure 9).

Donor site related adverse outcomes

Donor site related adverse outcomes are summarised in Table 3. Post-operative abdominal haematoma was more common in bilateral DIEP flap breast reconstruction but this was not statistically significant (3.6% vs. 0.7%, Figure 10). Post-operative abdominal seromas were more common in bilateral reconstructions (9.6% vs. 1.4%) but this was not statistically significant and meta-analysis was impossible as only one study was included (which originally reported no significant difference).[31] The risk of developing a post-operative abdominal hernia/bulge was not significantly different between groups (unilateral 4.7% vs. bilateral 4.9%, Figure 11).

Systemic adverse outcomes

Systemic adverse outcomes are summarised in Table 3. Post-operative infection was more common in unilateral reconstruction (10.8% vs. 3.1%) but meta-analysis was not possible as only one study contained direct comparisons, which did not originally report a significant difference between groups.[31] One paper described that blood transfusion was more frequently required in bilateral DIEP flap breast reconstruction compared to unilateral reconstruction (5.6 versus 3.2 units).[41] No case series reported any deaths as a result of the intervention.

Heterogeneity and Publication Bias

The funnel plot for total flap failure is displayed in Figure 10. It is not possible to comment on publication bias in this review due to the small number of studies for our primary outcome. Inconsistent outcome reporting, the size and variability of the sample sizes of included studies increased statistical heterogeneity and reduced the ability to detect differences between groups; this is represented by the abnormally low I^2 statistics shown in the forest plots. The small number of studies containing direct comparisons of unilateral and bilateral DIEP flap breast reconstruction and the heterogeneity of outcome reporting reduced the scope of our meta-analysis.

Discussion

Our review has highlighted a number of important issues, the most imperative being that the current literature related to DIEP flap breast reconstruction appears to be of low quality**,** consisting largely of case series alone.[72] Case series carry a significant risk of selection and reporting bias, and consequently the reliability of their results are reduced.[22] Our findings are in agreement with other recent systematic reviews in the field of breast reconstruction, concluding that the literature is lacking high quality (level 1 and 2) evidence.[24, 73-77] Randomisation in breast reconstruction research is a highly debated topic and clinical trials are currently investigating the acceptability and feasibility of this approach.[78] Until such evidence is available, researchers should aim to undertake prospective observational cohort studies considering both objective and patient-related outcomes on consecutively recruited patients. When conducted properly, such study designs may generate results of similar reliability to clinical trials.[79]

Our meta-analysis of studies directly comparing unilateral and bilateral DIEP flap breast reconstruction, suggests that bilateral reconstruction carries a significantly greater risk of total flap failure. The relative risk of total flap failure between unilateral and bilateral DIEP flap breast reconstruction was 3.31 [95% CI 1.50-7.28]; p=0.003, indicating a three-fold increase in risk of developing this adverse outcome after bilateral DIEP flap breast reconstruction. However, total flap failure is rare (2.2% to 3.4%) and considered in only four heterogeneous studies of 762 patients, so cautious interpretation of these results is essential. Moreover, the pooled analysis considered studies with relatively small sample sizes that were unlikely to be sufficiently powered to reliably detect uncommon events such as total flap failure. These limitations help to explain the wide confidence intervals of relative risk figures available in this meta-analysis. Nevertheless, this finding correlates with common clinical experience. This higher risk reflects the likelihood that the incidence of complications may be greater in bilateral DIEP flap breast reconstruction due to the need to utilise both sides of the lower abdomen as two single flaps, alongside the potential unfavourable effects of surgeon fatigue secondary to longer operative times. By definition, our direct comparison meta-analysis could not consider series, which reported on bilateral

reconstructions only. Interestingly, most of the bilateral DIEP flap breast reconstruction series reported no total flap losses despite equivocal numbers of major peri-operative complications requiring a return to theatre. When we informally compared the number of total flap failure in all included studies, using an indirect comparison meta-analysis (statistically not viable), the relative risks ranged between 0.92 and 1.09, which suggests comparable risk for patients undergoing unilateral or bilateral DIEP flap breast reconstruction. The inconsistency in cases of total flap failure between studies directly comparing unilateral and bilateral procedures versus series of bilateral reconstructions only, suggests a problem with selective outcome reporting in the DIEP flap breast reconstruction literature and further compounds our conclusion of the need for higher quality evidence in this field.

The risk of partial flap failure appeared to be higher in unilateral reconstruction compared to bilateral reconstruction, although was not statistically significant. This difference in risk is most likely to be due to the increased sample size of the unilateral group rather than any true difference in risk.

There was an increased incidence and relative risk of breast haematoma in bilateral DIEP flap breast reconstruction, but this was not statistically significant. From our own experience, there is a propensity for bilateral reconstructions to be performed as immediate procedures, whereas unilateral reconstructions may be more often delayed, which may account for this increased risk. Additionally, immediate reconstruction carries a higher risk of haematoma than delayed.[55]

The risk of post-operative breast seroma appeared to be significantly greater in bilateral DIEP flap breast reconstruction, based on our meta-analysis of two studies on a total of 183 women. However, the studies are not recent and reported on small sample sizes, which generated wide confidence intervals in our meta-analysis. Therefore, we cannot confidently advise clinical recommendations based on our results. Again, we believe that higher quality research is required in order to better investigate this complication.

The incidence of vascular complications was higher in unilateral reconstruction compared to bilateral reconstruction. Conversely, on meta-analysis the risk of vascular complications was higher in bilateral reconstruction, but was not statistically significant. We would expect the number of vascular complications to be higher in bilateral reconstruction as there are at least two micro-anastomoses performed. The higher number of vascular complications in unilateral cases in the pooled data may simply reflect the larger unilateral sample. The incidence of fat necrosis was similar for unilateral and bilateral DIEP flap breast reconstruction, with a similar risk on meta-analysis.

The increased incidence of abdominal haematoma in bilateral DIEP flap breast reconstruction may be explained by the additional surgical trauma to the abdominal wall but may simply reflect limited data. The incidence of abdominal bulge/hernia was similar across the pooled data and the meta-analysis. We expected the incidence to be higher in bilateral cases for the same reason described above but this was not borne out in our results.

Due to the strict inclusion criteria and due to the fact that we only performed meta-analysis where direct comparison was possible, our results are intrinsically limited by selection bias. Our meta-analysis was hindered by inconsistent outcome reporting in the series we encountered, an issue also highlighted by Potter et al.[24] There is a real need for comprehensive outcome reporting in DIEP flap case-series so that authors can more reliably synthesise outcome data in future meta-analyses. Standardisation of outcome reporting in DIEP flap breast reconstruction series is a feasible and practical way of improving the quality of future case-series and subsequent meta-analysis. Standardisation will also generate more accurate assessments of surgical interventions and progress evidence-based practice.

Conclusion

In the light of the increasing demand of bilateral breast reconstruction following bilateral mastectomy for breast cancer, the objective of this review was to assess the literature on DIEP flap breast reconstruction, focussing on identifying, evaluating and comparing the complications rates of unilateral and bilateral procedures. We found a statistically significant increased risk of total flap failure in bilateral DIEP flap breast reconstruction, alongside descriptive analysis suggesting increased risks of other adverse outcomes. Our findings were limited by the low quality of the included studies, susceptibility to selection and reporting bias and heterogeneous outcome reporting. Whilst the absolute risk of total flap failure in bilateral DIEP flap breast reconstruction is still very low (~3%), our figures may be used to better inform patients about the significantly higher risk of total flap failure compared to unilateral reconstruction; a three-fold increase in risk. We recommend improvements in study design, whereby researchers would ideally perform randomised trials or prospective cohort studies. Moreover, we suggest standardisation of outcome reporting in free flap breast reconstruction, as this will improve the reliability of future primary research and meta-analyses.

Word count: 3,110

Declarations of conflicting interest

None.

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Figure Captions

Figure 1

Study attrition chart.

Figure 2

Forest plot of unilateral versus bilateral DIEP breast reconstruction for the outcome: total flap failure.

Figure 3

Forest plot of unilateral versus bilateral DIEP breast reconstruction for the outcome: partial flap failure.

Figure 4

Forest plot of unilateral versus bilateral DIEP breast reconstruction for the outcome: breast haematoma.

Figure 5

Forest plot of unilateral versus bilateral DIEP breast reconstruction for the outcome: breast seroma.

Figure 6

Forest plot of unilateral versus bilateral DIEP breast reconstruction for the outcome: vascular complications.

Figure 7

Forest plot of unilateral versus bilateral DIEP breast reconstruction for the outcome: fat necrosis.

Figure 8

Forest plot of unilateral versus bilateral DIEP breast reconstruction for the outcome: abdominal haematoma.

Figure 9

Forest plot of unilateral versus bilateral DIEP breast reconstruction for the outcome: abdominal hernia/bulge.

Figure 10

Funnel plots of direct comparison meta-analysis for total flap failure.

Appendix Caption

Bespoke ‘In/Out’ form for assessing eligibility of a study for inclusion/ exclusion.