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Title

The Importance of the Unit of Analysis

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Commentary on Beugels et al (2016). Complications in unilateral versus bilateral deep inferior epigastric artery perforator flap breast reconstructions: A multicentre study¹

Dear Professor Hart,

We thank the authors for their interesting report on the complications of unilateral versus bilateral DIEP flap breast reconstruction. This retrospective cohort study was performed to a high standard and authored in accordance with STROBE guidance², so is a welcome addition to the literature.

We were interested by the authors' choice to use 'the flap' as their unit of analysis for recipient site complications. Altman and Bland^{3,4} outlined the importance of correctly selecting the unit of analysis in medical research, particularly when data is paired or based on symmetrical anatomy (eg. eyes, hands, breasts, etc). Accordingly, in our published meta-analysis of complications in unilateral versus bilateral DIEP flap breast reconstruction⁵, the patient was the unit of analysis. Conversely, Beugels et al¹ chose to analyse their data 'per flap' which does present some critical problems. Both the chi square and Fisher exact tests assume that data values are independent, but clearly two DIEP flaps from the same woman are not independent and so should not be pooled into one group for comparative analyses. Also, artificially inflating the sample size (n=104 women became n=208 flaps) will reduce the estimate of the standard error of the mean, thus erroneously narrow the confidence interval and increase the chance of Type 1 errors. On a more practical level, we feel that generating risk statistics 'per patient' is more useful than 'per flap', particularly for surgeons communicating the risks of adverse outcomes to women seeking bilateral breast reconstruction. For example, using the risks from our meta-analysis⁵, explaining to a patient

that “you are 3 times as likely to lose a flap if you choose bilateral reconstruction, than if we reconstruct just one breast” or using Beugel’s data, “your chance of total flap loss is 6.7% if you chose bilateral reconstruction, compared to is 2.8% if you choose just one breast reconstruction” is more accurate and understandable than a risk statistic ‘per flap’. Therefore, we have revised Table 3 from Beugels at al’s article¹ to show recipient site complications ‘per patient’, which demonstrates that bilateral DIEP flap breast reconstruction is not risk-free, as suggested.

Interestingly, when we performed ‘per patient’ analyses, major complications occurred significantly more often in bilateral DIEP flap breast reconstructions and the true relative risk of major complications is somewhere between 1.15 and 3.23 (with 95% confidence). Similarly, total flap loss occurred in 6.7% of bilateral reconstructions compared to 2.8% in the unilateral group; note that the confidence interval for the relative risk of total flap loss spans from 1 (meaning the groups are the same) to 6 (meaning that bilateral reconstruction is 6 times as risky as unilateral reconstructions). The true relative risk of total flap loss in the population (as this is an estimate from a sample) is plausibly somewhere between 1 and 6 but the reason there is no statistically significant difference in this comparison is likely due to lack of power. To detect a 4% proportional difference in total flap loss, a power calculation ($\alpha=0.05$, $\beta=0.80$) suggests that a sample size of approximately 932 would be required. We appreciate that recruitment of such a large sample of women seeking breast reconstruction is extremely difficult and equally don’t intend to devalue the findings of this otherwise excellent work.

We think it is useful to show how changing the unit of analysis from ‘per patient’ to ‘per flap’ underestimates the risks of adverse outcomes for women undergoing bilateral DIEP flap breast reconstruction. Therefore, although this study was performed and reported to a high

standard, we are concerned that the conclusion “bilateral DIEP flap breast reconstructions can be performed with the same percentage of complications” is not supported by their data or the established literature and so may mislead some readers.

References

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Tables

Revised Table 3	Women Undergoing DIEP flap Breast Reconstruction		p-value	Relative Risk	95% Confidence Interval
	Unilateral	Bilateral			
	(n=322)	(n=104)			
Major Complications	32 (9.9)	20 (19.2)	0.012	1.94	1.15, 3.23
Total Flap Loss	9 (2.8)	7 (6.7)	0.074	2.41	0.92, 6.31
Partial Flap Loss	17 (5.3)	8 (8.7)	0.363	1.46	0.65, 3.28
Venous Congestion	10 (3.1)	8 (7.7)	0.049	2.48	1.00, 6.11
Minor Complications	75 (23.3)	32 (30.7)	0.119	1.32	0.93, 1.87
Infection	18 (5.6)	4 (3.9)	0.490	0.689	0.24, 1.99
Haematoma	17 (5.3)	10 (9.6)	0.117	1.82	0.86, 3.85
Seroma	4 (1.2)	3 (2.9)	0.265	2.32	0.53, 10.2
Fat Necrosis	45 (14.0)	16 (15.4)	0.720	1.10	0.65, 1.86
Wound Problems	38 (11.8)	15 (14.4)	0.479	1.22	0.70, 2.13