Meta-analysis of antibiotic prophylaxis in breast reduction surgery

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BACKGROUND: Breast reduction surgery is a very common procedure; however, there is still no consensus as to whether antibiotics should be used perioperatively.

OBJECTIVE: To review the world literature and perform a meta-analysis of studies comparing wound infection rates with antibiotic use in breast reduction surgery.

METHODS: A literature search was performed using the MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Database of Clinical Trials, Embase and CINAHL databases. Subject headings and relevant subheadings for “Breast”, “Breast Reduction”, “Reduction Mammoplasty”, “Mammoplasty” were combined with “Antibiotics” and “Antibacterial Agents”. The list of titles was assessed by the study’s authors and abstracts were reviewed. All relevant articles were then independently reviewed by the two primary authors, and Jadad scoring was used to assess the quality of the included articles.

RESULTS: From the original search, three randomized controlled trials were included in the meta-analysis of preoperative antibiotics. The meta-analysis revealed a 75% reduction in wound infections with preoperative antibiotics (OR 0.25 [95% CI 0.09 to 0.72]). Because only one randomized controlled trial analyzed postoperative antibiotics, no meta-analysis could be performed.

CONCLUSIONS: Preoperative antibiotics should routinely be used before breast reduction surgery. The use of postoperative antibiotics remains controversial. Additional randomized studies investigating postoperative antibiotics are needed.

Key Words: Antibiotics; Breast; Meta-analysis; Reduction mammoplasty; Surgical site infection

Breast reduction surgery (BRS) is a very commonly performed operation. However, questions remain regarding the role of prophylactic antibiotics. A survey of American plastic surgeons showed myriad antibiotic use for different plastic surgery procedures, including breast reduction (1). Similar to all elective breast surgery, reduction mammoplasty has historically been defined as ‘clean surgery’, with an expected infection rate <3.4% (2). As such, prophylactic antibiotics have not been recommended. However, numerous studies have shown that the actual infection rates after BRS are much higher, ranging from 4% to 36% (3-8). In spite of these studies, to the best of our knowledge, there has been no conclusive study in the literature to guide surgeons with regard to prophylactic antibiotic use in BRS.

A similar question plagued the breast oncology surgery literature until it was clarified by a systematic review in the Cochrane Database of Systematic Reviews (9). This review included six articles in its final analysis that compared preoperative antibiotic use with no antibiotic or placebo. The result was a significant reduction in the rate of surgical

La méta-analyse de la prophylaxie antibiotique après une chirurgie de réduction mammaire

HISTORIQUE : La chirurgie de réduction mammaire est une intervention très courante. On ne s’entend toutefois pas sur l’utilisation d’antibiotiques pendant la période périopératoire.

OBJECTIF : Examiner les publications mondiales et effectuer une méta-analyse des études comparant le taux d’infection des plaies malgré l’utilisation des antibiotiques en cas de chirurgie de réduction mammaire.

MÉTHODOLOGIE : Les chercheurs ont effectué une analyse bibliographique dans les bases de données de MEDLINE, de la *Cochrane Database of Systematic Reviews*, de la *Cochrane Database of Clinical Trials*, d’Embase et de CINAHL. Les rubriques et les sous-rubriques pour *Breast*, *Breast Reduction*, *Reduction Mammoplasty*, *Mammoplasty* ont été combinées à *Antibiotics* et *Antibacterial Agents*. Les auteurs de l’étude ont évalué la liste des titres et révisé les résumés. Les deux auteurs principaux ont également fait une évaluation indépendante de tous les articles pertinents, puis l’échelle de Jadad a été utilisée pour déterminer la qualité des articles inclus.

RÉSULTATS : À partir de la recherche originale, trois essais aléatoires et contrôlés ont été inclus dans la méta-analyse des antibiotiques préopératoires. La méta-analyse a révélé une réduction de 75 % des infections des plaies grâce aux antibiotiques préopératoires (RC 0,25 [95 % IC 0,09 à 0,72]). Puisque seulement un essai aléatoire et contrôlé a porté sur les antibiotiques postopératoires, aucune méta-analyse n’a pu être effectuée.

CONCLUSIONS : Il faudrait toujours utiliser des antibiotiques préopératoires avant une chirurgie de réduction mammaire. L’utilisation d’antibiotiques postopératoires demeure controversée. Il faudra effectuer d’autres études aléatoires sur les antibiotiques postopératoires.

site infection for patients undergoing breast cancer surgery without reconstruction who received preoperative antibiotics (RR 0.66 [95% CI 0.48 to 0.89]). One may suggest that this review could be used to guide treatment with respect to BRS. However, various complicating factors specific to oncology patients may alter their infection risk, making them more prone to infection (10).

Therefore, the purpose of the present study was to perform a meta-analysis to determine the effect of prophylactic antibiotics on surgical site infections in BRS patients.

METHODS

A literature search for published and unpublished trials using the following five electronic health databases was performed for the specified time periods: MEDLINE (1966 to July 26, 2007) (Box 1), Cochrane Database of Systematic Reviews (July 2007), Cochrane Central Register of Controlled Trials (July 2007), Embase (1980 to July 26, 2007) and CINAHL (1982 to July 26, 2007).

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BOX 1**Search strategy used to search MEDLINE
(1966 TO August 26, 2007)**

1. Breast reduction
2. Mammoplasty/ exp. Mammoplasty
3. Exp. Breast
4. Breast Surgery
5. Exp. Breast Surgery
6. Antibacterial agents
7. Exp. Antibacterial agents
8. Antibiotic\$
9. 1 or 2 or 3 or 4 or 5
10. 6 or 7 or 8
11. 9 and 10

The same search strategy was used to search all databases. Minor adjustments were made to match medical subject headings used by the different databases. No language restrictions were applied to the search. In addition to the above database search, all reference lists from appraised articles were screened to ensure no articles were overlooked.

Inclusion criteria were outlined before selecting articles for the meta-analysis. Only randomized controlled trials (RCTs) that assessed perioperative prophylactic antibiotic use in BRS patients were included. The primary outcome of interest had to be breast wound infection. Finally, the interventions compared were: preoperative antibiotics with placebo (or no antibiotic); postoperative antibiotic with placebo (or no antibiotic); or preoperative antibiotic with preoperative plus postoperative antibiotic. Articles were excluded if they did not have BRS as at least part of their patient population.

Data collection was performed by the studies primary authors (RS and MC). The two authors jointly assessed titles and abstracts from the literature search to determine which articles would be reviewed. After obtaining seemingly pertinent articles, a decision was made regarding which papers would be given a Jadad et al (11) score. Articles were then independently reviewed and a Jadad score assigned. An a priori decision was made to include RCTs with a score ≥ 2 .

Statistical analysis

The surgical site infection was considered to be an outcome measure for data analysis. Before analyzing the data, the authors developed their hypotheses regarding potential sources of heterogeneity in surgical site infection rates (ie, differences in study quality and whether randomization was concealed). The tests of heterogeneity using Cochran's Q statistic were applied to evaluate the extent of variability in results among trials. This method tests the null hypothesis that all of the apparent variability is due to chance. The analysis was conducted on an intention-to-treat basis. A meta-analysis of pooled ORs was computed using Mantel-Haenszel fixed-effect or random-effect models. The random-effect model was applied when the P value for the test of heterogeneity was <0.10 . ORs with 95% CIs were reported. In addition, the number of patients needed to treat (NNT) was calculated using the Newcome method to estimate the number of patients that would need to receive treatment before reducing the risk in one. An alpha level of 0.05 was considered to be a criterion for statistical significance. Comprehensive Meta-Analysis Version 2 software (Biostat, USA) was used for data analysis.

RESULTS

From the original literature search, 84 articles were identified as potentially relevant based on title. This was reduced to 28 articles after abstracts were reviewed (Figure 1). After reading the complete article, this total was further reduced to four articles, which were independently assessed and given a Jadad score. One additional article was excluded for a Jadad score <2 , leaving three RCTs of sufficient quality to be included in the meta-analysis. There was 100% Jadad scoring

Figure 1) Summary of the literature search results. Reasons for exclusion from the meta-analysis are shown in the side boxes

agreement between the two primary authors. Articles were excluded for the following reasons: 37 were oncology related; 20 focused on augmentation or reconstructive breast surgery; seven pertained to generalized surgical site infections; one pertained to antibiotic resistance; one investigated bacterial growth in breast tissue; and 14 were related to BRS but were not prospective trials. Tables 1 and 2 summarize the relevant details of the three studies.

The Mantel-Haenszel fixed-effects model was used to combine studies (Figure 2). Test of heterogeneity was not significant for the above analysis ($P=0.542$). Overall, the rate of infection for patients who received preoperative prophylactic antibiotics was 10% versus 31% in those untreated. The summary OR was 0.255 (95% CI 0.09 to 0.72; $P=0.01$). The NNT to reduce one wound infection with preoperative antibiotics was five (95% CI 3 to 25).

To ensure the conclusions were stable when only the highest quality studies were included, the analysis was recalculated after removing the inferior article. When the Ahmadi et al (3) study, with a Jadad score of 2, was removed from the analysis (Figure 3), the effect remained significant with a narrower CI. The summary OR was 0.261 (95% CI 0.066 to 0.706). The test for heterogeneity was not significant for the above analysis (0.966).

Only the study by Ahmadi et al (3) prospectively assessed the role of postoperative antibiotics. It showed no statistically significant benefit by adding postoperative antibiotics to preoperative antibiotics. Given the paucity of data, no meta-analysis could be performed with regard to the benefit of postoperative antibiotics.

DISCUSSION

BRS is one of the most common procedures in plastic surgery in which the routine use of perioperative prophylactic antibiotics remains debated. Its classification as a 'clean surgery' has been questioned and reported infection rates are higher than expected (3-8). Compounding the debate is the lack of a standard definition for 'wound infection'. Additionally, inconsistency in follow-up protocols and reporting times have likely underestimated the incidence of wound infection because most occur following patient discharge. The present meta-analysis was an attempt to summarize the best data available on the subject of BRS and prophylactic perioperative antibiotic use.

The present meta-analysis showed a 75% reduction in the wound infection rate when antibiotics were given preoperatively, compared with placebo or no antibiotics. This resulted in an NNT of five patients to reduce one postoperative wound infection. Three RCTs were used to draw this conclusion (3-5). Each study had similar

TABLE 1
Study details

Author (reference), year	Jadad score (of 5)	Control	Intervention	Follow-up
Ahmadi et al (3), 2005	2 - poor blinding technique	No antibiotics (n=16)	1. Preoperative antibiotics alone (cefazolin or levofloxacin) (n=17) 2. Preoperative and postoperative antibiotics (addition of cephalexin or levofloxacin for three days) (n=17)	At least 3 times
Amland et al (4), 1995	5	No antibiotics (n=22)	1. Preoperative antibiotics (azithromycin 1000 mg per oral the night before) (n=25)	Several days and at 30 days
Platt et al (5), 1990	5	No antibiotics (n=15)	1. Preoperative antibiotics (cefonicid 1 g intravenous 90 min before surgery) (n=18)	Daily then day 6 and day 15

TABLE 2
Study details

Author (reference), year	Results	Definition of infection
Ahmadi et al (3), 2005	1. Trend toward decreased infection from 29% to 18% with preoperative antibiotics ($P>0.20$) 2. No difference with the addition of postoperative antibiotics	"Cellulitis, purulent drainage, infected hematoma, infected seroma, or abscess"
Amland et al (4), 1995	1. Statistically significant reduction in infection rate from 36% to 8% with preoperative antibiotics ($P=0.018$)	Scoring system, in which 4 of 7 considered to be positive "Pus or hemoserous discharge with two of the following: erythema, edema, or increased pain"
Platt et al (5), 1990	1. Trend toward decreased infection rate from 27% to 6%, with preoperative antibiotics ($P=0.092$)	"Erythema and drainage, a wound with purulent drainage or a wound that was opened and not reclosed"

Figure 2) Forrest plot using Mantel-Haenszel fixed-effects model shows a significant reduction in surgical site infections in favour of preoperative antibiotic use versus placebo or no antibiotics

participants, methodology, interventions and outcomes of interest. All three studies suggested that preoperative antibiotics lowered infection rates. However, only one of these articles showed a significant result (4) while the others showed strong trends (3,5). We performed a meta-analysis of these studies to decrease random error inherent in smaller studies and to increase the strength of our conclusions. Based on this meta-analysis, we believe we have level Ia evidence to substantiate a level A recommendation in favour of the use of preoperative antibiotics before BRS (12). This concurs with results of a recent article that also included lower-quality evidence in a systematic review (13).

Even after initial statistical analysis, the data were re-analyzed after excluding the study by Ahmadi et al (3), which had received a Jadad score of 2. This left two studies, which each received a Jadad score of 5 (4,5). By doing so, the OR resulted in a slightly greater effect of preoperative antibiotics and a narrower CI. However, the pooled effect size after excluding the poor-quality study yielded results very similar to the original analysis.

The secondary objective of the present meta-analysis was to determine the value of postoperative antibiotics on wound infections after BRS. However, the search did not identify satisfactory data to address this goal. There was only one prospective study that examined this question. Even a recent (August 2013) review of the literature using the same search criteria (13) showed no additional studies for inclusion. An RCT published in 2010 (14) that compared no antibiotics with a group that received both preoperative and postoperative antibiotics was identified. However, the impact of the antibiotics given before versus after could not be determined. Given the lack of data to pool, it is not possible to address the role of postoperative antibiotics. A well-powered RCT should be performed to answer this question. We

Figure 3) Forrest plot using Mantel-Haenszel fixed-effects model of the two studies that received a Jadad score of 5 (4,5). The significant reduction in surgical site infections is still demonstrated in favour of preoperative antibiotic use versus no antibiotics or placebo

believe this to be particularly important given that even patients treated with preoperative antibiotics had an infection rate of 10%.

The conclusions of a meta-analysis that combines several RCTs is considered to be level I evidence – the top of the research hierarchy (12). However, even a meta-analysis is only as good as the RCTs from which it is based. Therefore, to eliminate poorly designed studies, the Jadad et al (11) scoring system was used to evaluate the RCTs before their inclusion. An a priori decision was made to include only studies with a score of ≥ 2 on the Jadad et al (11) scale. This score has been used in previous meta-analyses published in peer-review journals (15). The articles studied were all considered to have good methodological design based on the Jadad scoring system.

Despite efforts to include only good-quality studies, limitations still exist. All studies had small sample sizes and the pooled effect size yielded very wide 95% confidence limits. Fortunately, by pooling the data, the cumulative sample size was sufficient to yield meaningful results. For two of the articles, BRS was one of several procedures studied (4,5). Therefore, subgroup analysis was performed on the BRS patients. Neither of these studies published tables to ensure that the treatment groups and the control groups were evenly matched within these BRS subgroups. It is possible that some other confounding factor may have influenced the results. Although both studies used block randomization, only Platt et al (5) stated that it was used for the subgroup randomization.

We are confident that other areas of variability do not diminish the conclusion. For example, each study used a slightly different treatment protocol. Although each used a preoperative antibiotic that targeted the most common pathogens, it is possible that this influenced the results. Intuitively, an inappropriate antibiotic would be expected to have

diminished the treatment effect. Regardless of this possibility, results were still found to be significant. Variation in patient follow-up assessment time periods was noted but each study protocol would capture the significant infections and had minimal loss to follow-up. Slight differences were noted in each study's criteria for what they considered to be a wound infection. It would have been ideal if each used the Centers for Disease Control and Prevention (Georgia, USA) criteria (16). Fortunately, their definitions of infection were comparable. Finally, from a methodological viewpoint, the study by Ahmadi et al (3) maintained blinding only until the day of surgery. Beyond that point, only the patient remained blinded to the treatment. This could have introduced bias to the assessment. Because of its methodological concerns, the analysis was calculated excluding this study and a significant benefit to preoperative antibiotics was still found. Finally, we add that unpublished data from unregistered, well-designed RCTs could have changed the results.

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CONCLUSIONS

The present meta-analysis demonstrated that preoperative prophylactic antibiotics are beneficial in reducing postoperative wound infections following BRS. A 75% decrease in infection rate was found, resulting in only five patients requiring treatment to reduce one infection. Therefore, based on this level I evidence, we recommend that preoperative antibiotics be used routinely in patients undergoing BRS.

The role of postoperative antibiotics remains uncertain. Considering how common this procedure is and the seriousness of infectious complications, it appears wise that the answer be sought. We propose that a large, multicentred RCT be performed.

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