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ORIGINAL ARTICLE BREAST

The Role of Hydroxyethyl Starch in Preventing Surgical-Site Infections and Nipple Necrosis in Patients Undergoing Reduction Mammaplasty: A Prospective Case–Control Study of 334 Patients

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Abstract
Background Surgical-site infections after reduction mammaplasty are associated with poor cosmetic results. This study investigated the postoperative antiinflammatory influence of hydroxyethyl starch and its effect on surgical-site infections after breast reduction.
Methods In this prospective case–control study, 334 patients undergoing reduction mammaplasty were prospectively assigned in a 2:1 ratio to receive either 2 × 250 ml of hydroxyethyl starch 6 % or saline solution 0.9 % for 3 days postoperatively. Patient follow-up evaluation was at least 1 month. Using uni- and multivariate analyses, this study aimed to identify risk factors for surgical-site infections and nipple necrosis.
Results Surgical-site infections occurred in 6.6 % of the hydroxyethyl starch group and in 3.6 % of the control group ($p = 0.704$). Hydroxyethyl starch had no effect of reducing surgical-site infections [$p = 0.212$; odds ratio (OR), 0.317; confidence interval (CI), 0.052–1.925]. According to univariate analyses, hydroxyethyl starch reduced the occurrence of postoperative fever ($p = 0.085$; OR 0.608; CI 0.345–1.072), and fever was associated with increased infection rates ($p = 0.033$; OR 2.335; CI 1.071–5.089). Additional risk factors for postoperative infections were diabetes ($p = 0.051$; OR 4.051; CI 0.997–16.463) and obesity (normal weight vs grade ≥2: $p = 0.003$; OR 7.612; CI 2.031–28.529). Multivariate analysis showed no independent predictors for surgical-site infections. Nipple necrosis were equally observed in the two groups ($p = 0.458$; OR 1.643; CI 0.443–6.097).
Conclusion The antiinflammatory approach of hydroxyethyl starch did not lead to a decrease in infections or nipple necrosis. No difference in surgical-site infections was observed between aesthetic and oncologic procedures.
Level of Evidence III This journal requires that authors assign a level of evidence to each article. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors www.springer.com/00266.

Keywords Breast surgery · Hydroxyethyl starch · Reduction mammaplasty · Surgical-site infection

Reducing surgical-site infections after major breast operations is of recurring concern. In breast cancer surgery, infection rates are documented to be 3–15 % higher than the average for clean surgical procedures [1]. The application of intravenous peri- and postoperative antibiotics is described as a common procedure for reducing surgical-site infections in breast and axillary surgeries [2, 3]. The potential morbidity caused by infections such as delays in wound healing, reoperation, prolonged hospital stay, increased use of antibiotics, costs, unsatisfactory aesthetic result, and delayed adjuvant treatment in oncologic patients is not to be underestimated [4].

Our approach to decreasing postoperative infections after breast reduction was the application of an intravenous isotonic crystalloid solution: hydroxyethyl starch 6 %. Hydroxyethyl starch frequently is used for septic patients

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and severe inflammatory situations because of its antiinflammatory effect. It causes a medium- to long-term increase in blood volume, greater blood flow, and improved blood oxygen transport, supporting the healing process because diminished peripheral blood flow and impaired vasculogenesis are characteristics of poorly healing wounds [5, 6]. Hydroxyethyl starch additionally decreases hematocrit, blood viscosity, and aggregation of erythrocytes, positively influencing the complex components regulating wound healing [7]. Blood coagulation itself is not inhibited, which is an advantage in the postoperative setting [8].

This prospective study investigated patients undergoing breast reduction to receive either hydroxyethyl starch 6 % or normal saline solution 0.9 % for 3 days after surgery. Using uni- and multivariate analyses, we aimed to identify risk factors for surgical-site infections and nipple necrosis.

Materials and Methods

Between 2000 and 2007, 334 patients undergoing reduction mammaplasty were randomized in a 2:1 ratio to receive either 2 x 250 ml of hydroxyethyl starch 6 % or 2 x 250 ml saline solution 0.9 % for 3 days postoperatively. All the patients had surgery in the Breast Unit of the Department of Obstetrics and Gynecology, University Rostock, Germany by one of the coauthors (T. R. or G. B.).

Surgical-site infection was defined as the appearance of local redness or swelling and the need for prolonged postoperative antibiotic therapy, positive microbiologic wound culture, or secondary surgery due to infection or fluid collection [4, 9]. Patients experiencing postoperative hematoma that required immediate revision, patients with free nipple–areola grafts, and patients with previous radiation therapy were excluded from the study.

All the patients received a peri- and postoperative antibiotic treatment for 3 days (2 x 2 g cefotiam a day), as requested by the institutional review board. Drainage systems were used in all the patients and removed when drainage volume was less then 25 ml within 24 h.

Patient characteristics and postoperative events were defined as follows: postoperative fever as a temperature exceeding 37.7 °C (99.9 °F) measured orally, hematoma as superficial intracutaneous hematoma, blood loss during surgery as more than 500 ml versus less than 500 ml, and obesity in concordance with the body mass index [10–12]. Anemia was defined as hemoglobin less than 12 mg/dl (7.4 mmol/l) according to the World Health Organization (WHO) definition [13, 14]. After discharge, all the patients were reappointed to our outpatient center within 14 days and after 4 weeks to achieve a follow-up period of 30 days as demanded for the standard definition of surgical-site infections by the Centers of Disease Control and Prevention and the National Nosocomial Infection Surveillance System [15].

Statistical analysis was performed using IBM SPSS 19.0. (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.). Descriptive statistics were computed for continuous and categorical variables. Unequal randomization was used to maximize allocation to the experimental group because fewer events were expected and to increase the power of the secondary analysis.

Testing for differences in continuous variables between the study groups was accomplished by the two-sample t test for independent samples. To compare frequencies between groups, the Chi square test was performed for larger contingency tables and Fisher's exact test for 2×2 contingency tables.

First, univariate analyses were performed to show unadjusted significant associations between prognostic variables and surgical-site infection. Thereafter, variables yielding p values of 0.10 or lower in the univariate analyses were entered into the multivariate model to highlight some adjusted associations between the outcome and covariates, which were univariate of borderline significance. All p values resulted from two-sided statistical tests, and p values of 0.05 or lower were considered significant.

Results

During 7 years, 334 patients (628 breast reductions) completed the study. Of these 334 patients, 291 had breast reduction for aesthetic reasons and 33 for oncologic reasons. Overall infections occurred in 6.6 % ($n = 22$) of the hydroxyethyl starch group versus 3.6 % ($n = 12$) of the saline solution group ($p = 0.704$). The patients in the saline solution group had significantly more diabetes and less cardiac disease (Table 1).

In the majority of cases, a bilateral procedure for aesthetic reasons was performed, and a central pedicle was preferred. Culture-positive wound infections were detected in only four cases (2 cases of *Propionibacterium*, 1 case of *Enterococcus,* and 1 case of *Staphylococcus aureus*).

Univariate logistic regression analysis showed no reduction in surgical-site infections for patients receiving hydroxyethyl starch [odds ratio (OR), 0.317; 95 % confidence interval (CI), 0.052–1.925; $p = 0.212$; Table 2]. Patients with diabetes were at increased risk for postoperative infections (OR 4.051; 95 % CI 0.997–16.463; $p = 0.051$). Smoking was no risk factor. Obesity in general ($p = 0.009$) and postoperative fever (OR 2.335; 95 % CI 1.071–5.089; $p = 0.033$) were significantly associated with surgical-site infections, and the application of hydroxyethyl starch reduced the incidence of postoperative fever (OR

Table 1 Patient characteristics and surgical factors of the prospective case–control study (randomization with a 2:1 ratio)

Variable	Hydroxyethyl starch 6 % ($n = 225$)	Saline solution 9 % ($n = 109$)	p value
Age: years (range)[a]	44.19 ± 14.1 (16–73)	42.89 ± 14.975 (17–75)	0.443[b]
Body mass index: kg/m^2 (range)[a]	28.029 ± 4.2 (20.1–42.3)	28.046 ± 5.3 (17.4–47.6)	0.975[b]
Hypothyroidisms			0.196[c]
Yes	9	8	
No	216	101	
Hyperthyroidism			0.554[c]
Yes	3	0	
No	222	109	
Diabetes			0.003[c]
Yes	2	8	
No	223	101	
Hypertension			0.069[c]
Yes	69	23	
No	156	86	
Coronary heart disease			0.183[c]
Yes	6	0	
No	219	109	
Smoking			1.000[c]
Yes	46	22	
No	179	87	
Uni- or bilateral procedure			0.208[c]
Unilateral	23	17	
Bilateral	202	92	
Indication for surgery			0.491[c]
Aesthetic	198	93	
Oncologic	27	16	
Flap pattern			0.961[d]
Superior pedicle	56	26	
Central pedicle	152	74	
Inferior pedicle	17	9	

[a] Data are given as mean ± standard deviation

[b] t test used to compare means of groups

[c] Fisher′s Exact test

[d] Pearson

0.608; 95 % CI 0.345–1.072; $p = 0.085$) to some extent. Multivariate logistic regression could not confirm postoperative fever ($p = 0.884$) or obesity ($p = 0.673$) as an independent factor for infection.

The rates of nipple necrosis were not affected by hydroxyethyl starch (OR 1.643; 95 % CI 0.443–6.097; $p = 0.458$), Table 3). Regarding the postoperative treatment, no difference in postoperative anemia (OR 0.788; CI 0.288–2.156; $p = 0.643$) or superficial hematoma (OR 0.599; CI 0.158–2.278; $p = 0.452$) was found. The modeling of the pedicle for the nipple–areola complex significantly influenced surgical-site infections ($p = 0.020$). A central pedicle was performed in 67.6 %, a superior pedicle in 24.6 %, and an inferior pedicle in 7.8 % of the cases.

The central pedicle was used as a comparison group because this was the predominantly used technique. The patients with a central pedicle had significantly more infections than those with a superior pedicle (OR 2.938; 95 % CI 1.379–6.259; $p = 0.005$), whereas the patients with a central pedicle and those with inferior pedicle showed no difference in infections (OR 1.712; 95 % CI 0.464–6.320; $p = 0.420$). Multivariate logistic regression showed no independent risk factors for surgical-site infections (Table 4).

Table 2 Logistic regression

Factor	Univariate analyses OR (95 % CI)	*p* value
(Yes vs no)[a]		
Therapy		
Hydroxyethyl starch 6 % versus saline solution 0.9 %	0.317 (0.052–1.925)	0.212
Diabetes	4.051 (0.997–16.463)	0.051
Hypothyroidism	2.944 (0.903–9.599)	0.073
Hyperthyroidism	4.515 (0.399–51.146)	0.224
Coronary heart disease	1.195 (0.568 –2.517)	0.639
Hypertension	1.500 (0.710–3.171)	0.288
Fever postoperatively[b]	2.335 (1.071–5.089)	0.033
Anemia postoperatively[c]	0.767 (0.222–2.649)	0.675
Uni- versus bilateral procedure	2.321 (0.534–10.078)	0.261
Aesthetic versus oncologic procedure	1.583 (0.631–3.970)	0.327
Blood loss during surgery		0.671
>500 versus ≤500 ml[a]	0.856 (0.417–1.757)	
Smoking		0.379
≤10 per day versus nonsmoker[a]	1.635 (0.627–4.267)	0.315
>10 per day versus nonsmoker[a]	1.921 (0.609–6.057)	0.265
Obesity[d]		0.009
Normal weight[a] versus grade 0 + 1	2.592 (0.870–7.721)	0.087
Normal weight[a] versus grade ≥ 2	7.612 (2.031–28.529)	0.003
Preparation of pedicle[e]		0.020
Superior versus central pedicle[a]	2.938 (1.379–6.259)	0.005
Inferior versus central pedicle[a]	1.712 (0.464–6.320)	0.420

Odds ratio for risk of surgical-site infection

OR odds ratio, *CI* confidence interval

[a] Reference category

[b] Temperatures >37.7 °C (99.9 °F) measured orally

[c] Anemia: measured only in patients with clinical signs of circulation problems. Anemia was defined as hemoglobin <12 mg/dl (7.4 mmol/l) according to the World Health Organization (WHO) definition

[d] Obesity in concordance with body mass index: normal weight (18.5–24.9 kg/m^2), overweight [>25–30 kg/m^2 (preaadiposity)], grade 1 (>30–35 kg/m^2), grade 2 (>35–40 kg/m^2), grade 3 (>40 kg/m^2)

[e] Central versus superior/inferior pedicle was chosen because the majority of cases had a central pedicle

Table 3 Distribution of secondary study goals

Variable (yes vs no[a])	Hydroxyethyl starch 6 % ($n = 225$)	Saline solution 0.9 % ($n = 109$)	*p* value[b]
Nipple necrosis (partial and complete)	10	3	0.558
Need for secondary surgery	9	6	0.577
Hematoma postoperatively[c]	5	4	0.482
Anemia after surgery (hemoglobin <7.4 mmol/l)[d]	52	33	0.803

Only patients with the presence of a mentioned complication are listed

[a] Reference category

[b] Fisher's exact test

[c] Superficial intracutaneous hematoma. Hematomas due to severe postoperative bleeding needing immediate revision were excluded

[d] Postoperative hemoglobin was not measured on a routine basis, but only when clinical signs of circulation problems were observed

Table 4 Multivariate analysis of risk factors for surgical-site infection

Factor (yes vs no[a])	Multivariate OR (95 % CI)	*p* value
Diabetes	0.389 (0.015–10.134)	0.570
Hypothyroidism	0.482 (0.028–8.404)	0.617
Fever postoperatively	0.908 (0.249–3.314)	0.884
Obesity[b]		0.673
Normal weight[a] versus grade 0 + 1	1.401 (0.383–5.28)	0.611
Normal weight[a] versus grade ≥2	2.383 (0.352–16.134)	0.374
Preparation of pedicle[c]		0.394
Superior versus central pedicle[a]	2.080 (0.710–6.098)	0.182
Inferior versus central pedicle[a]	1.040 (0.155–6.962)	0.968

All parameters with $p < 0.1$ in the univariate analyses were included in the multivariate analysis

OR odds ratio, *CI* confidence interval

[a] Reference category

[b] Obesity in concordance with body mass index: normal weight (18.5–24.9 kg/m^2), overweight [> 25–30 kg/m^2 (preaadiposity)], grade 1 (>30–35 kg/m^2), grade 2 (>35–40 kg/m^2), grade 3 (>40 kg/m^2)

[c] Central versus superior/inferior pedicle was chosen, because the majority of cases had a central pedicle

Discussion

Previous studies of patients undergoing breast reduction focused mainly on the application of different antibiotic treatment regimens and identification of patients at risk for postoperative infections [16–18]. Other strategies to reduce surgical-site infections included drainage protocols or controlled intraoperative hypotension to reduce blood loss during surgery and showed no differences [19–22]. Our complication rate was comparable with those in the literature, which vary between 1.1 and 28.6 % [23–32].

By applying hydroxyethyl starch, we observed only the indirect benefit for patients of reduced postoperative fever, which was in turn associated with a decrease in infection. This observation does not allow the conclusion that hydroxyethyl starch can reduce surgical-site infections.

Although it can downregulate the inflammatory response, the pathophysiologic mechanism of hydroxyethyl starch is controversial. Xie et al. [33] showed a reduction of proinflammatory cytokines such as tumor necrosis factor alpha and interleukin-1 beta when infusing hydroxyethyl starch. Other effects result through inhibition of proinflammatory pathways (inhibition of nuclear-factor-kappa B activation, toll-like receptor expression), whereas Dubin et al. [34] observed improved microcirculation [35, 36]. Our approach to enlarging blood volume, increasing blood flow, and improving blood oxygen transport after surgery did not lead to a reduction of surgical-site infections [37].

Although anemia is a potent risk factor for mortality and morbidity in surgical patients, postoperative blood samples were purposely collected only when clinical signs of circulation problems or clinical relevant anemia was suspected. The clinical relevance and usefulness of a routine postoperative blood sample is doubtful and does not influence the postoperative course [38].

Obesity was a risk factor for surgical-site infections in our and other studies that surgeons will increasingly need to confront because of increasing obesity and patient demands for breast reduction after massive weight loss. Nevertheless, breast reduction is well tolerated in these patients, and obesity does not represent an absolute contraindication [39, 40].

We did not observe a difference in postoperative infections in patients undergoing breast reduction for oncologic reasons, and cancer surgery was consequently no risk factor for infections. No delay regarding further necessary adjuvant treatment such as radiation and chemotherapy is expected in this subgroup. Smoking was not identified as a risk factor, but this might have been influenced by the low rate of smokers in our group.

This study had several limitations. It was a single-center unblinded study instead of the prospective randomized trial anticipated initially. A prospective trial with a power of 80 % needed for a statistical reduction in surgical-site infections would have required a sample of ~1,000 patients, which would have been hard to accomplish. Nevertheless, this was one of the largest studies investigating surgical-site infections after breast reduction. A weakness to our study was that resected volumes for each breast were not evaluated, although other studies showed no increase in wound infections related to the resected breast volume [26, 41]. All the patients received prophylactic postoperative antibiotics, which might have biased the antiinflammatory effect of hydroxyethyl starch, but this was required by the institutional review board. A possible bias resulting from inclusion of aesthetic and oncologic procedures was not observed by the authors.

Conclusion

The additional use of hydroxyethyl starch 6 % to reduce the antiinflammatory response in patients undergoing breast reduction does not decrease the incidence of surgical-site infections. No difference was observed between aesthetic and oncologic procedures. Improved postoperative microcirculation did not influence the occurrence of partial or total nipple necrosis.

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