Use of polysaccharide hemostatic agent (HaemoCerTM) in breast cancer surgery to reduce postoperative complications: a randomized controlled trial

Veronica Falcone[1], Pavla Krotka[1], Christine Deutschmann[1], Sabine Danziger[1], Theresa Reischer[1], Georg Pfeiler[1], Christian Singer[1], and Marianne Koch[1]

[1]Medical University of Vienna

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Abstract

Objective: To evaluate whether the application of polysaccharide hemostatic agent during breast conservative surgery affects the perioperative period. Design: Randomized, masked, single-center study Setting: Breast-care unit, at the Medical University of Vienna Population: Pre- and postmenopausal women affected by intraductal or invasive breast cancer, undergoing breast conservative surgery. Methods: Women were randomly assigned polysaccharide hemostatic agent or not, intraoperatively. Main outcome measures: Primary outcome was the total volume of postoperative drained fluid from the surgical site. Secondary outcomes were number of days until drain removal, rate of immediate postoperative surgical site infection, and total volume of postoperative drained fluid from the surgical site. Results: Patients in the intervention group had significantly higher drainage output volumes compared to the control group 85ml (IQR 46.25-110) vs. 50ml (IQR 30-75), respectively; (p=0.003). A univariable linear regression analyses, showed a significant association between the surgical specimen and the primary outcome (p<0.001). After multivariable analysis, the use of absorbable polysaccharide hemostatic product was no longer significantly associated with a higher drainage output and only the size of the surgical specimen remained a significant predictor. The number of days until drainage removal and the postoperative seroma formation were higher in the intervention group, (p=0.004) and (p=0.003), respectively. Conclusion:In our study, intraoperative application of polysaccharide hemostatic agent during breast-conserving surgery did not decrease postoperative fluid production.Only the size of the surgical specimen was significantly associated with postoperative drainage volume. Tweetable abstract:Intraoperative polysaccharide hemostatic does not reduce the volume of postoperative fluid drained after breast conservative surgery

Introduction

Quadrantectomy followed by radiotherapy represents the standard treatment for the vast majority of early breast cancer cases, with comparable survival rates as mastectomy, but with shorter operating time, reduced blood loss, a more appropriate cosmetic outcome and thus higher quality of life [1,2]. Postoperative complications like bleeding, wound site infection or seroma formation are however still sources for morbidity and are associated with hospital readmission and high health care costs [3–5]. During surgery, a delicate balance between bleeding and clotting has to be reached, in order to maintain tissue perfusion and to avoid postoperative bleeding, infections or tissues necrosis[6]. Studies conducted on the murine model have shown neoangiogenesis and fibrosis in the wound site after the application of local hemostatic agents, with no significant increase of tissue inflammation or necrosis [7]. However, adverse events such as allergic skin reactions and seroma formation have also been described [8]. To minimize postoperative complications, surgeons frequently insert hemostatic agents into the wound site during breast-conserving surgery. Within axillary lymphadenectomy, the application of local hemostatic agents has been associated with shorter time to drainage removal or hospital stay, but did not influence the rate of seroma [9,10]. However, results seem controversial. While

Benevento et al. have shown lower drainage serum outputs within patients treated with low-thrombin fibrin glue into the axillary fossa [11], no significant reduction in seroma formation [11,12] or magnitude [13] has been described. On the other hand, a significant reduction in seroma formation was described in patients treated with Sapylin in the axillary fossa [14]. Fewer data exists on the effect of hemostatic agent application into the wound site during breast-conserving surgery. Available data from a study based on retrospective chart reviews however also suggests a benefit regarding reduction of postoperative bleeding complications and time until drain removal [15].

HaemoCer^{TM} is a plant-based medical device, which initiates a rapid dehydration of blood and enhancing the concentration of coagulation particles (e.g. platelets, clotting proteins and red blood cells) into the bleeding site. (7 Entwicklungs-GmbH B. HaemoCer^{TM} [cited 2016 12.12.2016]. Available from: (http://www.biocergmbh.de/en/produkte/blutstillung/haemocertm-plus/) There is no adequate data available on the efficacy of HaemoCer^{TM} regarding seroma formation or drainage output. Hence, the aim of our randomized controlled trial was to compare the postoperative outcome between patients who received HaemoCer^{TM} during breast-conserving surgery and those who did not receive any hemostatic agent.

Patients and methods:

Study design:

The prospective randomized controlled, single blinded clinical trial was performed at the Medical University of Vienna, Department of Obstetrics and Gynecology, between March 2018 and September 2020. Institutional Review Board approval was obtained from the Ethics Committee of the Medical University of Vienna (1178/2017). All participants gave their written informed consent. During their participation, patients were insured as defined by legal requirements (Zurich Versicherungs Aktiengesellschaft, Insurance number: 07229622-2). This manuscript was structured according to the CONSORT guideline for reporting of randomized controlled trials.

Participants:

All patients with breast cancer undergoing breast-conserving surgery at the Department of Obstetrics and Gynecology of the Medical University of Vienna were considered eligible for inclusion. Patients with previous breast-conserving surgery at the same site were excluded.

Recruitment:

Patients were recruited on the day of admission (one day before scheduled surgery) and were informed about the study design, randomization to intraoperative application of HaemoCer^{TM} or no application of HaemoCer^{TM} and the length of study participation.

Interventions:

Randomized application of 3g hemostatic powder (HaemoCer^{TM}), into the wound site during breast-conserving surgery.

Outcomes:

Primary outcome of this study was the total volume of postoperative drained fluid from the surgical site. Secondary outcomes were number of days until drain removal, rate of immediate postoperative surgical site infection and total volume of postoperative drained fluid from the axillary fossa in case of axilla surgery. When simultaneous breast-conserving surgery was conducted on both breasts, the side with higher total volume of drained fluid was used for analysis. Further exploratory outcomes were number of hospitalization days, postoperative complications such as fever, bleeding, need of antibiotics and wound infection, surgical hematoma evacuation, hospital readmission and seroma formation.

Sample size:

Based on previous studies concerning the volume of postoperative drainage output (ml), we assumed an effect size of 0.51 (Cohen's d). At a two-sided level of significance of 5% a total sample size of 122 patients (61 per group) would result in a power of 80% for a t-test to detect the difference between groups. To account for a possible drop-out rate of 10% we planned to recruit 68 patients per group (total 136). In order to evaluate the number of postoperative days until drain removal, we assumed an effect size of 0.53 (Cohen's d). A total sample size of 114 patients (57 per group) would result in a power of 80% for a two-sided t-test at 5% level of significance.

Randomization:

Sequence generation: Sequence generation was provided by the Department of Statistics, Medical University of Vienna. Single-blinded (principal investigators) blocked simple randomization with a 1:1 allocation ratio and randomly varying block size was performed.

Allocation:

Sealed envelopes containing information on one of the two treatment options (application of HaemoCer^{TM} into the wound site versus no application of HaemoCer^{TM} in the wound site) were prepared according to the generated randomization sequence. All study envelopes were securely stored at the coordination center. A sealed envelope according to the randomization sequence was added to each patient chart at the time of admittance to the ward (one day before surgery).

Implementation:

Participants were allocated at the time of pre-surgical sign-in procedure (preoperative checklist), immediately before the start of the operation. Sealed envelopes were opened by the responsible surgeon. Surgery staff was informed about the allocated procedure by the responsible surgeon. Patients in the intervention arm received 3g haemostatic powder (HaemoCer^{TM}) into the wound site during breast conservative surgery. Patients in the control arm did not receive any hemostatic product into the wound site. A drainage was inserted into the wound site in both arms. Volume of the resected sample and drainage output were carefully documented. After surgery, all patients received parenteral analgesia and anticoagulant therapy with low-molecular weight heparine.

Blinding:

Patients and surgeons were not blinded to the type of intervention. Principal investigators, who did not participate in the surgical procedures, were blinded to the type of intervention. Outcome parameters (post-operative drainage output, duration of hospitalization) were independently documented by nursing staff (routine documentation). Final data collection was performed by VF.

Statistical methods

Quantitative variables are presented as median (IQR) and mean (SD), while categorical variables are shown as counts and percentages. Associations between the use of HaemoCer^{TM} and continuous outcomes were tested with Mann–Whitney U test. Chi-squared test was used to compare binary outcomes between treatment groups. All tests were conducted two-sided and p -values <0.05 were considered statistically significant. To correct for possible confounders, at first univariable linear regressions were performed to investigate the association between the drainage output volume and the following variables with potential influence on this outcome: BMI, age, tumor size, educational status of the surgeon (resident or consultant) and the size of the surgical specimen. Out of the possible confounders, only the size of the surgical specimen was significantly associated with the primary outcome. Subsequently, a multivariable linear model for the primary outcome was computed, including HaemoCer^{TM} and the size of the surgical specimen as independent variables. Statistical analysis was performed using R (4.1.3).

Results

Participant flow

Recruitment

A total of 152 patients with breast cancer were recruited on the day before surgery between April 2019 and September 2020. Sixteen of them did not give their consent to the study and were therefore not randomized, leaving 136 patients who were randomized to the intervention or control group. Three patients withdrew their consent shortly before surgery and were therefore excluded from the final analysis. Moreover, 2 patients did not receive HaemoCer^{TM}, although they have been allocated to the study group and 4 patients received a hemostatic powder, although they were randomized for "no hemostatic treatment". We performed our study with fidelity to the protocol.

Hence, data of 127 patients were analyzed (Figure 1).

Patient characteristics

The baseline characteristics of our study population are shown in Table 1. Out of the 127 patients, 66 were assigned to the intervention group, while 61 were assigned to the control group. Tumor characteristics, as well as lymph node status at diagnosis and before surgery were similar in both groups. Surgical specimens' sizes were comparable between the study and the control groups.

Outcomes and estimation

Primary and secondary outcomes

The use of HaemoCer was significantly associated with the postoperative drainage output volume (p=0.003), as well as with the number of days until drainage removal (p=0.004) in the univariable analysis. Our data shows tendency to increased values of both, postoperative drainage output and number of days until drainage removal in the intervention group (Table 2). However, no major adverse events (defined as any adverse event that leads to death, life-threatening injury, or illness, or to permanent impairment of a body structure or function) occurred within the study group.

To correct for possible confounders, at first univariable linear regressions were performed to investigate the association between drainage output and the following variables with potential influence on this outcome: BMI, age, tumor size, surgeons 'educational status (resident vs consultant) and the size of the surgical specimen. Only the size of the surgical specimen was significantly associated with the outcome (p<0.001). (Table 3)

Subsequently, a multivariable linear model for the primary outcome was computed, including HaemoCer and the surgical specimens' size as independent variables. In this model, the association between the primary outcome and HaemoCer was no longer significant (Table 4).

Other exploratory outcomes

Results for further exploratory outcomes are presented in Table 5. There were no statistically significant between-group differences in hospitalization days, postoperative fever, bleeding, need of antibiotics, wound infection, surgical hematoma evacuation and hospital readmission. The incidence of clinically relevant seroma formation was significantly higher in the intervention group [11 (16.67%) vs 0 (0%) (p=0.003)].

Discussion

It is well established that short hospitalization length and early discharge after surgery is associated with improved patient satisfaction and health-care cost reduction [16,17]. However, postoperative complications such as wound site infection or bleeding can often lead to discharge delays. While intraoperative control of bleeding remains pivotal for the reduction of postoperative complications, the application of topical hemostatic agents has become very common in the last two decades [18]. Specifically the effect of fibrin sealant containing human thrombin or combined hemostatic powder containing collagen, thrombin and chondroitin sulfate has been evaluated in the past, resulting in early drainage removal and increased day-case surgery [15,17,19] . Furthermore, natural polysaccharide hemostatic agents have as well shown high biocompatibility and good hemostatic characteristics [20], but there is a paucity of data regarding the application during breast-conserving

surgery and its effect. Hence, we aimed to evaluate the hemostatic performance of polysaccharide agents in breast-conserving surgery with a prospective randomized-controlled study.

In this randomized controlled trial, the administration of an absorbable polysaccharide hemostatic agent was not associated with a reduction of postoperative drainage output, time until drainage removal or number of hospitalization days. In a multivariable analysis, the size of resected tissue was the only factor significantly associated with the primary outcome. We analyzed whether the educational status of the surgeon (consultant vs. resident) would significantly influence the size of resected tissue and thus the immediate postoperative outcome, but our data showed that educational status was irrelevant regarding the primary outcome. One could draw the assumption that a larger tumor size would result in a larger resected tissue sample and thus a higher drainage output. However, the tumor size was not significantly associated with drainage output. We can therefore discuss that breast surgeons need to be aware of this fine balance during surgery to guarantee tumor-free resection borders, but also to avoid too large tissue resection sizes.

We have to acknowledge that our primary and secondary outcomes (postoperative drainage volume and number of days until drainage removal) are only surrogate parameters for intermediate-term postoperative complications, such as clinically relevant seroma formation and surgical wound site infection. Overall, the rate of immediate postoperative complications was low. Postoperative bleeding and subsequent secondary surgery occurred in only 3 patients (intervention group: 1; control group: 2), and 10 patients developed postoperative fever (intervention group: 5; control group: 5) Immediate postoperative seroma formation, that required an intervention (e.g. seroma puncture-aspiration) was documented in 17% of patients in the intervention group (n=11) compared to none in the control group, but this difference is as well attributed to the size of resected tissue rather than the application of polysaccharide hemostatic agent.

Largely due to the SARS Cov-2 pandemic, a majority of included participants were lost to follow-up after discharge from hospital. Our results are therefore limited to the immediate post-operative period and do not allow conclusions beyond that period. However, according to our results, the application of polysaccharide hemostatic agent did not shorten the number of days until drainage removal and thus the length of hospital stay. It seems therefore unlikely that the application of polysaccharide hemostatic during breast-conserving surgery would lead to a reduction of immediate postoperative health-care costs or higher patient satisfaction.

Conclusion

The intraoperative application of an absorbable polysaccharide hemostatic agent into the surgical wound site during breast-conserving surgery was not associated with reduced postoperative drainage volume or number of days until drainage removal, nor with the occurrence of immediate postoperative bleeding or surgical wound site infection. However, results from this randomized controlled trial suggest that the size of resected tissue during breast-conserving surgery is the most determinant factor regarding postoperative drainage output, irrespective of polysaccharide hemostatic agent application.

Disclosure of interests

G.P. received honoraria from Roche, AstraZeneca, Pfizer, Novartis, Lilly, Amgen.

C.S. received honoraria from Amgen, Novartis, AstraZeneca, Pfizer, Eli-Lilly, and Roche.

S.D. has received speaker honoraria from Eli Lilly und Roche; has served as an advisor to Roche; and has received travel expenses from Amgen, Eli Lilly, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Roche, and Sandoz.

The funding sources were not involved in study design, in the writing of the manuscript and in the decision to submit the article for publication.

Contribution to authorship

The study was designed and conceptualized by MK and CS. VF, CD, TR and SD performed patient recruitment. VF and MK wrote the manuscript, performed data interpretation, and designed data tables.

PK performed statistical analysis. GP and CS reviewed critically the manuscript. All authors approved the submission of this manual.

Details of ethics approval:

This trial was approved by the Ethics Committee of the Medical University of Vienna with the IRB 1178/2017. ClinicalTrials.gov Identifier: HaemoCerTM Application in Breast Cancer Surgery NCT04811378

Funding: BioCer Entwicklungs-GmbH provided financial resources in the amount of 8.100 Euro and provided the product, which is investigated in this study (HaemoCer). The funding company was not involved in the planning of this study and had no rights or saying regarding the conduction of this study. The funding company furthermore had no rights or saying in the interpretation or publication of the results. A Research funding agreement between BioCer Entwicklungs-GmbH and the Medical University of Vienna has been signed.

This manuscript was structured according to the CONSORT 2010 checklist for the reporting of randomized controlled trials.

Haemocer

Substance of content and effects of HaemoCer^{TM}:

100% plant-based polysaccharide. ,,HaemoCer PLUS Absorbable Polysaccharide Haemostat (APH) is a proprietary patent pending technology created via BioCers' Polysacchidaride Ultra-hydrophilic Resorbable Engineering (PURE) process. HaemoCer PLUS APH incorporates a sophisticated, plantbased polymer crosslinking that creates ultra-hydrophilic, biocompatible particles. Upon contact with blood HaemoCer PLUS enhances the natural clotting cascade by rapidly dehydrating the blood and accelerating the concentration of platelets, red blood cells and coagulation proteins at the bleeding site. HaemoCer PLUS also on blood interaction rapidly produces a gelled matrix that adheres to and forms a mechanical barrier with the bleeding tissue. "

http://www.biocer-gmbh.de/en/produkte/blutstillung/haemocertm-plus/

Acknowledgments:

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Data availability statement:

The data that supports the outcomes of this randomized, controlled trial are available from the corresponding author upon reasonable request.

References:

1. Veronesi U, Volterrani F, Luini A, Saccozzi R, Del Vecchio M, Zucali R, et al. Quadrantectomy versus lumpectomy for small size breast cancer. Eur J Cancer. 1990;26(6):671–3.

2. Zehra S, Doyle F, Barry M, Walsh S, Kell MR. Health-related quality of life following breast reconstruction compared to total mastectomy and breast-conserving surgery among breast cancer survivors: a systematic review and meta-analysis. Breast Cancer. 2020 Jul;27(4):534–66.

3. Ebner F, Friedl TWP, de Gregorio A, Lato K, Bekes I, Janni W, et al. Seroma in breast surgery: all the surgeons fault? Arch Gynecol Obstet. 2018 Nov;298(5):951–9.

4. Nakada H, Inoue M, Furuya K, Watanabe H, Ikegame K, Nakayama Y, et al. Fat necrosis after breast-conserving oncoplastic surgery. Breast Cancer. 2019 Jan;26(1):125–30.

5. Xue DQ, Qian C, Yang L, Wang XF. Risk factors for surgical site infections after breast surgery: a systematic review and meta-analysis. Eur J Surg Oncol. 2012 May;38(5):375–81.

6. Eden C, Buonomo OC, Busch J, Gilabert-Estelles J, Medrano R, Nosotti M, et al. An international multidisciplinary peer-driven consensus on the optimal use of hemostatic powders in surgical practice. Updates Surg. 2021 Aug 1;73(4):1267–73.

7. Franceschini G, Visconti G, Sanchez AM, Di Leone A, Salgarello M, Masetti R. Oxidized regenerated cellulose in breast surgery: experimental model. J Surg Res. 2015 Sep;198(1):237–44.

8. Franceschini G, Visconti G, Di Leone A, Masetti R. "Warning" to postoperative complications when using hemostatic agents! Acta Neurochir. 2019 May 1;161(5):871–2.

9. Gilly FN, François Y, Sayag-Beaujard AC, Glehen O, Brachet A, Vignal J. Prevention of lymphorrhea by means of fibrin glue after axillary lymphadenectomy in breast cancer: prospective randomized trial. Eur Surg Res. 1998;30(6):439–43.

10. Medl M, Mayerhofer K, Peters-Engl C, Mahrhofer P, Huber S, Buxbaum P, et al. The application of fibrin glue after axillary lymphadenectomy in the surgical treatment of human breast cancer. Anticancer Res. 1995 Dec;15(6B):2843–5.

11. Benevento R, Santoriello A, Pellino G, Sciaudone G, Candilio G, De Fatico GS, et al. The effects of low-thrombin fibrin sealant on wound serous drainage, seroma formation and length of postoperative stay in patients undergoing axillary node dissection for breast cancer. A randomized controlled trial. Int J Surg. 2014 Nov;12(11):1210–5.

12. Llewellyn-Bennett R, Greenwood R, Benson JR, English R, Turner J, Rayter Z, et al. Randomized clinical trial on the effect of fibrin sealant on latissimus dorsi donor-site seroma formation after breast reconstruction. Br J Surg. 2012 Oct;99(10):1381–8.

13. Cipolla C, Fricano S, Vieni S, Graceffa G, Licari G, Torcivia A, et al. Does the use of fibrin glue prevent seroma formation after axillary lymphadenectomy for breast cancer? A prospective randomized trial in 159 patients. J Surg Oncol. 2010 Jun 1;101(7):600–3.

14. Yang Y, Gao E, Liu X, Ye Z, Chen Y, Li Q, et al. Effectiveness of OK-432 (Sapylin) to reduce seroma formation after axillary lymphadenectomy for breast cancer. Ann Surg Oncol. 2013 May;20(5):1500–4.

15. Bloom JA, Foroutanjazi S, Erlichman Z, Beqiraj Z, Jonczyk MM, Persing SM, et al. The Use of Hemostatic Agents to Decrease Bleeding Complications in Breast Cancer Surgery. Am Surg. 2021 Jun 27;31348211029866.

16. Jackson IJB, McWhinnie D, Skues M. The British Association of Day Surgery Directory of Procedures. AMBULATORY SURGERY. 2010;3.

17. Wells M, Harrow A, Donnan P, Davey P, Devereux S, Little G, et al. Patient, carer and health service outcomes of nurse-led early discharge after breast cancer surgery: a randomised controlled trial. Br J Cancer. 2004 Aug 16;91(4):651–8.

18. Eden C, Buonomo OC, Busch J, Gilabert-Estelles J, Medrano R, Nosotti M, et al. An international multidisciplinary peer-driven consensus on the optimal use of hemostatic powders in surgical practice. Updates Surg. 2021 Aug;73(4):1267–73.

19. Harrison C, Remoundos DD, Harvey KL, Stoker GV, MacLean G, Adwani A, et al. Increasing the incidence of drain-free day-case mastectomies with the use of a fibrin tissue sealant; data from a single surgical center in the United Kingdom. Breast J. 2019 Nov;25(6):1090–6.

20. Wang Y, Wang P, Ji H, Ji G, Wang M, Wang X. Analysis of Safety and Effectiveness of Sodium Alginate/Poly(γ-glutamic acid) Microspheres for Rapid Hemostasis. ACS Appl Bio Mater. 2021 Aug 16;4(8):6539–48.

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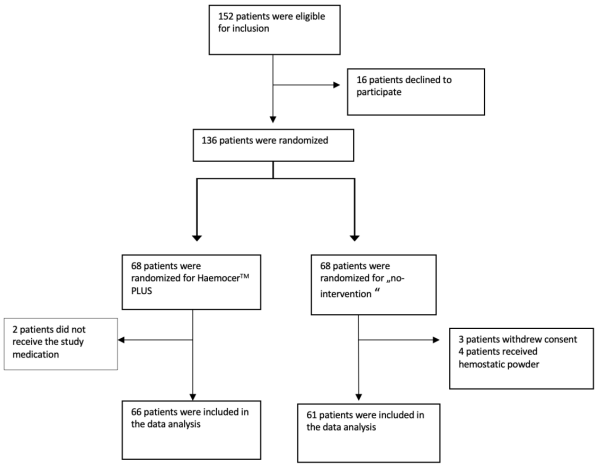

Figure 1: Flow-chart of the study participants