Journal of SURGICAL ARTS
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Original study

Effects of Ankaferd® blood stopper on the postoperative outcomes of breast surgery for gynecomastia and breast hypertrophy

Ankaferd® kanama durdurucusunun jinekomasti ve meme hipertrofisi cerrahisi sonuçlarına etkisi

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How to cite: Altuntaş SH, Uslusoy F, Dilek ÖF, Aydın A. Effects of Ankaferd® blood stopper on the postoperative outcomes of breast surgery for gynecomastia and breast hyperthrophy. J Surg Arts: 2022;15(2):43-53.

Received: 01.01.2023 Accepted: 13.01.2023

ABSTRACT

Bleeding after skin closure is a disturbing complication commonly observed in almost all kind of surgical operations. Ankaferd blood stopper (ABS), a topical hemostatic agent of plant origin, has been registered for the management of clinical hemorrhages when the conventional methods to control bleeding by ligature and/or hemostatic measures are ineffective.

This study investigated whether topical ABS application alters postoperative bleeding complications in patients undergoing symmetrical red uction mammoplasty or symmetrical subcutaneous mastectomy in a randomized, placebo-controlled, double-blind design. Twenty-two patients underwent either reduction mammoplasty (n=13) or subcutaneous mastectomy (n=9). ABS or placebo was randomized between both breasts in the same patient. Total amount running from the drain was found significantly greater in ABS group in comparison to the placebo group.

Hematoma was seen in one case, seroma in 8 cases and infection and wound healing problem requiring intervention in 6 cases. Hematoma complication occured in placebo group and a significant difference was not found between groups in terms of this complication. Of the 8 seroma complications all were in ABS group. Relationship between seroma development and ABS use was found significant.

Similarly, all of 6 cases who developed infection and wound healing problem requiring intervention were in ABS group. Infection and wound healing problem requiring intervention were also found to be significantly correlated with ABS use. Any finding suggesting a constant hemostatic effect on the post-surgical hemorrhages despite conventional hemostatic methods could not be obtained in this study.

Keywords: Ankaferd; hemostasis; hemorrhage; gynecomastia; surgical approach.

ÖZET

Cilt kapatma sonrası kanama, hemen hemen her türlü cerrahi operasyonda yaygın olarak görülen rahatsız edici bir komplikasyondur. Bitkisel kökenli topikal bir hemostatik ajan olan Ankaferd kan durdurucu (ABS), ligasyon ve/veya hemostatik önlemlerle kanamayı kontrol etmek için geleneksel yöntemlerin etkisiz olduğu durumlarda klinik kanamaların yönetimi için tescil edilmiştir.

Bu çalışmada, simetrik redüksiyon mamoplasti veya simetrik subkutan mastektomi uygulanan hastalarda topikal ABS uygulamasının ameliyat sonrası kanama komplikasyonlarını değiştirip değiştirmediği randomize, plasebo kontrollü, çift kör bir tasarımla araştırılmıştır. Toplam 22 hastaya redüksiyon mamoplasti (n=13) veya subkutan mastektomi (n=9) uygulanmıştır. Konvansiyonel tekniklerle yapılan hemostazın ardından ABS veya plasebo aynı hastada her iki meme arasında randomize edilmiştir. Dren sıvısı miktarı ve mahiyeti postoperatif dönemde analiz edilmiştir.

ABS grubunda drenden akan toplam miktar plasebo grubuna kıyasla anlamlı olarak daha fazla bulundu. Bir olguda hematom, 8 olguda seroma ve 6 olguda müdahale gerektiren enfeksiyon ve yara iyileşmesi sorunu görüldü. Hematom komplikasyonu plasebo grubunda görülmüş ve bu komplikasyon açısından gruplar arasında anlamlı bir fark bulunmamıştır. 8 seroma komplikasyonunun tamamı ABS grubunda görülmüştür.

Seroma gelişimi ile ABS kullanımı arasındaki ilişki anlamlı bulunmuştur. Benzer şekilde, müdahale gerektiren enfeksiyon ve yara iyileşmesi sorunu gelişen 6 olgunun tamamı ABS grubundaydı. Enfeksiyon ve müdahale gerektiren yara iyileşmesi sorunu da ABS kullanımı ile anlamlı şekilde ilişkili bulunmuştur. Bu çalışmada konvansiyonel hemostatik yöntemlere rağmen cerrahi sonrası kanamalar üzerinde sabit bir hemostatik etkiye işaret eden herhangi bir bulgu elde edilememiştir.

Anahtar kelimeler: Ankaferd; hemostaz; kanama; jinekomasti; cerrahi yaklaşım.

INTRODUCTION

Bleeding after skin closure is a disturbing complication commonly observed in almost all kind of surgical operations. Although the surgery-associated bleeding can be controlled by the proper use of surgical hemostatic methods, bleeding after skin closure can cause numerous complicated clinical manifestations unless it is properly managed (1-3). While negative-pressure suction tubes are often utilized to remove accumulating blood from the surgical field (4), normal tissue pressure in a closed surgical wound is also expected to limit bleeding when these tubes are not used. However, suction tube use can never replace a good hemostasis to avoid hemorrhage-related complications in breast reduction mammoplasties (5-7). Normal hemostasis and wound healing mechanisms of the body enables gradual reduction of the bleeding and serous leakage from the vascular structures. It would not be surprising to expect that any additional hemostatic intervention to reduce or eliminate leaks that persist despite routine surgical hemostasis methods will result in less pain, edema, or ecchymosis, and will be associated with better tissue perfusion, faster wound healing, and earlier removal of suction tubes. Recently, outpatient surgical procedures have become popular especially in the countries with high overnight hospital costs. As a matter of fact, some authors have reported that they reduced the postoperative hospital stay time to 5 hours (8). Hematoma in breast reduction is mainly related with the inadequate intraoperative hemostasis, bleeding disorders and postoperative hypertension (7). Postoperative oozing, leakage and hemorrhage constitute the major number of early complications of breast surgeries, such as reduction mammoplasty (RM) and subcutaneous mastectomy (SC) (1-21).

Ankaferd blood stopper (ABS), a topical hemostatic agent of plant origin, has been registered for the management of clinical hemorrhages when the conventional methods to control bleeding by ligature and/or hemostatic measures are ineffective (22-23). ABS includes standardized preparation of the plants Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum, and Urtica dioica (24,25). ABS provides vital erythroid aggregation covering the entire physiological hemostatic process via a unique protein network depending primarily on the interactions between ABS and blood proteins, particularly with fibrinogen gamma and prothrombin (26). Vital erythroid aggregation takes place with the spectrin and ankrin receptors on the surface of red blood cells (RBC). Those RBC proteins and the required ATP bioenergy are included in the ABS protein library (26, 27). On the other hand, controlled clinical trials indicated the safety and efficacy of topical ABS in distinct clinical backgrounds (28-32).

The aim of this study is to investigate whether bleeding that persists despite routine surgical hemostasis can be reduced by topical ABS application in patients undergoing symmetrical reduction mammoplasty (RM) or subcutaneous mastectomy (SCM) in a randomized, placebo-controlled, double-blinded study design.

MATERIAL and METHOD

Study design

This study was performed as a placebo-controlled, double-blinded controlled clinical trial with the approval of Ethic Committee of Suleyman Demirel University Medical Faculty. All patients read and signed informed consent. While patients with a desire for either reduction mammoplasty or subcutaneous mastectomy for symmetrical breast hypertrophy or gynecomastia were included in the study, patients with coagulation disorders, prescribed aspirin, anticoagulant or antithrombotic therapy were excluded. Preoperative records included the blood type, co-morbidities (diabetes, hypertension, and others), medications, whole blood count, biochemistry and coagulation panels, blood pressure values, and prophylactic antibiotics. Intraoperatively, weight of bilateral tissues resected, hemostasis status after routine coagulation methods were noted. In addition to daily whole blood count and biochemistry

panels, while the amount and type of accumulated fluid in suction tubes were recorded on daily basis, sampling of these fluids for laboratory analysis were also conducted. Preoperative ultrasonography was performed in all patients to exclude any abnormal mass lesions in their breasts.

Surgical procedures

Reduction mammoplasty was performed through a vertical scar that areola-nipple complex was carried over a superomedial pedicle like the technique described by Findlay (37). A short horizontal incision was also added when needed. A standard hemostasis was obtained with electrocautery after planned tissue resections. ABS or placebo was implemented for right side first (Figure 1). After suction tube placement and subcutaneous closure of the right side, same procedures were applied for the opposite breast. In patients who were admitted for gynecomastia, breast skin was lifted through a peri areolar incision at the right side first. This was followed by resection of underlying fibrolipoglandular tissue over pectoral fascia. Sequence of ABS/placebo implementation and suction tube placement, as well as closure of the breast tissue was same as described for breast reductions (Figure 2).

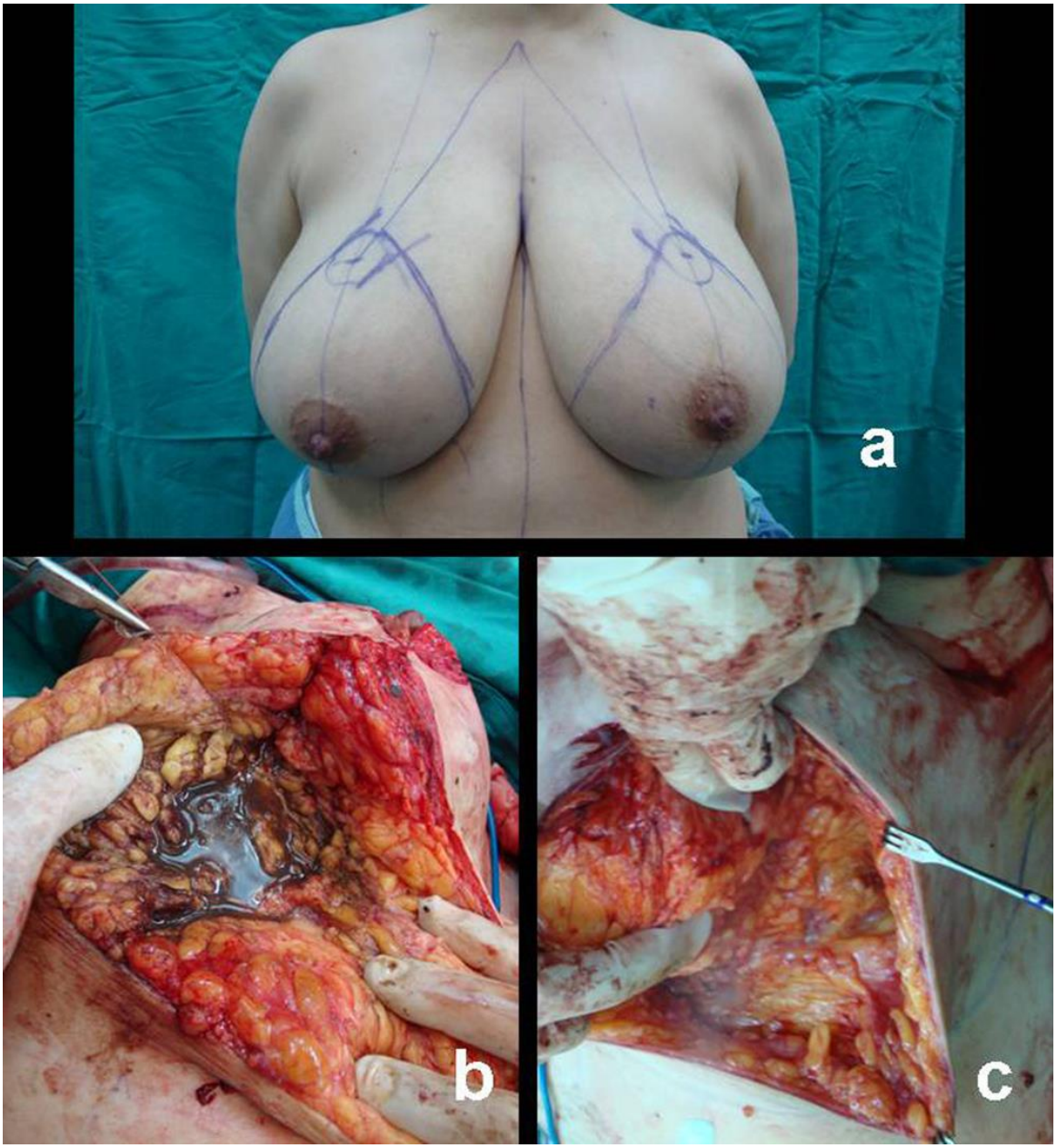

Figure 1: Substance use in breast reduction operation planned for bilateral breast hypertrophy (a). Brownish black color change caused by ABS in tissues (b). Normal tissue colors were preserved following placebo administration in operative field (c).

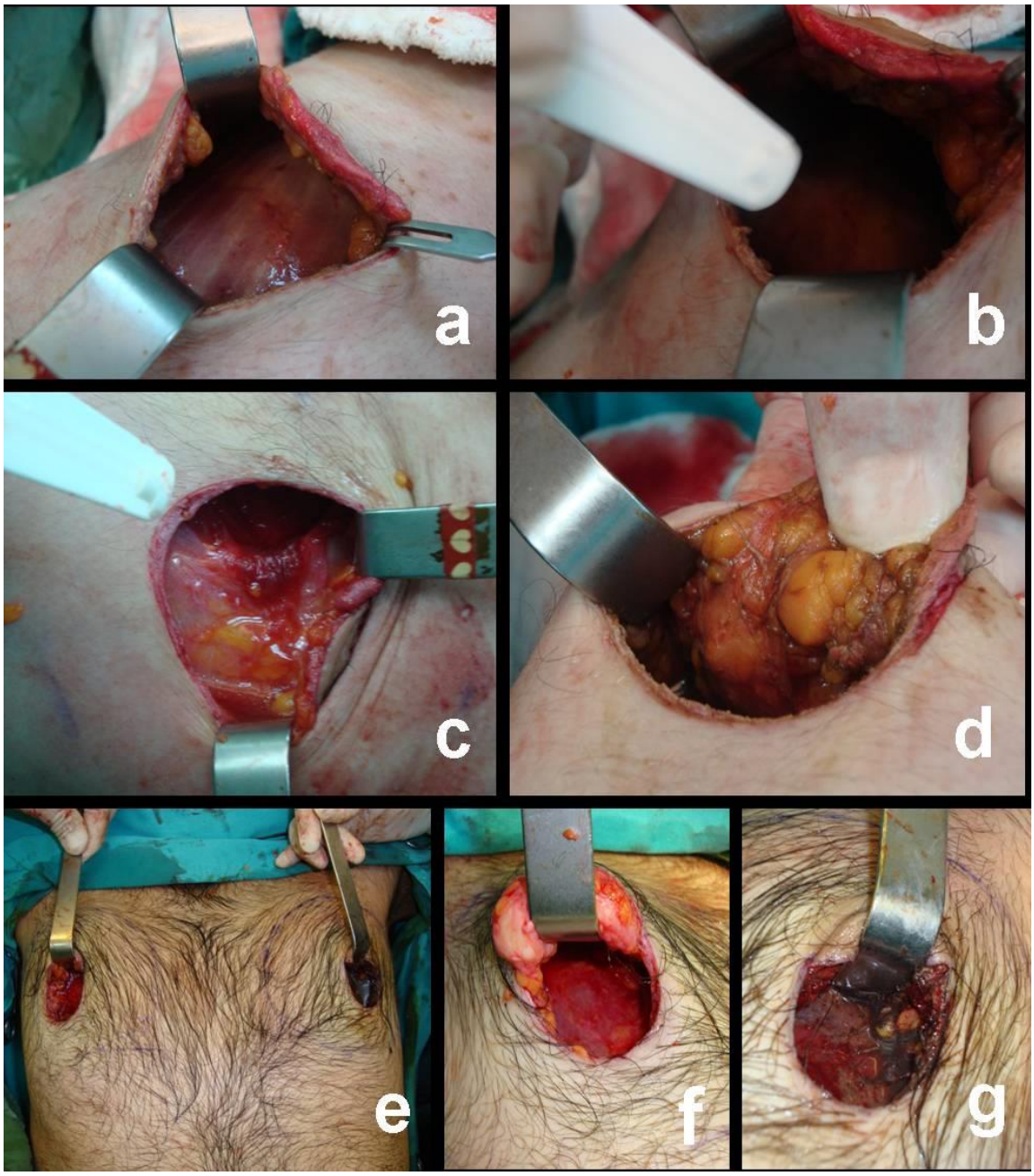

Figure 2: Pectoral fascia following subcutaneous mastectomy for bilateral gynecomastia (a). Substance administration (b). Difference in tissue colors after placebo and ABS administration(c,d). In another case, not the significant color change in both sides following ABS and placebo administrations (e,f,g).

Preparation and implementation of drug and placebo

Spray form of ABS was used in the study. Drug and placebos were provided by Ankaferd Health Products (Beykoz, İstanbul). The drug and placebo were identical in appearance, color, odor, and viscosity and were delivered in paired (one drug and one placebo), sterile and ready-to-use 10 milliliter vial packs for each patient. (Figure 3). Randomization of the treatment group between breasts was made by Yorum Health Counseling and Publishing Services (Nişantaşı, İstanbul). Substances were used only after conventional hemostasis methods performed appropriately and sufficiently. The quality of hemostasis obtained with conventional hemostasis methods was recorded as good, moderate, and poor subjectively. During the administration of the substances, the surgeon's estimation of the substance (drug or placebo) was also noted.

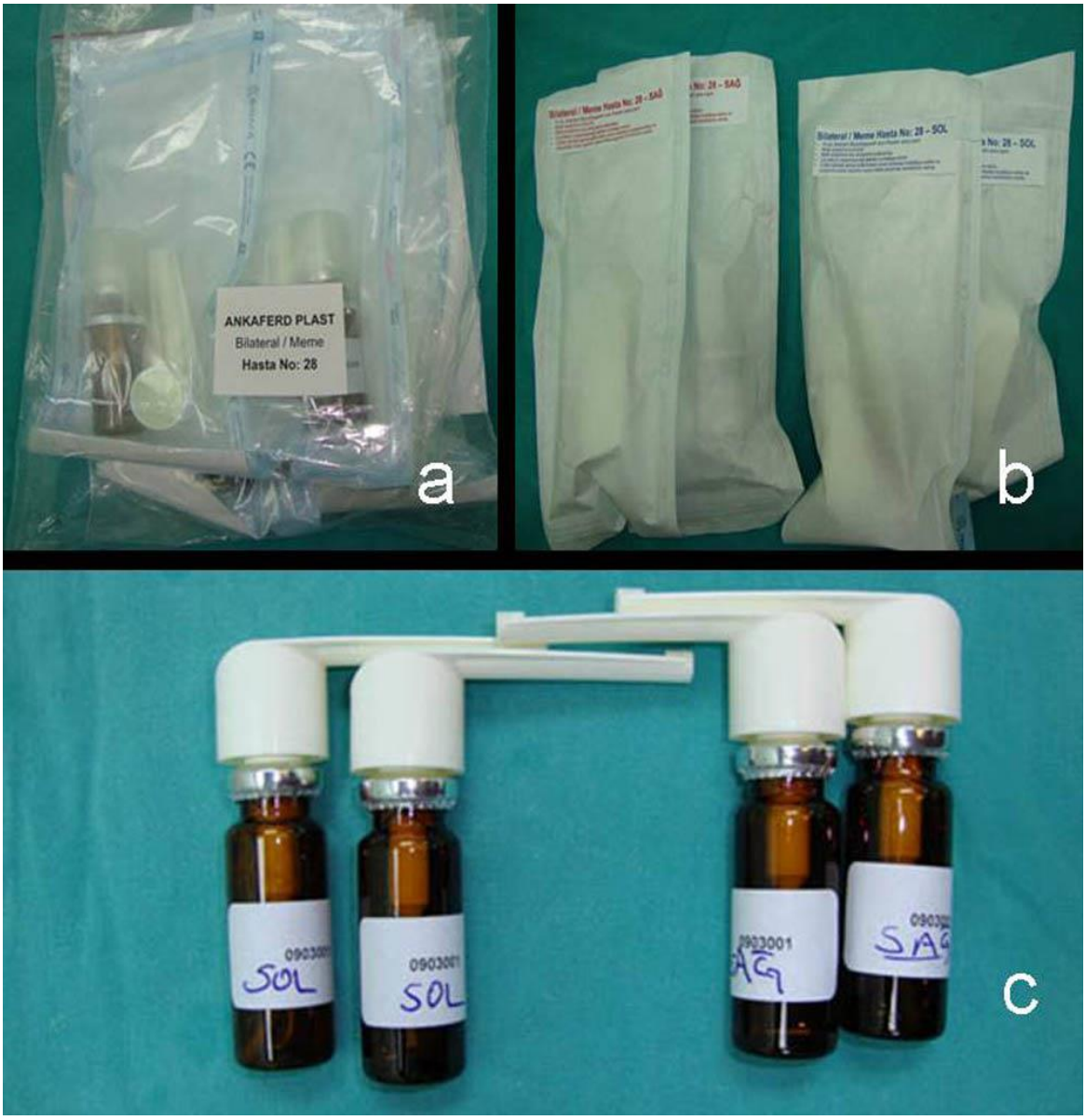

Figure 3: Package prepared for bilateral breast operations (a). Packages marked as right or left by the company in a sterile manner (b) sterile vials and labels indicating right or left (c). Vials and contents did not have any identifying property that differs ABS and placebo from each other.

Postoperative follow up

Volume of fluid accumulation in suction tubes was recorded each morning beginning from the first day after bilateral breast operations. Color of drainage fluid was also recorded as hemorrhagic, serohemorrhagic and serous. Additionally, sampling was made from the drainage fluid in the first two days and hematocrit (hct) and hemoglobin (hb) concentration were measured. Variables of "hb mass in the drainage" and "blood cell mass in the drainage" that would be used for comparison of bleeding amount were obtained using the following formula with hb and hct values and fluid amount running from the drainage tube in the first two days.

Hb mass in the drain (gr)= (Hb density of drainage fluid (g/dl) x fluid amount running from the drainage tube (ml))/100.

Erythrocyte mass volume in the drain (ml) = (Hct value of drainage fluid (%) x fluid volume running from the drainage tube (ml)) /100.

When the fluid amount running from the suction tube was below 50 cc in two consecutive days and serous or serohemorrhagic, suction tubes were removed.

Statistical assessment

The constant variables belonging to bilateral breasts of the same patient was compared using paired t test. The relationship between categorical variables and ABS use was analysed using Fisher's exact test. A p value below 0.05 was considered as statistically significant.

RESULTS

Twenty-two patients underwent reduction mammoplasty (n=13) or subcutaneous mastectomy (n=9). Demographics and follow-up data are shown both as a whole and specifically for ABS and placebo groups in Table 1. The statistical significance of the differences in the studied variables between the two groups are also depicted in Table 1. There was not a statistically significant difference between ABS and placebo groups in terms of the amount of removed tissue, the quality of surgical hemostasis and suction tube performance.

The total volume running from the suction tube was found significantly greater in ABS group in comparison to the placebo group. When these volumes were analyzed separately for the 1st, 2nd, and 3rd days, they were found to be greater in ABS group at 2nd and 3rd days. On the contrary to these findings, hb and cell densities of the fluid volumes was less in 1st and 2nd days in the ABS group. Although hb mass and cell mass amount were noted less during the first and the second day, the difference was not significant. While hematoma was seen in one patient, seroma was detected in 8 patients. Infection and wound healing problem requiring intervention detected in 6 cases. Hematoma complication that occurred in placebo group did not predicate statistical significance. All 8 seroma complications were in ABS group. Relationship between seroma development and ABS use was found significant. Similarly, 6 cases who developed infection and wound healing problem requiring intervention were all in ABS group and this was significantly correlated with ABS use. Infection and wound healing problems requiring intervention were detected on follow-ups of 3 patients who also developed seroma. The p value of the relationship between infection or wound healing requiring intervention and seroma complications was 0,063.

Table 1: Demographic features of patients who underwent reduction mammoplasty (RM) and subcutaneous mastectomy (SCM) and comparison of parameters evaluated in the study between ABS and placebo groups (h: hemorrhagic, s: serous, sh: serohemorrhagic)

Number of patient (RM : SCM)		22 (13, 9)		
Age (RM : SCM)		34,8±2,5 (41±2,5 : 23±1,76)		
		ABS (RM : SCM)	**Placebo (RM : SCM)**	**p**
Removed tissue (gr)		902±158	917±169	0,55
Surgical hemostasis	*Good*	13	13	0,56
	Moderate	7	8	
	Poor	2	1	
Drain performance	*Good*	21	21	0,75
	Poor	1	1	
Amount of drainage (ml)				
Day 1		83±10,6 (103 : 47)	79±9,4 (98 : 63)	0,66
Day 2		58±6,2 (67 : 43)	36±5,5 (47 : 17)	**0,003**
Day 3		45±4,9 (48 : 31)	32±4,8 (36 : 20)	**0,005**
Total		199±23 (244 : 120)	157±22 (205 : 74)	**0,033**
Fluid of drainage Hb (g/dl)				
Day 1		3,8±0,7 (3,4 : 4,8)	5,7±0,8 (4,6 : 8,7)	**0,002**
Day 2		1,6±0,2 (1,5 : 2,1)	3,5±0,8 (2,5 : 6,5)	**0,024**
Fluid of drainage Htc (%)				
Day 1		9,8±2,1 (8,6 : 13,2)	16±2,4 (12,9 : 25,9)	**0,001**
Day 2		3,6±0,7 (3,2 : 4,8)	11,7±2,7 (9 : 19)	**0,007**

DISCUSSION

We estimated the amount of ongoing hemorrhage in the surgical wound bed postoperatively by measuring hemoglobin mass and cell mass volume of fluid contents of the suction tubes. ABS use in RM and SCM significantly increased the amount of fluid running from the drain and complications of seroma, infection and wound healing problem requiring intervention. Increased amount of fluid running accumulated in suction tubes with decreased hb and red cell mass values suggested that ABS use increased the exudation from surgical field. The amount of fluid in suction tubes was not different in the first day, but significantly higher in ABS group in 2nd and 3rd days. On the other hand, hb amount in the tubes measured in 1st and 2nd days was not

different on both sides, suggesting increased exudation especially after first 24 hours. Significantly higher seroma, infection and wound healing problems with ABS use indicates persistent exudation even after removal of the suction tubes at 3-5 days. Increased seroma formation can also be ascribed to the increased exudation due to ABS-associated inflammation.

In three different randomized controlled studies (4,15,16), a significant difference was not shown between using and not using suction tubes in reduction mammoplasties. On the other hand, independent determinants of total amount running from the suction tubes in reduction mammoplasties were found to be age and amount of excised breast tissue in the study of Ngan et al. (33). The authors recommended drain use in cases above 50 years and in whom more than 500 gr tissue excision would be made. The amount of the excised tissue was above 500 gr in all of breast reduction operations in our study.

Fluid infiltration was made with tumescence method and an equal amount of fluid was infiltrated in both sides of all breasts. Several studies have found that adrenaline fluid infiltration reduces intraoperative hemorrhage in breast reduction mammoplasties (34-43). In those studies, adrenaline fluid infiltration-related reactive hyperemia and rebound bleeding was found clinically insignificant. However, tumescence method did not change the amount of fluid running from the suction tube (39). Varma and Henderson (41) compared the effects of adrenaline fluid infiltration in gynecomastia surgery. They found that while tumescence method reduces intraoperative blood loss, it does not affect postoperative drainage. Hematoma, seroma, infection, and wound healing problems are the most expected complications after reduction mammoplasty and subcutaneous mastectomy operations. Table 2 shows variable ratios of hematoma, seroma, infection, and wound healing problems reported in different case serials in the English literature.

Table 2: Distribution of complications of hematoma, seroma, infection and wound healing in reduction mammoplasty and subcutaneous mastectomy case serials reported in the English Literature.

Authors	Number of cases	Hematoma	Seroma	Infection	Wound healing problem
Reduction Mammoplasty					
Lejour (1994) (42)	100	2	8	-	8
Buenaventura et al. (1995) (12)	338	6 (1*)	8	Minor: 11	Minor: 35
Blomqvist et al. (1996) (35)	104	5 (1*)	-	3	-
Mandrekas et al. (1996) (10)	371	1	-	-	17
DeBono ve Rao (1997) (38)	100	2	-	11	11
Metaxotos et al. (1999) (37)	24	-	-	-	-
Lejour (1999) (6)	250	6 (6*)	5 (%)	2	5,4 (%)
Hussien et al. (2001) (11)	238	16 (4*)	-	-	-
Wrye et al. (2003) (16)	49	2 (1*)	-	-	5
Collis et al. (2005) (4)	150	8 (7*)	2	Minor: 9 Major: 1	Minor: 42 Major: 5
Scott et al. (2005) (8)	581	51 (3*)	-	Minor: 21	Minor: 51 Major: 3
Stevens et al. (2008) (13)	444	4	1	Minor: 8	Minor: 56 Major: 12
Henry et al. (2009) (9)	485	5 (%) (1*)	-	1,8 (%)	Minor: 26 (%)
Ngan et al. (2009) (33)	333	1.2 (%)	-	-	Minor: 3.3 (%) Major: 0.9 (%)
(* =evacuated surgically)					

Hematoma complication was reported in varying rates in almost all of case series (6,8-10). In those studies, wound healing, nipple areola complex necrosis, and rare flap necrosis were reported. However, the association of these complications with hematoma development was not stated explicitly. Seroma formation was reported as a minor complication in many case series and this was often treated with repeated needle aspirations (12,13). Need for re-operation for hematoma evacuation was

reported in varying rates between 0% and 12% after gynecomastia surgery (17-20). While the frequency of infection-wound healing problem and seroma were correlated in some series, some other did not find this correlation. This condition suggests that infection-wound healing problems may coexist with other problems like fat and flap necrosis. However, the coexistence of seroma and infection-wound healing problems were near-significant in our study, and this suggests that infection-wound healing problems are mostly related with seroma.

In our study, ABS or placebo was administered in operative field after sufficient surgical hemostasis had been achieved by conventional bipolar cauterization. Data analysis showed that, hb mass was measured as 1.28 g-0.64 g and 0.64 g-0.05 g in ABS and placebo sides in 1 and 2. days, respectively. This condition prompted us to consider that ABS may be insufficient alone, using ABS in addition to conventional surgical hemostasis methods would be an acceptable preference. The procedure was begun on the right in all operations. Dependent variables were not different between right and left in the analyses.

The study was interrupted in reduction mammoplasty group due to infection in two patients. Different microorganisms grew in cultures as *Staphylococcus aureus* in one, *Enterobacter cloacae* and *Enterococcus species* in another. Cultures were sent also from vials of the used substances and no growth occurred. Thus, infections were not substance-related contamination, and this led us to resume the study. Additionally, such infections were not seen in the following cases. Those two infections were on the ABS side, and we consider that they developed due to excessive exudation leading to seroma that continued after suction tube removal.

Along with not having a significant effect on postoperative hemorrhage in breast operations, it was observed that ABS increases the exudation from operative field that leads to increased seroma, infection, and wound healing problems.

In in vitro studies performed with ABS, the hemostatic agent was shown to cause an encapsulated protein network that would induce erythrocyte aggregation by affecting fibrinogen-erythrocyte agglutination relationship (24-27). The network formed by ABS was reported to be related with interactions with blood proteins, mainly fibrinogen. However, no reduction was detected in coagulation factor levels. Therefore, this network was reported to be able to be effective in patients with normal hemostasis and primary and secondary hemostasis deficiencies (26). Although the protein network was stated to be resistant to heat and detergents, we observed in our study that this structure could easily be broken with in vivo condition via mechanical effects. This may diminish the hemostatic properties of the agent.

In the swine bleeding model that in vivo ABS effectiveness was shown. ABS was observed to be effective in acute bleedings from skin, liver, spleen, saphenous vein, and artery. However, while bleeding from spleen did not stop with spray form of ABS, it could only be controlled with repeated applications of ampoule and compress (44). The hemostatic effects of ABS was also evaluated in the following in vivo situations: urinary bladder hemorrhage model (45), partial nephrectomy model (46), renal trauma model (47), and experimental liver injury model (48). Statistically significant results in favor of ABS were reported in these studies. Additionally, in Kosar et al. (49) studied ABS in a hemostasis disorder, and a significant reduction in the amount of bleeding was detected in ABS group following the hind leg amputation. In another study conducted with administration of acetyl salicylic acid and enoxaparin sodium, less bleeding duration and amount were obtained in ABS group in bleeding model that constituted through tail incision (50).

In a prospective controlled clinical study, ABS was used along with the ligation for hemostasis in children who underwent tonsillectomy and was reported to lead to significant reduction in the time of hemostasis and the amount of bleeding (51). In acute anterior epistaxis cases, another randomized controlled study compared ABS and phenylephrine. While any difference was not found between ABS and phenylephrine, re-bleeds were found to be less in ABS group (52). Other studies performed with ABS are composed of case reports and case series. Endoscopically intervened gastrointestinal bleedings constitute vast majority of case reports and case serials (53-63). Successful topical treatments in active gastrointestinal bleedings are reported in these cases. ABS was also reported to achieve hemostasis in anatomic areas that are difficult to reach such as, coronary artery by-pass grafting surgery (56), retropubic radical prostatectomy (57), and rectal carcinoma (63). ABS was also used in a patient with Glanzman Thrombocytopenia due to gingival bleeding however, after a few minutes it started to rebleed and in this case the effects of ABS were temporary in the setting of platelet function defects (64).

As observed in all these studies, ABS seems to be highly effective in acute hemorrhages and provides a rapid and successful hemostasis.

However, any finding suggesting a constant hemostatic effect on the postoperative surgical field hemorrhages or leakages was obtained in this study. Additionally, an exudative effect of ABS that emerges in the second day of ABS and continues for following days was encountered after breast surgery. In a study investigating the effectiveness of ABS in prevention of postoperative seroma after radical mastectomy and axillary lymph node dissection in rats, while the bleeding time was found to be diminished significantly, the amount of seroma was greater in ABS group when compared to controls (65).

The strength of this study is being a randomized controlled and double blinded study. It also

bears the paired comparison of the symmetrical interventions toward symmetrical breast deformities. Additionally, rather being based on subjective observations, data in this study is based on objective measurements which is another strong point. There are two major weakness for this study: [1] it was conducted in a small group and [2] ABS colored administered tissues differently from placebo and thereby gave a clue for surgeon's estimation (Figure 1 and 2). Although it may be considered to cause bias, the most important step that would affect the study, the surgical hemostasis, was completed just before substance administration and thereby surgeon did not know which substance had been applied before surgical hemostasis. Follow-ups were also made through patient numbers via blinded investigators. Additionally, estimation of hemorrhage is based on laboratory measurements and numerical measurements is another factor for eliminating bias.

Conclusion

ABS use in reduction mammoplasties and subcutaneous mastectomy operations did not reduce the hemorrhage or leakage that continues postoperatively. Despite the sufficient surgical hemostasis, however, ABS led to an increase in exudation and exudation-related seroma, infection, and wound healing problems. Further investigations are needed to elucidate clinical application fields of this unique hemostatic agent.

Declaration of interest

Based on the ethics committee application, it was recorded that the company who provided the related drug and placebo would not contribute to the study except providing product and there is no conflict of interests between the company and the researchers. The authors alone are responsible for the content and writing of the paper.

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