Effect of Acetylsalicylic Acid on Microvascular Thrombosis in Autologous Breast Reconstruction

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Abstract

Although advances in microsurgery have increased success rates of autologous breast reconstruction, microvascular thrombosis still remains a major concern as a cause of flap failure. At present, no evidence-based guidelines on pharmacological prevention of microvascular thrombosis exist. This study investigates the effect of acetylsalicylic acid on the incidence of microvascular complications in patients undergoing autologous breast reconstruction.

Patients undergoing deep inferior epigastric artery perforator or free transverse rectus abdominis myocutaneous flap breast reconstruction at two academic centers in the Netherlands between 2005 and 2011 were included. Patients at one center received once daily 0.6 mL of nadroparine and 40 mg acetylsalicylic acid, while patients at the other center received 0.6 mL nadroparine only.

A total of 430 consecutive patients underwent 592 breast reconstructions. No statistically significant differences were found between the two groups in the incidence of flap failure (2.8 and 2.5%), microvascular thromboembolic complications (2.6 and 3.8%), venous congestion (3.4 and 2.8%), or overall complications (28.0 and 32.3%). Hematoma tended to occur more often in the group receiving acetylsalicylic acid (9.2 and 4.7%). It was found that no protective effect of acetylsalicylic acid on microvascular complications was present. Given its known risks and the somewhat increased occurrence of hematoma in the present study, we stopped to routinely administer acetylsalicylic acid after autologous breast reconstruction.

Keywords
- DIEP
- TRAM
- breast reconstruction
- acetylsalicylic acid
- thrombosis

Advances in microsurgical techniques and increased experience with the deep inferior epigastric artery perforator (DIEP) and free transverse rectus abdominis myocutaneous (TRAM) flap have led to flap survival rates of more than 95%.[1] However, microvascular thrombosis remains a major concern and can occur even in the absence of microsurgical errors. Endothelial trauma caused by the incision, manipulation, and suturing of the vessels is thought to play a central role in the pathophysiology.[2,3] During this process, also known as the primary hemostasis, platelets adhere to the vascular subendothelium, release granules containing multiple mediators, and aggregate to form a hemostatic plug.[4] In addition, the coagulation system is activated (secondary hemostasis), resulting in the generation of clotting factors and ultimately

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thrombin. Thrombin converts fibrinogen to fibrin, the final substrate of the clot and linkage between platelets. Primary and secondary hemostasis are not separate events but are intimately linked.[4]

Free flap failure occurs in 1 to 9% of the cases[5] and is generally caused by microvascular thrombosis in the area of the vascular anastomosis or the distal flap microcirculation.[2,6–8] While early diagnosis and revision of a thrombosed anastomosis have been shown to salvage free flaps, prevention of microvascular thrombosis remains of primary importance.[9] Several experimental and clinical studies have investigated the preventive effect of various pharmacological agents. These agents include acetylsalicylic acid,[10–12] heparin,[6,13,14] dextran,[15–18] various thrombolytics,[19–29] and glycoprotein IIb/IIIa inhibitors.[20] Results of these studies are inconclusive,[21] some agents have significant potential side effects,[23] and all agents are known to carry risks of bleeding and hematoma formation.[4,22] Therefore, at present still no consensus has been established on treatment guidelines in terms of ideal antithrombotic agents, timing, and dosage in reconstructive microsurgery.[21,24] Few *clinical* studies have investigated the effects of acetylsalicylic acid on free flap survival.[6,9,25] These studies present conflicting outcomes because of different prophylaxis regimens and patient groups. Several literature reviews have been published as well, which made conflicting recommendations based on different inhomogeneous groups of patients.[7,21,22,26,27]

The development of evidence based algorithms to prevent microvascular thrombosis is essential to optimize outcomes and to increase comparability of postoperative results and complications. Therefore, the aim of this study was to investigate the value of acetylsalicylic acid for maintenance of postoperative microvascular patency in a homogeneous patient group undergoing DIEP or free TRAM flap breast reconstruction.

Patients and Methods

All consecutive patients that underwent a DIEP or free TRAM flap breast reconstruction in the period of January 2005 to January 2011 at the Erasmus MC, University Medical Center Rotterdam (EMC) and Maastricht University Medical Center (MUMC), were included in this retrospective review. Patient demographics and perioperative data were extracted from the electronic medical record system and from hard copy medical charts.

The primary outcome was the incidence of complete flap failure. Secondary outcomes were all clinically significant microvascular complications including microvascular thrombosis, venous congestion, partial flap necrosis, and hematoma leading to reoperation.

At both the centers, to prevent systemic thromboembolic events all patients received perioperative elastic compression devices and once daily subcutaneous low molecular weight heparin (LMWH; nadroparine 5,700 aXa-IE = 0.6 mL fraxiparine) until discharge, usually the 6th postoperative day. Administration of LMWH was initiated 12 hours before surgery with a second dose at 12 hours after the surgery. In the early postoperative period patients were positioned and nursed in a low- or semi-Fowler position. To prevent microvascular thrombosis, the vessels were intraoperatively locally irrigated with a heparinized solution before anastomosis at both the centers. At EMC all patients received additional 40 mg acetylsalicylic acid once daily from the first postoperative day during a period of 6 weeks. At both the centers postoperative monitoring was performed clinically by an experienced nursing staff by checking flap color, temperature, and capillary refill. At the 1st postoperative day the flaps were monitored every 1 hour, the 2nd day every 2 hours, and from the 3rd postoperative day till discharge the flaps were monitored once every 4 hours.

Statistical Analysis

Fisher exact and chi-square tests were performed to analyze categorical variables and student *t*-test was used for continuous variables. Version 17.0 of SPSS (SPSS Inc., Chicago, IL) was used for statistical analyses. Two-sided p values < 0.05 were considered statistically significant.

Results

A total of 430 consecutive patients underwent 592 breast reconstructions, out of which 261 cases were included from EMC and 169 patients from MUMC. Patient demographics were similar between EMC and MUMC (►**Table 1**), except for body mass index, which was significantly higher at EMC (EMC 27.2 kg/m^2, MUMC 26.4 kg/m^2; $p = 0.02$). Mean age at the time of breast reconstruction was 47.5 years at EMC and 47.8 years at MUMC ($p = 0.54$). At both the departments DIEP flaps were favored over free TRAM flaps. Timing of reconstruction was mostly secondary. Small but statistically significant differences between the two centers were found in operative approach. At EMC DIEP flaps were used more frequently than in MUMC ($p = 0.011$), while at MUMC primary breast reconstructions were performed more often ($p < 0.001$). There were no statistically significant differences in potential risk factors for microvascular complications between the two groups (►**Table 1**).

The overall complication rate was similar at both centers (►**Table 2**). We did not observe a statistically significant difference in the primary outcome of complete flap failure (2.5% at MUMC and 2.8% at EMC; $p = 1.00$). Neither did we find any statistically significant differences in major microvascular complications such as arterial or venous thrombosis, venous congestion, partial flap necrosis, and hematoma leading to reoperation (►**Table 2**).

Discussion

Several experimental and clinical studies have investigated the effect of acetylsalicylic in prevention of thrombosis after arterial intimal injury.[10–13,28] However, at present no consensus has been established on treatment guidelines. We analyzed the value of acetylsalicylic acid in preventing microvascular thrombosis and its complications in a homogeneous patient group undergoing DIEP and free TRAM flap

Table 1 Patient, perioperative, and surgical characteristics of 430 ABR patients

	EMC $N = 261$	MUMC $N = 169$
	Mean (SD)	Mean (SD)
Patient characteristics		
Age in y	47.5 (8.9)	47.8 (8.5)
BMI in kg/m^2	27.2 (4.2)	26.4 (4.1)
Perioperative characteristics		
Total operating time in h	7.8 (2.2)	8.2 (2.6)
Total operating time for unilateral reconstruction in h	6.5 (1.3)	7.0 (1.7)
Total operating time for bilateral reconstruction in h	10.0 (1.8)	10.1 (2.6)
Hospitalization duration in d	8.7 (5.5)	7.6 (2.3)
Surgical characteristics		
Flap Type		
DIEP flap	96.6%	90.5%
TRAM flap	3.4%	9.5%
Laterality of breast reconstruction		
Unilateral	61.8%	63.8%
Bilateral	38.2%	36.2%
Timing of breast reconstruction		
Primary	23.0%	47.5%
Secondary	77.0%	52.5%
Potential risk factors for microvascular complications		
Smoking	7.3%	4.1%
Adjuvant therapy (chemo, hormonal, radiotherapy)	41.8%	43.3%
Previous thromboembolic events	1.1%	0.6%

Abbreviations: ABR, abdominal flap breast reconstruction; d, days; EMC, Erasmus MC, University Medical Center Rotterdam (nadroparine 5,700 aXa-IE + 40 mg acetylsalicylic acid once daily); h, hours; MUMC, Maastricht University Medical Center (nadroparine 5,700 aXa-IE once daily); y, years.

Table 2 Occurrence of complications after ABR in 430 patients

Complications	EMC $N = 261$ (%)	MUMC $N = 169$ (%)	p[a]
Overall complication rate	28.0	32.3	0.33
Complete flap failure	2.8	2.5	1.00
Partial flap necrosis	5.4	8.4	0.25
Arterial thrombosis	1.5	1.6	1.00
Venous thrombosis	1.1	2.2	0.45
Venous congestion	3.4	2.8	0.79
Hematoma leading to reoperation	9.2	4.7	0.09

Abbreviations: ABR, abdominal flap based breast reconstruction; EMC, Erasmus MC, University Medical Center Rotterdam (nadroparine 5,700 aXa-IE + 40 mg acetylsalicylic acid once daily); MUMC, Maastricht University Medical Center (nadroparine 5,700 aXa-IE once daily).
[a]Fisher exact tests.

breast reconstruction. In our study, patients received a postoperative anticoagulation regimen consisting of either once daily 40 mg acetylsalicylic acid combined with 5,700 units LWMH subcutaneously, or 5,700 units LMWH subcutaneously once daily as a single prophylaxis.

Acetylsalicylic acid, or aspirin, is a platelet aggregation inhibitor which acts as an inhibitor of thromboxane synthesis by antagonizing cyclooxygenase. It is widely used for secondary prevention of myocardial infarction or stroke due to its ability to particularly inhibit platelet aggregation which prevents arterial occlusions. This characteristic is presumed advantageous in microvascular surgery as well. Side effects include (gastrointestinal) bleeding, gastritis, allergic reactions, and nephrotoxicity. Nadroparin is a LMWH which, when bound to antithrombin III, accelerates the inactivation of factor II and factor Xa. Nadroparin halts the secondary coagulation pathway by inhibiting the activation of thrombin (factor IIa) by factor Xa. The amplification of the fibrin clotting cascade is stopped once factors Xa and IIa are inactivated.

The effect of acetylsalicylic acid on anastomotic patency has been studied in several animal models with conflicting outcomes reported.[10–12,29–31] Some studies support the conclusion that low dose acetylsalicylic acid inhibits anastomotic venous thrombosis and improves microcirculatory perfusion.[10,29] Other studies support the idea that platelets play a major role in arterial thrombosis, whereas fibrin is more important in venous thrombosis.[30,31]

Also several clinical studies have investigated the effects of acetylsalicylic acid on free flap survival.[5,6,8,25] Ashjian et al compared a thromboprophylactic regimen consisting of 325 mg acetylsalicylic acid once daily with 5,000 units of LMWH once daily in a population of patients undergoing free flap surgery for reconstruction of oncological defects of the head and neck, upper and lower extremity, trunk and breast and concluded that LMWH and acetylsalicylic acid 325 mg daily are equally effective as postoperative anticoagulation agents in oncological free flap reconstruction.[8] Chien et al concluded that 325 mg acetylsalicylic acid once daily and subcutaneous heparin twice a day at 5,000 IU in head and neck free flap reconstruction was equally effective in preventing microvascular complications and flap failure compared with other existing regimens.[25]

Several studies made different recommendations based on a review of existing literature.[7,26,27] Conrad et al proposed an anticoagulation algorithm for free flap thromboprophylaxis, consisting of low dose acetylsalicylic acid at a dose of 1.4 mg/kg/d starting 2 weeks preoperatively which has to be continued for 2 weeks postoperatively, and heparin which is given intraoperatively as a bolus and local topical agent.[26] Lecoq et al recommended the intraoperative use of heparin in microsurgery and the use of acetylsalicylic acid for inhibition of platelet aggregation.[7] Stephan et al concluded that the combined use of acetylsalicylic acid with another anticoagulant would increase the risk of bleeding.[27] Based on a recent literature review Brinkman et al recommended the use of LMWH monotherapy as this seems to be as effective as acetylsalicylic acid, and has the additional advantage to prevent systemic thromboembolic events, and unlike acetylsalicylic acid does not increase the risk of gastrointestinal bleeding.[21]

The aim of the present study was to analyze the effect of acetylsalicylic acid in preventing microvascular thromboembolic complications in a homogenous patient group undergoing DIEP and free TRAM flap breast reconstruction. Combined inhibition of primary and secondary hemostasis by administration of acetylsalicylic acid and nadroparine did not yield a lower rate of microvascular complications compared with monoprophylaxis by nadroparine. Our microvascular complication rates were comparable to previously reported incidence rates after DIEP and free TRAM flap breast reconstruction.[32] Although, our study population was relatively large, the low rate of flap failure and low rate of microvascular complications may have reduced statistical power such that a potentially protective effect of acetylsalicylic acid could not be observed.

We administered a rather low dose of acetylsalicylic acid 40 mg/d, which is markedly lower than the 325 mg once daily applied in the studies of Ashjian et al[8] (aspirin only) and Chien et al[25] (aspirin + heparin). The low dose of 40 mg/d was chosen because it has been shown that a dose from as low as 30 mg is sufficient to block approximately 95% of platelet cyclooxygenase 1 activity, which causes the antiplatelet effect.[33] Other reasons to administer such a low dose were the risk of hematoma formation and gastrointestinal side effects, which are also dose dependent.[33]

Another explanation we did not observe a protective effect of acetylsalicylic acid on flap failure rate could be that its administration had been started at the first postoperative day, which may have been too late. However, it has been shown that acetylsalicylic acid is rapidly absorbed in the stomach and upper intestine. Peak plasma levels occur 30 to 40 minute after aspirin ingestion, and inhibition of platelet function is evident by 1 hour after administration.[33]

Notably, we found a higher hematoma rate leading to reoperation in the LMWH and acetylsalicylic acid group (9.2%) as compared with the LMWH monotherapy group (4.7%). Although, this difference failed to reach a statistical significance, this higher hematoma rate could be explained by the addition of acetylsalicylic acid causing a synergistic effect with LMWH. Given the known risks associated with the use of acetylsalicylic acid and the trend to lead to an increased occurrence of hematoma formation in the present study, we stopped routinely administering it after autologous breast reconstruction.

This study has some limitations intrinsic to its retrospective design, which limits the levels of evidence and mitigates the conclusions that can be drawn from the results. In the present study, we retrospectively compared two institutions with different regimens, which may have introduced some sort of bias. As free flap failure is multifactorial, future studies should ideally have a randomized controlled design to be able to provide the best level of evidence on the efficacy of different thromboprophylactic regimens.

Disclosure

None of the authors has a financial interest in any of the products or drugs mentioned in this article.

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