Anticoagulants and Hematomas in Free Flap Surgery

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A review of systemic anticoagulant use in 517 free flap procedures was performed to determine the associated risk of hematoma formation. Patients were divided retrospectively (not randomly) into five groups: no anticoagulation (227 flaps, 5.3 percent hematomas), low-dose heparin bolus of 2000 to 3000 units and postoperative infusion at a rate of 100 to 400 units/hr for 5 to 7 days (192 flaps, 6.7 percent hematomas), intraoperative bolus of 5000 units of heparin without postoperative anticoagulation (46 flaps, 6.5 percent hematomas), high-dose heparin infusion at a rate of 500 to 1200 units/hr (30 flaps, 20 percent hematomas), and dextran 40 infusion at a rate of 25 ml/hr (22 flaps, 9.1 percent hematomas). Intraoperative blood loss was similar for all groups. The flap loss rate was lower in the bolus (1.0 percent) and low-dose (1.0 percent) heparin groups than in the no-anticoagulation group (4.4 percent), but this difference was not statistically significant. The pedicle thrombosis rate also was lower in the bolus (2.2 percent) and low-dose (2.1 percent) heparin groups than in the no-anticoagulation group (6.2 percent). A cause-and-effect relationship between the use of anticoagulants and flap loss or prevention of thrombosis could not be established. We can conclude, however, that the use of low-dose heparin does not increase significantly the risk of hematoma or intraoperative bleeding. (*Plast. Reconstr. Surg.* 96: 643, 1995.)

There is continuing controversy over the role of anticogulants in free tissue transfer, and preferences regarding the use of anticogulation vary widely among microvascular surgeons.[1–11] No studies have demonstrated conclusively that anticogulants will improve the patency rates of technically well-performed microvascular anastomoses. Nevertheless, because the failure of free tissue transfer always is associated with microvascular thrombosis, there may be a subset of patients who could benefit from the use of systemic anticogulants. Heparin, an anticoagulant that works primarily by inhibiting the formation of thrombin, has been used by some surgeons[1–8] in an effort to lower the incidence of intravascular thrombosis. Dextran also has been recommended for this purpose.[9]

The main risk of therapeutic anticoagulation with heparin is hematoma formation, a complication that can lead to obstruction of the vascular pedicle and flap failure. An alternative to full heparinization is low-dose, or "mini-dose," heparin, administered in amounts too small to cause a change in the partial thromboplastin time (PTT). Heparin used in this way seems to have a significant antithrombotic effect, as illustrated by the reduction in the incidence of deep-vein thrombosis in surgical patients.[12–17] Fortunately, this effect has been achieved without an increase in the risk of bleeding or hemtoma. Consequently, some have recommended low-dose (G. Trengove-Jones, personal communication) or bolus[1,18] heparin for use in microvascular surgery.[19] In the present study, we present a review of our experience with systemic anticoagulation during and after free tissue transfer, specifically addressing the risk of hematoma formation and the incidences of flap loss and pedicle thrombosis.

Materials and Methods

Heparin use, flap success, pedicle thrombosis, and bleeding complications were reviewed in all patients who underwent free tissue trans-

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fers at The University of Texas M. D. Anderson Cancer Center between January 1, 1988, and November 30, 1992. Although the review was retrospective, the data concerning flap survival, thrombosis, and hematoma had been collected prospectively and therefore were believed to be accurate.

The use of heparin was based on the personal preference of each surgeon and varied in dose and duration of administration. For analysis, the patients were grouped into five categories: no anticoagulation, low-dose heparin, bolus heparin, high-dose heparin, and dextran. The no-anticoagulation group received no systemic anticoagulation during surgery or the postoperative period. The low-dose heparin group received an intravenous bolus of 2000 to 3000 units of heparin in the operating room, followed by a postoperative infusion at a rate of 100 to 400 units/hr for 5 to 7 days. The bolus heparin group received an intravenous injection of 5000 units in the operating room, possibly enough to elevate transiently the PTT, but no subsequent anticoagulation. The high-dose heparin group was anticogulated fully for indications deemed appropriate by the surgeon at the time of surgery (e.g., severe atherosclerotic disease or observed intraoperative thrombosis at a microvascular anatomosis). This group was given an intraoperative bolus of 5000 to 10,000 units followed by an intravenous infusion at a rate of 500 to 1200 units/hr, with the exact amount depending on the level of anticoagulation as demonstrated by the PTT. The dextran group was given intravenous low-molecular-weight dextran (dextran 40) at a rate of 25 ml/hr. Heparinized saline (1:100 solution) was used in all patients for local irrigation during the microvascular anastomosis.

For the purposes of the present study, free flap survival was considered to be an all-or-none event, so distal flap edge necrosis (which was rare) was ignored. A hematoma was considered to be present if surgical evacuation was required. Pedicle thrombosis was defined as thrombosis that occurred after completion of the free tissue transfer and that required a return trip to the operating room for correction. Other consequences of heparin administration, such as thrombocytopenia, were not considered.

Statistical significance was determined by chi-squared analysis and by the use of Fisher's exact test where appropriate. Because there were multiple tests performed on the data, the Bonferroni correction was applied. Differences therefore were considered statistically significant only at $p < 0.0083$.

Results

In the period covered by the study, 517 free flap procedures were reviewed. Of these, 179 were free TRAM flaps for postmastectomy breast reconstruction, whereas 338 flaps were variety used for reconstruction in the head and neck (Table I). There were 36 hematomas (7.0 percent in the series (Table II), of which 12 (5.3 percent) occurred in the no-anticoagulation group, 3 (6.5 percent) occurred in the bolus heparin group, and 13 (6.8 percent) occurred in the low-dose heparin group. The differences in hematoma incidence among these three groups were not significant. In the high-dose heparin group (30 procedures), there were 6 (20 percent) hematomas, and the difference between this group and the no-anticoagulation group was almost statistically significant ($p = 0.0097$).

Of the 517 free flaps, 21 (4.1 percent) were lost. Nine other free flaps (1.7 percent) developed thrombosis in the vascular pedicle but were salvaged successfully. Therefore, the over-

TABLE I
Types of Free Flaps and Anticoagulation Used

Type of Flap	*n*	No Heparin	Low-Dose Heparin	Bolus Heparin	High-Dose Heparin	Dextran 40
TRAM	179	61	87	19	9	3
Rectus abdominis	59	17	34	4	4	0
Radial forearm	93	59	19	7	2	6
Fibula	68	24	26	6	11	1
Iliac crest (DCIA)	20	10	5	1	0	4
Jejunum	50	28	11	6	2	3
Latissimus dorsi	22	13	4	1	2	2
Scapula	16	11	3	0	0	2
Other	10	4	3	2	0	1

DCIA, deep circumflex iliac artery.

TABLE II
Thrombosis, Flap Loss, and Hematoma

Group	*n*	Flap Loss	Thrombosis	Hematoma
All flaps	517	21 (4.1%)	30 (5.8%)	36 (7.0%)
No heparin	227	10 (4.4%)	14 (6.1%)	12 (5.3%)
Low-dose heparin	192	2 (1.0%)	4 (2.1%)	13 (6.8%)
Bolus heparin	46	0 (0.0%)	1 (2.2%)	3 (6.5%)
High-dose heparin	30	3 (10%)	4 (13.3%)	6 (20%)
Dextran 40	22	6 (27.2%)	7 (31.8%)	2 (9.1%)

all thrombosis rate was 5.8 percent. In the no-anticoagulation group, the flap loss rate was 4.4 percent and the incidence of thrombosis was 6.1 percent. In the bolus heparin group, the incidences of flap loss (0.0 percent) and thrombosis (2.2 percent) were lower than those in the no-anticoagulation group (for flap loss, $p = 0.2210$). Similarly, in the low-dose heparin group, the incidences of flap loss (1.0 percent) and thrombosis (2.1 percent) were lower than those in the no-anticoagulation group ($p = 0.0437$ for flap loss). When the low-dose and bolus heparin groups were combined and compared with the no-anticoagulation group, the statistical significance of the observed difference increased ($p = 0.0184$ for flap loss; $p = 0.027$ for thrombosis).

In the group of 30 patients selected for treatment with a high (full anticoagulant) dose of heparin, the flap loss rate was 10.0 percent and the incidence of vessel thrombosis was 13.3 percent. These incidences, when compared with those of the no-anticoagulation group, were not statistically significant ($p = 0.242$), probably because of the small sample size. In the group of 22 patients treated with dextran 40, the flap loss rate was 27.3 percent and the incidence of vessel thrombosis was 31.8 percent.

When mean blood loss (in the operating room), units of blood transfused during the hospital stay, operating room time, and duration of hospital stay were compared, the values for all groups were roughly similar except that the groups receiving high-dose heparin or dextran required a greater mean number of transfusions (Table III).

Discussion

Prevention of thrombosis at the microvascular anastomoses of free flaps has been a concern of microvascular surgeons since the earliest days of free tissue transfer. Recent improvements in sutures, instruments, and techniques have reduced considerably the risk of such thrombosis, but thrombosis remains a threat that few who perform free tissue transfers are willing to ignore.

Heparin has been used extensively in many settings to reduce the likelihood of intravascular thrombosis. Combined with antithrombin III, it forms a potent inhibitor of thrombin and the factor Xa complex (prothrombinase). The central role of these enzymes in the generation and maintenance of clots only is now being elucidated. Very high local concentrations of thrombin are generated at sites of developing thrombi, leading to the generation of fibrin, activation or platelets, and alteration of the antithrombotic properties of the endothelial cell surface. Direct inhibition of thrombin is a logical, effective method of preventing clot formation, especially in microvasculature with a dis-

TABLE III
Blood Loss, Transfusions, Operative Time, and Hospital Stay

Group	*n*	Mean Blood Loss* (ml)	Mean No. of Blood Transfusions† (units)	Mean Operating Room Time (hours)	Mean Hospital Stay (days)
All flaps	517	518	1.1	10.1	12.7
No heparin	227	485	0.9	10.9	12.7
Low-dose heparin	192	548	1.1	9.8	12.6
Bolus heparin	46	546	1.1	9.9	9.8
High-dose heparin	30	511	2.1	11.9	15.2
Dextran 40	22	575	2.3	11.2	14.4

* In the operating room.
† During the hospital stay.

turbed endothelium. The contribution of the electronegative charge of heparin[20] to its antithrombotic efficacy is not known.

Heparin clearly is effective in reducing the risk of intravascular thrombosis. However, the use of full anticoagulant doses can lead to increased bleeding and risk of hematoma, limiting its usefulness. The main purpose of the present study was to determine whether patients treated with low-dose systemic heparin during the microvascular anastomoses and in the early postoperative period had a significantly greater risk of blood loss and hematoma than patients who did not receive heparin. It seems from our results that they did not; furthermore, the use of low-dose heparin had little clinically evident morbidity. In contrast, when full anticoagulant doses of heparin were administered to patients, both the mean units of blood transfused and the risk of hematoma were increased.

The high rates of flap loss and thrombosis in the patients treated with low-molecular-weight dextran demonstrate some of the problems inherent in the analysis of a retrospective review. Dextran 40 is less effective in prevention of thrombosis than heparin or warfarin,[21] but it is unlikely that it was the cause of the high rate of thrombosis observed in our patients treated with dextran. All of the patients in the dextran group were operated on early in the course of the study, when we were relatively inexperienced in microvascular surgery. It is likely that this factor, combined with the small number of patients who received dextran and the element of chance, is the explanation for the observed differences.

In comparison to patients treated with bolus or low-dose heparin, those treated with high-dose heparin had high rates of thrombosis and flap loss. However, the high-dose heparin group was composed of patients who were deemed to be at unusually high risk for postoperative anastomotic thrombosis. They usually were treated with high-dose heparin because thrombosis was observed in the recipient vessel before the anastomosis or at the anastomotic site immediately after the anastomosis or because significant intimal disease was present in the recipient or donor vessels. It was anticipated that this group of patients would have a high rate of thrombosis and flap loss, as was the case.

The effectiveness of bolus and low-dose heparin in reducing flap loss and anastomotic thrombosis rates is impossible to assess from our data alone. Use of bolus or low-dose heparin was associated with lower thrombosis and flap loss rates in our patients, but we cannot conclude that the relationship was one of cause and effect. The present study was not randomized, and many factors other than the use of heparin could have accounted for some of the observed differences. It is unlikely that the questions about the efficacy of heparin in preventing thrombosis and flap loss in microvascular surgery will be settled without a prospective randomized trial.

There are other unresolved questions about the use of heparin. Low-molecular-weight heparin has been licensed for use in the United States. Some investigators have proposed that it is associated with a lower incidence of hemorrhagic complications than is unfractionated heparin,[22] but experience with low-molecular-weight heparins is limited, and the agent's effect on microvascular surgery is unknown. Also, heparin requires antithrombin III as a cofactor. The effect of a slightly depressed antithrombin III plasma concentration on thrombosis, a factor that could influence the success of a microvascular procedure, remains unknown.

Caution is appropriate when using heparin. There is a small but finite risk of heparin-induced thrombocytopenia caused by the development of autoantibodies to platelet-bound heparin. These autoantibodies can cause platelet-rich arterial thromboses, which could lead to flap failure or even loss of limb or life. A decreasing platelet count in a patient receiving any dose of heparin therefore should be evaluated carefully.

The present study demonstrates that the systemic use of low-dose or bolus heparin in the perioperative period does not increase significantly the risk of hematoma formation. None of the differences we observed were considered to be statistically significant, but this was in part because we used a very rigorous standard (by including the Bonferroni correction) to define statistical significance. We believe that this was appropriate because we were not trying to prove a causative relationship between low-dose heparin and flap loss. The lack of statistical significance, however, does not necessarily imply a lack of clinical significance. Our findings do not prove that low-dose heparin is beneficial, but the data clearly suggest that further studies, including prospective randomized trials, of the

effect of low-dose heparin on anastomotic thrombosis and flap loss are warranted.

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