A survey of anticoagulation practice among German speaking microsurgeons – Perioperative management of anticoagulant therapy in free flap surgery

Erhebung über die antikoagulatorische Praxis unter deutschsprachigen Mikrochirurgen – Perioperatives Management der antikoagulatorischen Therapie bei freien Lappentransplantaten

Abstract

Background: Anticoagulation is a crucial element in microsurgery. Although various clinical studies and international surveys have revealed that anticoagulation strategies can vary and result in similar outcomes, anticoagulative regimens are far away from standardization. In Germany and german speaking countries standardized anticoagulation protocols concerning free flap surgery do not exist so far.

Methods: To evaluate the current practice of clinics in Germany, Austria and Switzerland with specialization in microsurgery we performed a questionnaire surveying the perioperative regimen of anticoagulant and antiplatelet therapy in free flap surgery. The microsurgeons were interrogated on several anticoagulant, rheologic and antiplatelet medications, their dosage and perioperative frequency of application pre-, intra- and postoperative.

Results: The questionnaire revealed that the used antithrombotic and perioperative regimes varied from department to department presumably based on the personal experience of the surgeon. Multiple approaches are used with a wide range of anticoagulants used either alone or in combination, with different intervals of application and different dosages.

Conclusion: Therefore consensus meetings should be held in future leading to conduct prospective multicenter studies with formulation of standardized anticoagulative and perioperative protocols in microsurgery reducing flap failure to other than pharmacologic reasons.

Keywords: perioperative anticoagulation, microsurgery, survey

Zusammenfassung


Methodik: Zur Erhebung der antikoagulatorischen Praxis unter mikrochirurgischen Kliniken in Deutschland, Österreich und der Schweiz erstellten wir einen Fragebogen zur Erfassung des jeweiligen perioperativen Regimes im Hinblick auf die Antikoagulation bei freien Lappenplastiken.

Erfasst wurden verschiedene Antikoagulantien, Rheologika und Thrombozytenaggregationshemmer, sowie deren prä-, intra- und postoperative Dosierung und Art der Anwendung.

Ergebnisse: Die perioperativen Regime und verwendeten Antikoagulantien zeigen von Klinik zu Klinik eine große Varianz. Diese Heterogenität
scheint am Ehesten auf der Erfahrung des Operateurs denn auf einer evidenzbasierten Datenlage zu beruhen. Sie zeigt sich sowohl in der Vielzahl der verwendeten Antikoagulantien als auch in der Art ihrer Anwendung und Dosierung.

**Schlussfolgerung:** Aus der erhobenen Datenlage ergibt sich die Forde rung nach Initiierung einer Multi-Center-Studie mit Formulierung eines evidenzbasierten Standards zur perioperativen Antikoagulation in der Mikrochirurgie, so dass sich die Ursachen für Verluste freier Lappen transplantate auf solche nicht pharmakologischer Art reduzieren lassen.

**Schlüsselwörter:** perioperative Antikoagulation, Mikrochirurgie, Survey

**Introduction**

Despite of the achieved success rates in free flap surgery of more than 98% standardized anticoagulative protocols do not exist among german speaking microsurgeons [1], [2].

Facing the promising success rates there seems to be no need for such protocols. But would microsurgeons exclusively rely on their surgical skills? Then numerous literature about anticoagulant therapy in free flap surgery answers this question negatively [3], [4].

Besides technical refinements anticoagulation minimizes the risk of intra- and postoperative thrombosis as a cause of flap failure and various antithrombotic agents are used in the perioperative setting among microvascular surgeons [5], [6], [7].

Although national and even international surveys of anticoagulation practice in microvascular surgery have already been published, such a survey does not exist among german speaking microsurgeons [8], [9].

**Materials & methods**

A questionnaire surveying the pre-, intra- and postoperative regimen was send to hospitals in Germany, Austria and Switzerland specialized in reconstructive microsurgery (Table 1 and Table 2). The questionnaire addressed the management of pre-, peri- and postoperative treatment of patients undergoing free flap reconstruction performed by plastic and reconstructive surgeon in german speaking countries. Completion of the survey was voluntary. Monetary compensation was not provided. The microsurgeons were interrogated on several anticoagulant, rheologic and antiplatelet medications. We asked for their dosage, frequency of application and interval from onset of application to start of the surgical procedure, the intraoperative regimen (application at the following time points: procedure start, -end, -start and -end, during the whole procedure, for vessel flushing before anastomosis, immediate after the anastomosis), and postoperative regimen. The following antithrombotic medications were prompted: aspirin, unfractioned heparin, dalteparin (Fragmin® 4 ml/10 ml - Multidose, Fragmin P® 2,500 IU, Fragmin P forte® 5,000 IU), enoxaparin (Clexane® 20/40 mg, Lovenoxm 20/40 mg), nadroparin (Fraxiparin® 0.1–1 ml resp. 1,000–10,000 IU), dextran and hydroxyethyl starch (HES 6%/10%).

**Results**

Out of 79 departments addressed, 33 surveys were returned successfully. This represents a response rate of 42%. The correlation between flap survival and regime of anticoagulation was not subject of this study. As expected the returned surveys for pre-, peri- and postoperative anticoagulation management showed a range of variability regarding the time of application and as well the medication used.

**Preoperative treatment**

Four different anticoagulative agents including aspirin 100 mg, dalteparin 2,500 IU (Fragmin P®), enoxaparin (Clexane®) and prednisolon 250 mg (Solu Decortin®) are used to prevent thrombosis without considering differences in duration of treatment. Enoxaprin and dalteparin were identified as the predominantly used agents. 49% of the departments perform preoperative anticoagulation and start their management 12 hrs before surgical intervention (n=16 out of 33). The majority of institutions (56.25%) (n=9 out of 16) use enoxaparin 2,000 IU (Clexane®) as anticoagulant while 43.75% (n=7 out of 16) use dalteparin 2,500 IU (Fragmin P®). In one department aspirin at a dosage of 100 mg (acetylsalicylic acid) is applied in combination with enoxaparin while in another prednisolon 250 mg is applied in combination with dalteparin. None of the participants use unfractioned heparin, HES 6%, HES 10% (hydroxyethyl starch 60/100 g/l) or dextran for preoperative anticoagulation. 51.5% of the departments (n=17 out of 33) do not utilize any preoperative anticoagulative treatment (see Figure 1).

**Intraoperative treatment**

For intraoperative management unfractioned heparin, HES 6% and 10%, low molecular weight dextran (dextran-40) and aspirin are used as anticoagulative agents (see Figure 2).
Table 1: Questionnaire on anticoagulation in microvascular surgery

Pre- and postoperative anticoagulation

yes / no

If yes, please fill in the following form.

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Dosage</th>
<th>Frequency</th>
<th>Interval</th>
</tr>
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<tbody>
<tr>
<td>Aspirin</td>
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<td></td>
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<tr>
<td>Dalteparin</td>
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<tr>
<td>Nadroparin</td>
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<tr>
<td>Heparin</td>
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<td>Enoxaparin</td>
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<td>HES</td>
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<td>Dextran</td>
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<tr>
<td>Dextran-40</td>
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<td>Others</td>
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</table>

Table 2: Questionnaire on anticoagulation in microvascular surgery

Intraoperative anticoagulation

yes / no

If yes, please fill in the following form.

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Dosage</th>
<th>Interval</th>
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<td>Aspirin</td>
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<td>Dalteparin</td>
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<td>Dextran-40</td>
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<td>Others</td>
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*Annotation: Application

a) at the beginning of the operation.
b) at the end of the operation.
c) at the beginning and end of the operation.
d) during the whole operation.
e) for flushing the vessels.
f) immediately after the anastomosis.
26 out of 33 departments reported the use of intraoperative anticoagulation indicating 79.8% whereas 21.2% (n=7 out of 33) do not use any anticoagulative medication.

Differences regarding time of application could be observed concerning unfractioned heparin (see Figure 3). In 16 departments unfractioned heparin is used for flushing the vessels before performing the anastomosis with a concentration ranging from 5 to 100 IU/ml. 6 departments apply an additional bolus of unfractioned heparin intravenously after completion of the anastomosis in a dosage ranging from 1,000 IU to 5,000 IU, whereas 4 participants administer unfractioned heparin in a dosage from 1,000 IU to 5,000 IU i.v. only after completion of the anastomosis.

Postoperative treatment

All 33 participants reported to perform postoperative anticoagulation routinely. All surveyed anticoagulants are administered in the postoperative setting either alone or in combination (see Figure 4). Aspirin 100 mg is given in 11 out of 33 departments. In all but one (application twice a day) it is administered once a day with great variability in the onset after the operation and duration of administration.

7 out of the 11 departments start with aspirin administration the day after the operation. 2 departments start at day 4 and 2 departments at day 6. The duration time of application varies from 24 hours up to 6 weeks.
Figure 4: Use of anticoagulants after microvascular surgery. Reporting of agents used in the postoperative regimen in 33 centers. (aspirin; dalteparin; enoxaparin; nadroparin; unfractioned heparin; hydroxyethyl starch 6%; hydroxyethyl starch 10%; dextran 40; clopidogrel)

Dalteparin is given by 7 departments with a dosage of 2,500 IU and 5,000 IU once a day for 7 or 10 days respectively until the patient is fully mobilized. In one department it is given twice in terms of a body weight adapted full heparinization. Aspirin is combined with dalteparin, enoxaparin, unfractioned heparin (continuously via infusion pump), dextran-40 and hydroxyethyl starch in 7 cases, whereas these drugs are administered once a day. One department performs a triple anticoagulation consisting of aspirin, unfractioned heparin and hydroxyethyl starch. Enoxaparin (n=16) is administered body weight adapted and plasma volume expander (n=24; dextran-40 and hydroxyethyl starch 6%/10%) are applied in a dosage of 500 ml/24 h for 3 days (n=3), 5 days (n=9), 6 days (n=1), 7 days (n=3) and 8 days (n=1) after the operation. 7 participants administer plasma volume expander once after the operation. Unfractioned heparin is administered in 15 departments with a dosage range from 7,500 IU/24 h to 20,000 IU/24 h and a span of duration from 24 hours to 7 days. Nadroparin is administered by three participants, in two cases until full mobilization and in one case for 5 days. Only one participant uses clopidogrel in a staged manner reducing the concentration from initially 225 mg starting two days after the operation to 75 mg on day 7. One participant combines the anticoagulatory regimen with sympatholysis of either the upper or lower extremity.

Discussion

The use of anticoagulative protocols and practices is widely differing and no evidence has been established for the use of one or the other clinical protocol. Xipoleas et al. could demonstrate a tremendous variability in both the agents used and therapeutic periods employed confirming our results [3]. Despite the plethora of available antithrombotic substances, acetylsalicylic acid, heparin (LMWH and unfractioned heparin), and dextran are still the most frequently used agents but are controversially discussed [10], [3]. While various clinical and animal studies have revealed the beneficial effects of unfractioned and low molecular weight heparin in prevention of venous thrombosis, Chen et al. [5] could not show a statistically significant effect on the incidence of microvascular thrombosis demanding a prospective randomized study to verify its role in preventing thrombosis in the intraoperative setting [11], [12], [13]. Furthermore one has to bear in mind the small but finite risk of heparin-induced thrombocytopenia which could lead to flap failure or even loss of limb or life [14]. Although heparin application is associated with a risk of bleeding and hematoma formation this is seemingly due to the applied dosage. Chen et al. [5] could not demonstrate any adverse effect of intraoperative systemic heparin when administered in a dosage of 3,000 units 10 minutes before flap pedicle ligation.

The ideal dose and length of time required for infusion of heparin is still not known, but a number of studies have shown that 72 hours is required for regeneration of endothelium in the area of anastomosis to prevent thrombosis formation [15], [16]. Peter et al. [17] could demonstrate in a rat cremaster model that low-dose aspirin (5 mg/kg systemically) inhibits anastomotic venous thrombosis and improves microcirculatory perfusion. In our study, aspirin was also applied predominantly in the postoperative setting. Although dextran is also a commonly used anticoagulant in microsurgery Disa et al. [18] demonstrated that patients receiving dextran had up to a 7.2 times greater rate of developing a systemic complication compared to patients receiving aspirin. This is probably due to its association with a dilutional coagulopathy as well as decreased fibrin clot formation and reduced factor VIII activity [19].

We previously published the relevance and implication of the updated S3-guidelines on prophylaxis of venous thromboembolic events for the field of plastic and reconstructive surgery [20]. In the results section of this paper, general and specific recommendations with regard to plastic and reconstructive surgery are outlined describing an algorithm for application with low molecular weight heparin for thrombosis prophylaxis. As expected the questionnaire in our survey revealed that the used antithrombotic and perioperative regimens vary greatly from department to department presumably based on the personal experience of the surgeon. Multiple approaches are used, ranging from pre-, intra- and postoperative anticoagulation locally or systemically using low molecular weight or unfractioned heparin, hydroxyethyl starch, dextran or acetylsalicylic acid, either alone or in combination with different intervals of application and a slight trend towards low molecular weight heparin (LMWH), aspirin and hydroxyethyl starch in the perioperative setting. Unfractioned heparin is predominantly used intraoperatively for flushing vessels and as bolus medication after completion of the anastomosis.
However these findings lack the evidence of standardization but could at least indicate a starting point for formulation of standard protocols in future consensus meetings.

Conclusions

The finding that we lack standardized anticoagulative and perioperative regimens in microsurgery should prime surgeons to conduct multicenter, nation- or world-wide surveys, and statistical cost-benefit analysis. In our view it is unlikely that a simple algorithm in microsurgery will be defining antithrombotic prophylaxis in general, rather, consideration and integration of the various pathogenetic aspects, comorbidities and risk factors will have to be included to define individual “standard operating procedures” for a given microsurgical scenario.

Notes

Competing interests

All authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) the work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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