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ANTITHROMBOTIC PROPHYLAXIS IN MICROSURGERY

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Summary

Background. The most common complication of microsurgical reconstruction is graft failure secondary to thrombosis. It is clear that thromboprophylaxis is helpful for a successful microsurgery. However, it's also obvious that thrombosis can't be avoided in cases of poor microsurgical technique. There is no consensus regarding the use of anticoagulation therapy during and after microsurgery. The authors compared two different antithrombotic prophylaxis protocols used in the past ten years, and analyzed the effectiveness and risks of different pharmacological protocols.

Materials and methods. The authors performed a retrospective review of microsurgical patients operated between 2005-2014 by the same surgical team. 37 patients (Group A) operated between 2005-2010 and 45 patients (Group B) operated between 2011-2014 were selected. The majority of patients had generic and specific risk factors. Different thromboprophylaxis therapies were used in the two groups. While reviewing medical records, the authors compared Hb values before and after surgery, the free flap success rate, the need for blood transfusions intra and post-op in order to assess the efficacy (failure rate), and safety of the administered antithrombotic therapies (bleeding complications).

Results. The pharmacological protocol used for the patients from Group B was more effective and less risky compared to results obtained from Group A. The therapy used in Group B did not increase the risk of bleeding and postoperative blood loss, and the flap success rate in Group B was significantly higher than that of Group A (p<0.000).

Discussion and Conclusion. This study suggests that even in a perfect microanastomosis, prothrombotic mechanisms are activated, which lead to flap failure. A reasoned and balanced drug therapy can counteract the natural tendency of pedicle thrombosis, without exposing the patient to bleeding complications. Vasoactive drugs, although still experimental in microsurgery, may be used in the near future in order to further improve the success rates of free flaps.

Introduction

The most common complication of microsurgical reconstruction is graft failure secondary to arterial or venous thrombosis.
Dissecting the pedicle, preparing the vessels and passing the needle through the wall

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all involve a lesion of the intimal layer with exposure of sub-endothelial layer, even in technically perfect microanastomoses.

Persistence of the thread within the vascular lumen and turbulent trans-anastomotic blood flow activate hemostasis, platelets aggregate and a white clot forms. This process alone can induce endovascular thrombosis.

Blood stasis at the anastomotic site activates the coagulation system.

Surgery (vessels kinking, compression by hematoma or edema) and/or medical condition (oncologic or infection disease, hypovolemia, hyponatremia) can cause blood stasis followed by arterial and venous thrombosis. [1-5]

Therefore, it is clear that thromboprophylaxis is helpful for a successful microsurgery. However it will not prevent thrombosis in case of poor microsurgical technique.

The reason for using antithrombotic prophylaxis is to act on a technically perfect microanastomosis, using drugs that selectively work with different mechanisms of action, and on different targets. Drugs can be administered for the following reasons:
- Avoid stasis.
- Increase the perfusion pressure.
- Reduce hyperviscosity, using a moderate normovolemic hemodilution and hematocrit correction.
- Reduce hypercoagulability, acting both on the primary and secondary hemostasis (platelets and the coagulation cascade).

The use of systemic vasoactive drugs (such as papaverine, lidocaine or prostacyclin) is still in the experimental stage. However, they have a limited use for the local irrigation of the anastomosis or in experimental conditions.

The use of streptokinase and urokinase is limited to rescue procedures for intra- or perioperative vascular thrombosis, not for prophylaxis because of the high risk of bleeding [6].

The three main pharmacological agents that had been used for thromboprophylaxis in microsurgery: aspirin, heparin and dextran. [5,8]

Therapeutic protocols suggest the combination of more drugs in order to reduce platelet aggregation and the activation of the coagulation cascade (aspirin and heparin), maintaining a constant blood flow and perfusion pressure during and after surgery (fluid therapy, steroids, dextran), and decreasing blood viscosity by reducing the hematocrit (isovolemic hemodilution). Nowadays, the use of dextran is no longer indicated because the benefits do not outweigh the risks (anaphylaxis, pulmonary and cerebral edema) [5-10].

The ideal antithrombotic agent should have an effective anticoagulation activity to successfully prevent pedicle thrombosis, minimal side effects, low complications rates related to perioperative and postoperative bleeding, and be easy to administer.

We compared our experience with two different perioperative protocols of thromboprophylaxis and we analyzed the reasons that led us to modify our thromboembolic prophylaxis protocol.

Materials and Methods

The authors performed a retrospective review of medical records of patients that had microsurgical reconstruction between 2005 and 2014. Only the patients who received prophylactic antithrombotic drug therapy were selected.

The majority of patients had generic and specific risk factors.

The clinically relevant risk factors were: high body mass index (BMI), diabetes, smoking, alcohol use, ASA III-IV (according to American Society of Anesthesiologists classification), associated diseases (cardiac, metabolic, neurological, infections, tumors), medical history of the neoadjuvant chemotherapy and radiotherapy.

For these patients the evaluated factors were postoperative hemoglobin, postoperative blood transfusions, the microsurgical flap failure rate, regardless of the type of flap (diep, alt, vastus lateralis, serratus, latissimus dorsi, forearm flap, etc.), of the anatomical region involved (head and neck, breast, lower or upper limbs), and the presence of comorbidities. It was not technically possible to make an assessment of blood loss

through drainage or dressing because the data was not always reported in the medical record, or was not reliable for all patients. In both groups, the post-operative blood loss was assessed comparing the values of pre-operative and post-operative Hb (24h after surgery). The antithrombotic drug protocol used between 2011 and 2014 was different from the one used between 2005 and 2010:

A total of 42 patients in the period between 2005 and 2010 that underwent a microsurgery had a specific antithrombotic drug protocol. Five of the 42 patients were excluded from the group because they received, in addition to the antithrombotic drug therapy, a preoperative normovolemic hemodilution by self-bloodletting. This procedure, which was initially part of the implemented antithrombotic protocol, could only be applied to few of the selected patients. Oncological patients or patients with complex drugs therapy were excluded, con-

sequently the 5 patients that received self-bloodletting were excluded from this study.

Group A: A total of 37 patients (Group A) were selected. 23 males and 14 females in which the prophylactic anti-thrombotic therapy used was:

- 12 hours before surgery: Intravenous infusion of high-dose aspirin (500 mg IV), methylprednisolone 500 mg, and pantoprazole 40 mg in 500 cc of saline.
- Before releasing the clamps: Intravenous bolus of unfractionated Heparin (UFH, 5000 U)
- Post-operation: A standard fluid therapy (1.5-2 liters) was administered for 24 hours (or more, up to recovery of oral ingestion), also ASA 500 mg, methylprednisolone 500 mg, and pantoprazole 40 mg intravenously every 24h for 3 days post-op.
- Antibiotic prophylaxis with amoxicillin and clavulanic acid or cefazolin (depending on the anatomical site treated) [11-12]
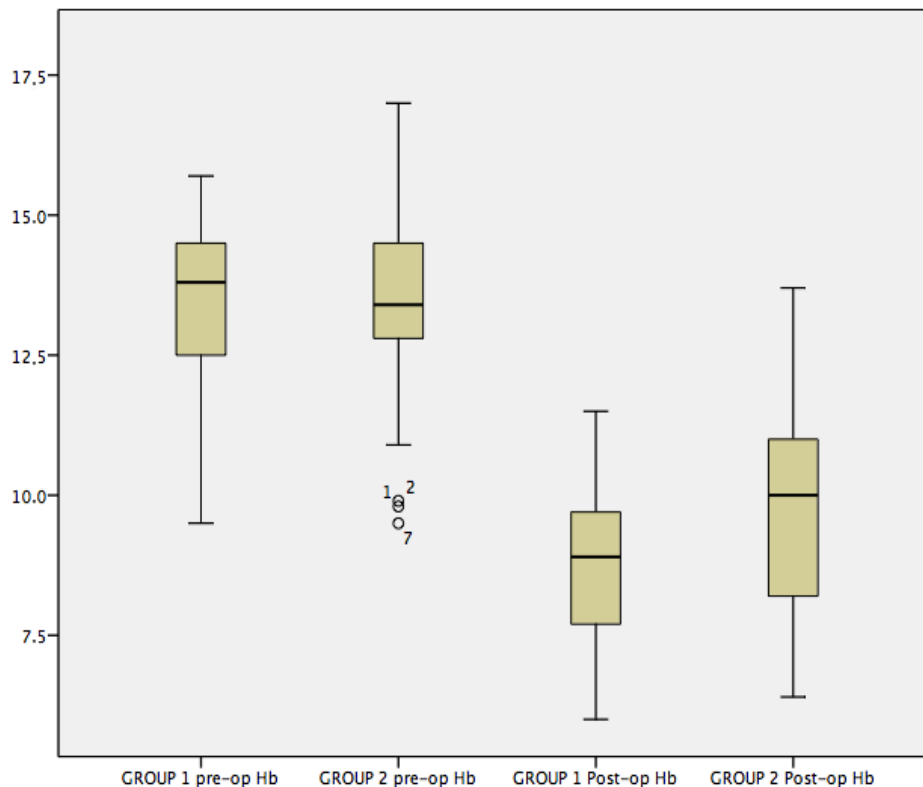

Figure 1. Pre-operative and post-operative hemoglobin values in Group A and B. There was no statistically significant difference between pre-operative hemoglobin values for the two groups (p>0.7). The samples were therefore considered homogeneous and comparable.

- 24 hours after surgery: subcutaneous injection of LMWH (dosage necessary for the prevention of DVT was calculated based on patient body weight), administered daily for 20 days;

Group B: A total of 45 patients, 28 males and 17 females that underwent microsurgery between 2011 and 2014, had a specific antithrombotic drug protocol:

- 48 hours before surgery: ASA 100 mg (Cardioaspirin) orally (1 per day);
- 12 h before surgery: slow I.V. 500 cc Infusion of saline with pantoprazole 40 mg and methylprednisolone 500mg;
- During surgery: 100 mg of ASA I.V. with fluid therapy support. (Ht control, never less than 30%);
- Before microsurgical step: intra-arterial and intravenous irrigation with heparin (LMWH), intra-arterial irrigation with prostacyclin and lidocaine.

Post-op:
-Subcutaneous injection of LMWH (dosage necessary for the prevention of DVT was calculated based on patient body weight) once a day for 30 days;
- Fluid therapy (1.5-2L, up to recovery of oral ingestion) and I.V. methylprednisolone 500mg + 100mg ASA + pantoprazole 40mg, after 24 hours for 3 days;
- 100 mg ASA orally, 1per day for 4 additional days.

Two patients from each group were excluded (total of 4 patients) because they had received blood transfusions or plasma expanders during or within 24 h after surgery.

Clinical data for the two selected groups was compared (see Figure1).

All diabetic patients that were administered methylprednisolone required careful monitoring of blood glucose levels and insulin treatment.

Statistical Analysis

For continuous variables, the mean, standard deviation, minimum and maximum were calculated.

For categorical variables, the corresponding percentages were calculated.

Considering the sample size, the Mann-Whitney nonparametric test was used. SPSS (IBM, New York) ver.20.0 was used for statistical analysis

Results

Pre-operative and post-operative hemoglobin, post-operative blood transfusions, and the failure rate of microsurgical flap were evaluated in the two groups of patients. Other parameters, such as blood loss in surgical drains, the anatomical site, and the type of flap, were not considered, because the data was not readily available or comparable. (Figure 1)

There was no statistically significant difference between pre-operative hemoglobin values for the two groups (p>0.7). The samples were therefore considered homogeneous and comparable.

Post-operative blood loss was assessed in both groups comparing pre-operative and post-operative hemoglobin (24 hours after surgery). The mean blood loss in Group A was 4.67 mg/dl of hemoglobin. Thirty five percent of these patients received at least one blood transfusion post-operatively and there was a 16% microsurgical flap failure. In Group B the mean blood loss 24 hours after surgery was 3.52 mg/dl of hemoglobin, and 22% of the patients who received a blood transfusion postoperatively had a 13.3% flap failure.

Blood loss in Group A was significantly greater than Group B (p<0,01).

This supports the hypothesis that drug therapy used in Group B did not increase the risk of bleeding and postoperative blood loss.

Moreover, the flap success rate in Group B was significantly higher than the results from Group A (p<0.000), suggesting that the antithrombotic therapy used in Group B was more effective.

The greater blood loss and flap failure in Group A may reflect various complications, including hematoma of the pedicle, vasospasm secondary to anemia, and infections secondary to hematoma and transfusion.

Discussion

A reasoned and balanced pharmacological thromboprophylaxis can counteract the natural tendency of pedicle thrombosis of microsurgical flaps, especially in patients with risk factors.

Our protocol has evolved.

As previously mentioned, our pharmacol-

ogical protocol has changed in recent years. Pre-operative autologous transfusion has been eliminated and replaced by pre-operative moderate hemodilution. Dosage and timing of drug administration have also been modified.

Initially the authors adopted a promising protocol of normovolemic hemodilution. Two weeks prior to surgery, patients underwent phlebotomy and simultaneous infusion of a corresponding amount of saline solution (removal of 300 cc of blood and infusion of 300 ml of saline). This procedure had several advantages:

1) If necessary, during or after surgery, the patient was transfused his own blood (reduction of heterologous transfusions).

2) Normovolemic hemodilution, with reduction in blood viscosity.

3) Phlebotomy stimulated the bone marrow, resulting in increased reticulocyte counts, which is advantageous during the postoperative period.

Although potentially useful, pre-operative phlebotomy is labor intensive and could not be applied to all patients (for example patients with comorbid diseases or multi drug therapy, cancer patients etc.). For this reason it was quickly abandoned and replaced with normovolemic hemodilution administering 500cc of saline intravenous the evening before surgery. Normovolemic hemodilution is a standard procedure in microsurgery aimed at reducing blood viscosity.

Normovolemic or isovolemic hemodilution [13-15] improves blood flow by reducing viscosity and platelet aggregation, and increases the number of unblocked capillaries. The optimal hematocrit value should be 30. However, patients without complications, also tolerate hematocrit values between 25 and 30. Further reductions in hematocrit did not result in greater benefits. In fact, any benefit may be overcome by the decrease in O2-carrying capacity. A low hematocrit value also increases cardiac work (important in patients with low cardiac reserve). 30% Ht offers the best balance between viscosity and O2-carrying capacity.

Thirty five percent of patients (13 out of 37) who underwent microsurgical reconstruction with prophylactic antithrombotic therapy between 2005 and 2010

(Group A) were transfused postoperatively due to anemia. This prompted the authors to revise the pharmacological therapy in order to minimize side effects without lowering the success rate of the microsurgical procedure. The flap failure rate in Group A was 16% (6 of 37 patients). The intravenous bolus of unfractionated Heparin was no longer administered before releasing the flap, because of high blood loss postoperatively. This was replaced with a subcutaneous injection of LMWH, starting the day after surgery (administered once per day for 20 days). For the same reason, aspirin, initially administered in high doses (500 mg IV pre-operative and post-operative, every day for 5 days), was administered in low doses (100 mg Cardioaspirin) at least one day prior to surgery.

The pharmacological protocol currently used by the authors is described in Table 1.

The rationale of the Protocol is:

Pre-, intra- and post-operative hemodilution (with HT 30) reduces blood viscosity, induces peripheral vasodilatation with improved perfusion of the microcirculation, and improves cardiovascular performance.

One of the innovations is to use an intravenous infusion of methylprednisolone. This is not described in the literature as a drug commonly used for antithrombotic prophylaxis in microsurgery. Methylprednisolone improves microcirculation; it has a protective action on the vessels, inhibiting phospholipase A2 (an enzyme involved in the metabolism of phospholipids, which leads to the formation of arachidonic acid, the substrate on which COX acts for the formation of thromboxane A2), improving the hypercoagulable state during the perioperative period through the reduction of inflammatory cytokines. Additionally, it increases and supports the systemic blood pressure. In fact, a reduction of systemic blood pressure during or after surgery is crucial because it induces peripheral vasoconstriction via catecholamine-mediated mechanisms, which are difficult to overcome.

The Low-dose ASA reduces platelet aggregation by electively inhibiting the production of TXA2 without interfering with

the production of prostacyclin. The effect of ASA lasts the lifetime of platelets (8-10 days), and it is the reason why administering low doses (100mg) 48-24 hours prior to the surgical procedure is sufficient. The ideal dose is 100 mg, orally or intravenously, per day for 7 days, and has little side effects. [17-19]

The subcutaneous injection of Low Molecular Weight Heparin after surgery should be administrated for prophylaxis of DVT, and this prevention therapy also affects the patency of the microanastomoses. Similarly to Unfractionated Heparin, intraluminal irrigation with LWMH increases the vessel patency, with minimal systemic side effects. LMWH is safer, in terms of hemorrhagic risk, than UFH and it is considerably easier to administer. [19-21]

Local intraluminal irrigation of the pedicle, before a microsurgical suture, is always done with LMWH and lidocaine. The use of urokinase or streptokinase is limited to the treatment of thrombosis in the immediate postoperative period, and never for antithrombotic prophylaxis. [22]

The use of vasoactive drugs systemically, such as prostacyclin, which is a powerful vasodilator, is still in the experimental stage on animal models. The systemic hypotensive effect of these drugs limits their use in a clinical setting because they may impair microcirculation in the free flap. There are some positive results from the local application (irrigation) of the drug within the lumen of the vessels, but further studies are required.

Intraluminal administration of prostacyclin before the vascular anastomosis induces a visible and lasting vasodilation (under the microscope) of the arterial flap, which becomes perfectly round and dilated. This technically facilitates micro-anastomosis. However, it is difficult to prove and quantify the extent of vessel dilatation.

The irrigation of the artery with prostacyclin does not replace irrigation with heparin, which should always be carried out immediately after disconnecting the flap from the donor site. Further studies are needed to demonstrate the vasodilating effect of the drug on the vessels of the pedicle. [23-26]

The pharmacological protocol does not increase the risk of intra and post-operative bleeding, and seems to improve the vascular patency and the perfusion of free flaps.

The low post-operative blood loss and the

Timing	Drug
48 h before surgery	**ASA**, 100 mg per day, orally
12h before surgery	NaCl 0.9% + **pantoprazole** 40mg + **methylprednisolone 500** mg I.V.
During surgery	**ASA**, 100mg I.V.
Before microsurgical time	Intravenous irrigation of **heparin** Intrarterial irrigation of **prostacyclin**
Post-operative	Subcutaneous injection of **LMWH**, 1 per day, Fluid therapy (1.5-2 liters up to recovery of oral alimentation)+500mg **methylprednisolone** + 40 mg **pantoprazole** in 24 hours for 3 days. 100 mg **ASA**, orally, 1 per day for 4 days more.

Table 1. The pharmacological protocol currently used by the authors.

absence of hematoma at the site of the anastomosis confirm the safety of the drug protocol employed. The free flap success rate is significantly increased in Group B. The vital signs, blood counts and APTT were almost normal. There was no change in drug-induced coagulation. No cases of complications related to drug therapy (such as HIT) were observed.

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