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Postoperative care in finger replantation: our case-load and review of the literature

E. CIGNA[1], F. LO TORTO[1], M. MARUCCIA[1,2], M. RUGGIERI[1], F. ZACCHEDDU[3], H.C. CHEN[2], D. RIBUFFO[1]

[1]Unit of Plastic and Reconstructive Surgery, Department of Surgery, "Sapienza" University of Rome, Rome, Italy
[2]Department of Plastic Surgery, China Medical University Hospital, Taichung, Taiwan
[3]Unit of Plastic Surgery, University of Cagliari, Cagliari, Italy

Abstract. – OBJECTIVE: Technical success of a finger replantation depends on several factors such as surgical procedure, type of injury, number of segments amputated, amputation level and individual patient factors. Among early complications that can occur in this type of surgery the onset of venous or arterial thrombosis is the most dreaded. Local irrigating solutions, oral and intravenous anticoagulants, thrombolytic agents, plasma expanders, vasodilating, and antiaggregant drugs are routinely used in patients undergoing microvascular procedures, but currently there is only a non-standardized practice based on anecdotal personal experience.

MATERIALS AND METHODS: The aim of our study is to review selected literature relating to perioperative therapy in microsurgical digital replantation. We also report our case-load of 16 patients with finger avulsion describing our particular protocol for postoperative anticoagulation and restoration of fluid and electrolyte balance.

RESULTS: Following our daily pharmacological protocol, the postoperative course of the replanted fingers was uneventful. The survival rate for finger replantations performed was 100% (n = 16) with no need for surgical revisions.

CONCLUSIONS: The association Dextran-40/Heparin/fluids in the proposed standardized pro-weight pharmacological protocol is an optimal postoperative prophylactic/therapeutic plan to reduce the incidence of endovascular thrombosis after replantation, so ensuring high rate of success in microvascular surgery.

Key Words:
Antithrombotic therapy, Digital replantation, Drug therapy, Finger replantation, Postoperative care.

Introduction

The advent of microsurgical tissue transfer including replantation greatly has expanded the scope of reconstructive surgery to correct various congenital, ablative and traumatic defects. Hand surgeons use microsurgical procedures to replant amputated digits or repair injured nerves and blood vessels. Since the first successful thumb replantation by Komatsu and Tamai[1], indications for digital replantation have been narrowed and surgical technique refined to maximize success rate[2,3]. Survival of replanted digits has become fairly reliable, with survival rates estimated to be 80% to 90% in the literature[4-13]. The advancement of various free flap also helps in replantation surgery, e.g. crush injury across the wrist or multiple fingers which may need replacement with healthy tissue been the amputated digits and wrist. Technical success of replantation depends on several factors: certainly surgical procedure[10,14] and type of injury[8,15,16] are the main prognostic factors of the patency of microsurgical anastomosis, but also other factors are involved such as the number of segments amputated, the amputation level and individual patient factors (age, smoking, vascular disease)[17]. Early complications that can occur in this type of surgery are the reduction of arterial perfusion caused by vasospasm or thrombosis, hemorrhage and venous insufficiency[18,19]. Among them the onset of venous or arterial thrombosis remains the most dreaded[16,19], especially in the first 3 postoperative days[20]. In fact the risk for thrombosis is highest (80%) during the first 2 postoperative days and decreases to 10% after postoperative day 3[21,22].

Zdeblick et al[23] put forward the theory according to which the suffering of endothelial cells of the injured vessels leads to destruction of intercellular junctions and formation of an intimal edema causing the exposure of the sub-intimal collagen. Contact of this collagen with blood cells and coagulation factors triggers the phenomenon of coagulation with formation of microthrombi which

Corresponding Author: Federico Lo Torto, MD; e-mail: federicolotorto@gmail.com

Table I. Patients characteristics

Patients	Gender	Age (years)	Smoking status	Type and mechanism of injury	Finger (R right hand, L left hand)	Complications
1	Female	35	Yes	Knife cut	III L	No
2	Male	38	Yes	Chainsaw amputation	II R	Local bleeding
3	Male	42	Yes	Car stripping	I R	No
4	Male	50	Yes	Door crush	IV R	No
5	Male	40	Yes	Knife cut	II R	No
6	Male	32	No	Ring avulsion amputation	III R	No
7	Male	34	No	Knife cut	I L	No
8	Female	35	Yes	Knife cut	II R	Dextran-40 allergic reaction
9	Male	25	Yes	Door stripping	V R	No
10	Female	38	Yes	Knife cut	II L	No
11	Male	33	Yes	Chainsaw amputation	IV R	No
12	Female	74	Yes	Ring avulsion amputation	IV L	No
13	Female	28	No	Glass amputation	I R	No
14	Male	31	No	Knife cut	II R	No
15	Male	46	No	Chainsaw amputation	III R	Local bleeding
16	Female	27	Yes	Ring avulsion amputation	IV L	No

obliterate vascular lumen. Eriksson et al[24] and Marzella et al[25] strengthened this theory demonstrating that vascular obstruction occurs between 10 and 60 minutes following reperfusion after a prolonged ischemia. Other authors suggest different pathophysiological hypothesis to explain the "phenomenon of non-vascularization" post-replantation: Acland et al[26,27] consider the responsibility of arterial microanastomosis in the genesis of platelet microemboli; Zamboni et al[28,29] support inflammatory mechanisms.

Surgical intervention for thrombosis generally involves anastomotic revision or interposition vein grafting, but the occurrence of re-intervention failure is high[21,30], so the primary prevention of thrombosis is of critical interest to microvascular surgeons. Clinical and experimental data suggest the benefit of perioperative antithrombotic drug therapy in microvascular surgery and free tissue transfer.

Several anti-coagulation and anti-platelet regimens have been proposed to maintain micro-anastomosis patency in the postoperative period, but a unified algorithm does not exist among microsurgeons regarding type, indications, timing and duration of medication administration for digital replantation-revascularization[16,31,32]. So currently there is only a non-standardized practice based on anecdotal personal experience[9,16,33-35].

The aim of this study is to review selected literature relating to perioperative therapy in microsurgical digital replantation. We report our caseload in 16 cases of finger avulsion describing our particular protocol for postoperative anticoagulation and restoration of fluid and electrolyte balance.

Patients and Methods

The study includes 16-microremplantations of the upper limb performed between September 2011 and September 2013. Patients' age ranged between 25 and 50 years (the mean age was 38), with 5 female and 11 males in the series. Eleven of the 16 patients were smokers (Table I). All patients reported traumatic amputation of a single finger. So, after stabilization of general clinical conditions, they underwent replantation performing a microsurgical procedure (Figures 1 to 3).

Postoperative Pharmacologic Protocol

After surgery, all the patients reported were included in the following standardized pro-weight pharmacological protocol, as shown in Table I:

- Fluids: 30-50 cc/kg/24h;
- Dextran-40 (molecular weight, 40 kd): 500 cc/24h;
- Heparin: 50-100 U/kg/24h intravenous.

This daily pharmacological protocol was carried out for a period of 5 days postoperatively.

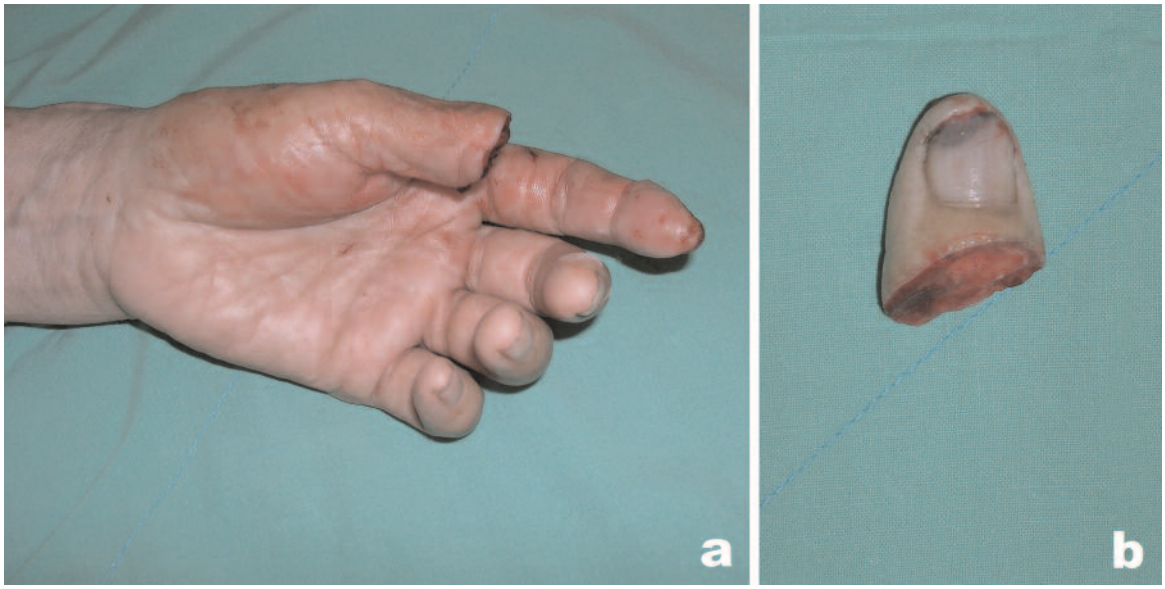

Figure 1. Patient 34 years old with a knife cut injury with amputation of the distal phalanx of the thumb of the left hand ***(A)***; distal phalanx ***(B)***.

Results

The postoperative course of the replanted fingers was uneventful. In fact, the survival rate for finger replantations performed was 100% (n = 16), without the need for surgical revisions. No case of necrosis was recorded. The complications related with the antithrombotic medication were almost irrelevant: there was only two cases of local bleeding that required the suspension of heparin therapy for 24 hours; while another patient manifested an allergic reaction to dextran-40 necessitating its definitive suspension.

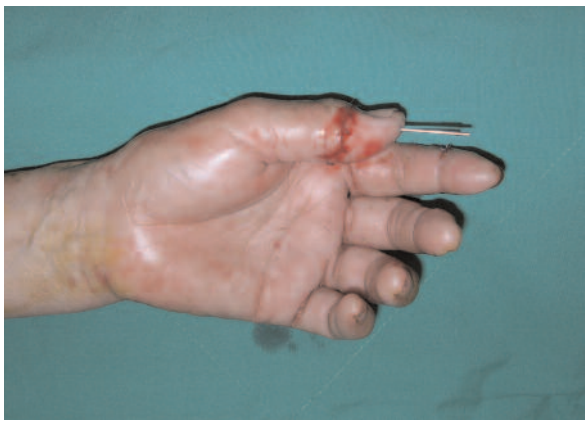

Figure 2. Intraoperative view after replantation.

Discussion

Recent reported failure rates in digital replantation vary between 7% and 22%[4-13], and this untoward event occurs mainly within the first 3 postoperative days[16-22].

The most feared complication and a common cause of digital replantation failure is vascular thrombosis[15]. It is the result of alteration of Virchow's triad: in fact endothelial damage, due to the direct action of the traumatic agent on vessel wall, is combined with blood stasis and hypercoagulable state, due to the primer of repair mechanisms.

Certainly, surgical technique and type/mechanism of injury are the main prognostic factors of success or failure of finger replantation, but also postoperative anti-thrombosis regimens are of prime importance in the prevention of thrombosis.

Local irrigating solutions, oral and intravenous anticoagulants, thrombolytic agents, plasma expanders, vasodilating, and antiaggregant drugs are routinely used in patients undergoing microvascular procedures. However, it is still a matter of debate for the most beneficial agent (or combination of agents), and the optimal time to start or end their administration. This has led to non-standardized practice based on anecdotal experience.

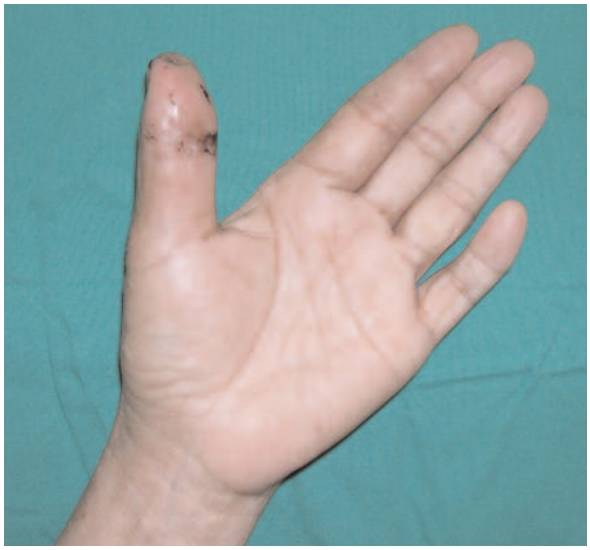

Figure 3. Post-operative view after 1 month.

Antithrombotic Therapy

Optimal antithrombotic therapy should target the coagulation cascade as well as platelet aggregation as their mechanisms appear to be synergetic[36-40].

Heparin (Heparin IV, Heparin SC)

Heparin has been used clinically for more than 50 years and it's currently the anticoagulant agent used most widely by surgeons to prevent both arterial and venous thrombosis. It is a polyglycosaminoglycan of varying lengths, that binds to antithrombin III enhancing its antiprotease activity and accelerating its attachment to its substrate approximately 1000-fold. As a result the active forms of coagulation factors II (thrombin), IX, X, XI, and XII are rendered inactive and the clotting cascade is impaired[41]. Through inhibition of thrombin generation heparin reduces the activation of coagulation factors V and VIII, recruitment of platelets, and formation of fibrin[42,43]. Moreover, large doses of heparin result in vasodilation that possibly is mediated by the release of nitric oxide from the endothelium[44]. The goal in heparin therapy is the efficient delivery of a minimal therapeutic dose to the site of vascular anastomosis. Maintaining low systemic heparin levels minimizes its adverse effects of anticoagulation mainly represented by hemorrhage from the surgical site[45], formation of hematoma[46,47], and also heparin-induced thrombocytopenia (HIT)[48-50].

Rooks et al[51] reported no significant difference in the protective effect of intra-arterial and systemically administered intravenous heparin or dextran-40. In other studies systemic heparin provided greater protection against rethrombosis after the repair of a thrombosed anastomosis[52,53]. Stockmans et al[45] showed that heparin, when administrated systemically to a therapeutic level reduces the rate of primary venous thrombosis by 60% whereas higher doses result in close to a 100% reduction. Hudson et al[54] used an in situ venous catheter inserting it proximal to the venous anastomosis to deliver high local doses oh heparin while maintaining low systemic levels, thus reporting satisfactory outcomes. Recently topical antithrombotic administration has been suggested as an alternate approach to local anticoagulation[36,55-59], but results are controversial. Fu et al[60] reported that topical administration of heparin results in 80% patency at the anastomosis sites, while Khouri et al[61] did not observe a benefit to using intraluminal heparin irrigation in reducing postoperative thrombosis. In fact, this procedure may increase vessel patency but the direct effect of the pressure can injure the vessel with a detrimental effect on microvascular anastomoses[62].

Low Molecular Weight Heparins (LMWH)

LMWH is a derivative of unfractionated heparin, prepared through the deaminative hydrolysis of standard heparin into short polysaccharide fragments. It has the same inhibitory effect on active factor X but has a weaker antithrombin (factor II) activity. So it results effective in preventing venous thrombosis with fewer adverse effects[63-65]. Instead, the efficacy of LMWH to prevent arterial thrombosis is a point of debate. Some studies found LMWH to be a less effective treatment than traditional heparin in reducing the frequency of arterial thrombosis[66,67], while others have reported better or equal results[65,68]. The protective effects of LMWH also include antithrombin-independent effects such as the release of tissue factor pathway inhibitor, interactions with heparin cofactor II, and platelet factor 4[64]. Therefore, attempts to standardize LMWHs on the basis of anti-Xa activity have not been completely successful. This explains the inherent difficulty in determining equivalent doses of unfractionated heparin to LMWHs. The pharmacologic profiles and efficacies of LMWHs vary; therefore, success with one LMWH at a certain dose does not generalize to the whole group. Similar to unfractionated heparin the application of topical LMWH minimizes systemic side effects[69].

Dextran

Dextrans are a group of variously sized polysaccharides that are synthesized from sucrose by *Leuconostoc mesenteroides streptococcus.* The antithrombotic effect of dextran is mediated through its binding to erythrocytes, platelets, and vascular endothelium, increasing their electronegativity and, thus, reducing erythrocyte aggregation and platelet adhesiveness through decrease of factor VIII-Ag (von Willebrand's factor). Platelets coated in dextran are distributed more evenly in a thrombus and are bound by coarser fibrin, which simplifies thrombolysis[70,71]. By inhibiting α-2 antiplasmin, dextran also serves as a plasminogen activator in thrombolysis. In addition, larger dextrans that remain in blood vessels act as potent osmotic agents to reverse hypovolemia[72,73]. Volume expansion causes hemodilution and this improves blood flow and further increases patency of microanastomosis. For these properties dextrans are used commonly by microsurgeons to decrease vascular thrombosis[74]. No difference has been observed in the antithrombotic efficacy of intra-arterial versus intravenous dextran administration[51]. The varying size of dextran, from 10 to 150 kd, results in prolonged antithrombotic and colloidal effects[72]. Larger dextrans are excreted poorly from the kidney and remain in the blood for weeks until they are metabolized[75]. The most popular dextran for anticoagulation is Dextran-40 (molecular weight, 40 kd). Close to 70% of it is excreted in the urine within the first 24 hours after intravenous infusion and the remaining 30% is retained for several more days, prolonging its effects[76,77]. Side effects associated with dextran use are relatively few but they can be very serious, such as anaphylaxis, volume overload, pulmonary edema, cerebral edema, platelet dysfunction, or acute renal failure.

Aspirin (ASA)

Aspirin (acetylsalicylic acid, ASA) acetylates and inhibits the platelet enzyme cyclooxygenase, impeding arachidonic acid breakdown to thromboxane and prostacyclin. Thromboxane is a potent vasoconstrictor that induces platelet aggregation and prostacyclin is a vasodilator that inhibits platelet aggregation. There is evidence that aspirin impairs thrombin generation and reactions catalyzed by this enzyme at the site of anastomosis[78]. Reconstructive surgeons frequently use aspirin in the perioperative period to improve flap survival. In fact, perioperative administration of aspirin is known to prevent microvascular thrombosis at both anastomoses sites[79,80], although it is less effective than heparin[52,81-83]. However, the protective effect of aspirin increases when co-administered during surgery with another antiplatelet agent[84,85]. Many surgeons prefer low-dose aspirin because it does not affect endothelial and smooth muscle cyclooxygenase. As a result prostaglandin I_2 (platelet antagonist and vasodilator) production is unaffected and there are fewer systemic side effects[86]. Unfortunately, the same mechanisms that make aspirin a powerful antithrombotic tool also can cause major problems. In fact, platelet dysfunction results in increased blood loss during surgery, which increases transfusion and re-operation rates[87]. Other aspirin side effects stem from its nonselective inhibition of cyclooxygenase, such as serious renal dysfunction or gastrointestinal bleeding. Howevers, these risks are dose dependent and a low-dose regimen (75 mg/d) minimizes them[88].

Thrombolytics (Streptokinase, Urokinase, Tissue-type Plasminogen Activator)

Thrombolytic agents available for clinical use include streptokinase, urokinase[89], and tissue-type plasminogen activator (recombinant tissue plasminogen activator, rt-PA)[90-92]. Their efficacy in reversing microvascular thrombosis is well documented in the animal model[93,94], instead most human studies look at small study populations and so there're no definitive conclusions on the relative efficacy and appropriate dosing of thrombolytics. However, Rooks et al[51] reported satisfactory results and they demonstrated, for an established thrombus, an advantage to intra-arterial over intravenous administration of thrombolytics because intra-arterially delivered urokinase results in significantly greater efficacy (100% for intra-arterial vs 40% intravenous). Thrombolytic agents are associated with a risk for bleeding but this risk can be minimized by draining the venous effluent to prevent systemic exposure to the agent[95]. After using thrombolytic agents hematoma should be checked to prevent compression to the vessels.

Prostaglandin E1

Medical scientists continue to search for new antithrombotic and anticoagulant therapies that maximize benefits while minimizing adverse effects. Between new therapies there is Prostaglandin E1 (PGE1)[96]. This molecule has been used for many years in the treatment of

claudication[97-98], peripheral arterial occlusive disease[99], Raynaud's syndrome[100-101], and as adjuvant treatment after profundaplasty. In fact, PGE1 has multiple effects on the microcirculatory level with relevant vasodilating, antithrombotic and anti-ischemic properties and it also have anti-inflammatory effects inhibiting monocyte and neutrophil function. Many authors demonstrated that PGE1 is effective in the prevention and resolution of microvascular spasm, a complication which can be a major issue after prolonged ischemia (replantations)[96,102-104]. However, its overall clinical efficacy and safety in microvascular surgery remains to be determined in larger, prospective clinical trials.

As reported in the literature, the antithrombotic drugs most commonly used in digital replantation/revascularization are the following: Aspirin (Acetylsalicylic Acid, ASA), with a dosage of 180-325 mg; Heparin (Heparin IV/Heparin SC, unfractionated; or Low Molecular Weight Heparins, LMWH, fractionated); and Dextran (plasma expander).

Instead our postoperative pharmacological protocol consisted in daily intravenous standardized pro-weight administration of heparin, dextran and fluids, in the first 5 postoperative days, which is the time interval within which the incidence of thrombosis is usually high.

The rational use of this pharmacological protocol is explained by synergic action of these drugs on the different components of Virchow's triad, thus, reducing the risk of intravascular thrombosis.

In particular our goal was based on four key points, as follows: to obtain an anticoagulant effect (1) and an antithrombotic effect (2); to achieve an effective reduction in hematocrit up to a minimum value of 27-28% (3); to reduce endothelial damage (4).

In fact, the synergistic action of heparin (inhibitory effect on coagulation cascade) with dextran (inhibitory effect on platelet aggregation) involves an effective improvement of the hypercoagulable state, which typically occurs as a defense mechanism in response to injury.

Blood fluidification and consequently slowing of the flow are achieved also thanks to continuous administration of postoperative fluids (plasma expander effect) with the aim to reduce hematocrit up to very low values.

Finally, a further strength of our therapeutic strategy in the medical approach to fingers amputation is certainly represented by rapidity of restoration of the vascular wall integrity. It is obtained by the most advanced microsurgical procedures/techniques which optimally allow to pull over damaged endothelial cells to each other. In fact, no anticoagulant or other medications can replace a perfect anastomosis. However, after trauma the success of replantation can be improved by adding medication to the perfect anastomoses.

In addition, regarding the possible complications related with the proposed antithrombotic medication, we affirmed that the association of different drugs (Dextran and Heparin) did not increase the postoperative bleeding, as reported in our series.

Conclusions

We suggest our standardized pro-weight pharmacological protocol as an optimal postoperative prophylactic/therapeutic plan to reduce the occurrence of endovascular thrombosis after replantation and therefore to ensure high rate of success in microvascular surgery.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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