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CURRENT CONCEPTS REVIEW

Leech Therapy Protects Free Flaps against Venous Congestion, Thrombus Formation, and Ischemia/ Reperfusion Injury: Benefits, Complications, and Contradictions

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Abstract

The use of free cutaneous or myocutaneous flaps in some surgeries, especially in reconstructive surgeries, is routine and imperative; nevertheless, it is controversial because of fear of flap loss due to tissue congestion and partial or complete necrosis. Different mechanisms are discussed in this process, and based on the involved mechanisms, various agents and approaches are suggested for flap salvage. Among these agents and strategies, leech therapy (hirudotherapy) can be a valuable complementary treatment; however, in this way, full attention should be given to all beneficial and harmful aspects to reach the best results.
This study included a literature review of the essential complications following free tissue transfer and explained the effects of leech therapy for the respective complications.
Based on the review of the literature, the essential complications following free tissue transfer were (I) venous obstruction and congestion, (II) delay in blood flow reestablishment, (III) ischemia/reperfusion injuries, and (IV) thrombus formation. Leech therapy can protect free flaps against the mentioned complications as a complementary treatment.
Leech therapy is an appropriate complement, however, not a definite approach for flap salvage. Therefore, in some patients, other alternative methods or even flap removal may be a better option.

Level of evidence: IV

Keywords: Benefits, Complications, Contradictions, Free flaps, Leech therapy

Introduction

In recent decades, limb salvage has progressed in orthopedic reconstructive techniques and plastic and vascular reconstructions. These techniques have been promoted to restore biology and anatomy to near normal. Anyway, failures and complications, mainly as complete or partial flap failure, still do occur (1). Postoperative complications, such as congestion, can lead to cell death and, finally, flap loss. In this case, different agents and approaches are suggested for flap salvage. Leech therapy (hirudotherapy) can be a valuable complementary treatment among these agents and strategies. Leech therapy has been approved by the Food and Drug Administration as a medical device for plastic and reconstructive surgery since July 2004 (2). However, full attention should be given to all beneficial and harmful aspects to achieve the best results. This review aimed to investigate the use of medical leeches in microvascular and flap surgeries and compare leech therapy with other treatment approaches in tissue transfer. Moreover, this study provided a review of scientific concepts and findings of the benefits, complications, and contradictions of leech therapy and the supporting theories.

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This updated review of medical leech therapy focused on microvascular and flap surgeries and compared them with other treatment approaches. A discussion of accepted concepts of the potential mechanisms of action, benefits, complications, and contradictions of leech therapy was also provided. A comprehensive literature search was carried out on different electronic databases, including PubMed, Google Scholar, Scopus, Medline, and Web of Knowledge, and on the reference lists of published reviews to identify published studies exploring the main complications in free tissue transfer and also the therapeutic effects and side effects of leech therapy in patients undergone free tissue transfer. The search process was performed using the following keywords: “Leech therapy”, “Cutaneous flap”, and “Free tissue transfer”.

Results

In a review of 10 studies, among 298 patients who required leech therapy, 60.73% of flaps were entirely or partially salvaged, 16.77 % of flaps were lost entirely, and the outcomes in 22.5% of patients were unknown [Table 1].

Main free tissue transfer complications

Free tissue transfer for reconstructive and plastic surgery is commonly used; however, flap viability is threatened due to some causes and disorders. Based on the review of the literature, the most important reasons are (I) venous obstruction and congestion, (II) delay in blood flow reestablishment, (III) ischemia/reperfusion injuries, and (IV) thrombus formation. On the other hand, these causes and mechanisms can have synergism effects. Therefore,

Table 1. Results of leech therapy for flap salvage reported in different studies

Authors	Flap recipient site	Study type	Total number of patients	Patients with total or partial salvage of flap (%)	Patients with total flap loss (%)
Herlin et al., (3)	Unknown	Systematic review	43	84% (Total salvage: 60.6 Partial salvage: 23.5)	16%
Whitaker et al. (4)	Head and neck	Meta-analysis	27	88.8%	11.1%
Utley et al., 1998 (5)	Head and neck	Retrospective case series	4	100%	0%
Pannucci et al., (6)	Breast	Retrospective case series	4	25% (Partial salvage)	75%
Cornejo et al., (7)	Lower extremity (37.9%), Upper extremity (34.5%), Head and neck (14.9%), and Trunk (12.6%)	Retrospective case series	87	60.9% (Total salvage: 51.7% Partial salvage: 9.2%)	39.1 %
Butt et al.(8)	Posterior interosseous artery flap, Anterolateral thigh flap, Deep inferior artery perforator flap, Superior gluteal artery perforator flap	Retrospective case series	13	77%	23%
Nguyen et al. (9)	Head and neck	Retrospective case series	10	100%	0
Gröbe et al.(10)	Head and neck	Retrospective case series	105	36.5% (included free, authors did not isolate)	Unknown
Frodel et al. (11)	Head and neck	Retrospective case series	4	100%	0%
Tashiro et al., (12)	Thoracic wall	Case report	1	100%	0%

different agents and approaches are reported to reduce or prevent these disorders that many of which are based on decreasing congestion, thromboprophylaxis, and/or thrombolytic, anti-inflammatory, and antioxidative agents. It appears that leech therapy is a practical approach against the mentioned causes and can increase flap viability. Nevertheless, leech therapy can still have some side effects and complications.

(I). Venous congestion

Any surgical manipulation of veins has the potential risk of venous congestion. In flap surgery, tissue congestion and hematoma are important problems and increase the possibility of tissue loss (13). It has been reported that 8-11% of patients with free tissue transfer require re-exploration for threatened flap viability which may lead to second free flap surgery (14-17). Venous obstruction may lead to tissue congestion by direct and indirect pathways and lead to tissue necrosis. Studies on animal models have shown that secondary venous-related ischemia bears more risk to flap survival than primary arterial dysfunction (18, 19). When venous obstruction occurs in the flap, the venous outflow is stopped, and congestion is an inevitable phenomenon (direct pathway) that potentially progresses to tissue hypoxia, acidosis, and eventually, tissue necrosis and wet gangrene. Venous obstruction and congestion can cause blood stasis. These conditions are predisposing factors for platelet trapping, platelet activation, and microcirculatory thrombosis formation that increase the venous obstruction, and subsequently, tissue congestion (indirect pathways) (19, 20). In tissue transfer surgeries, if venous congestion occurs, the patients require an emergent intervention to establish venous outflow, and tissue failure probably increases with delay in congestion elimination. The salvage rate varies from 19% to 100% in emergent exploration (14-17, 21, 22). Nonetheless, in some situations, such as in free tissue transfer or when microvascular problems are presented in the flap, the venous obstruction may not be surgically salvageable. In these patients, leech therapy can be used as an alternative method until inosculation, and subsequently, the reestablishment of venous outflow occurs (10). In this case, aggressive leech therapy protocol is crucial in the effectiveness of leech therapy, and delay in protocol application increases tissue failure. The early use of leech therapy for free flaps is well discussed for digit, auricle, nose, lip, head, and neck tissue replantation (23-28). In a systematic review on 277 clinical cases in plastic and reconstructive surgery, the overall reported success rate following leech therapy was 77.98% (4). In another study, the total flap loss and salvage rate in patients with leech therapy after flap reconstruction or replanted appendages were reported as 20.6% and 79.3%, respectively (7). Leech therapy can decrease venous congestion by both mechanical and biological effects. Blood extraction during leech therapy and blood loss related to the oozing from the leech bite site after the leech detachment are initial factors in relieving venous congestion (29). On the other hand, the saliva of medical leeches contains coagulation and platelet inhibitors and vasodilator agents that decrease the microthrombus formation and increase arterial inflow and venous outflow (5, 30). The results of experimental studies have shown that hirudin, the most important anticoagulant in leech saliva, can improve flap venous congestion and promote angiogenesis and neovascularization in congested venous flaps by increasing vascular endothelial growth factor expression and reducing endostatin and thrombospondin-1 production (31, 32). However, some surgeons do not believe in the effectiveness of leech therapy to correct venous congestion. They suggest total flap removal, rather than leech therapy, as a salvage procedure in patients with surgically uncorrectable venous congestion. In a study, patients with surgically correctable venous congestion were compared with patients with surgically uncorrectable venous congestion requiring medicinal leech therapy (6). In the current study, the total flap loss rate was significantly higher in the leech therapy group (75.0% in the leech therapy group vs. 42.1% in the surgery group). However, the differences were not significant between the groups. Furthermore, most patients in the leech therapy group were obese (75% vs. 31.6%; $P<0.05$). Obese patients develop higher complications, such as partial or major flap necrosis, hernias, abdominal bulge, deep vein thrombosis, and infection (33, 34). On the other hand, the size, type, and place of the flap and concurrent conditions in each patient could have determinative roles in treatment outcome and may increase the risk of flap loss. In another study, venous catheterization (VC) was employed to treat venous congestion of sural flaps and compared with leech therapy (35). In the mentioned study, although blood removal was higher in the leech group than in the VC group, flap necrosis, infection, and wound issues were higher, and nurses and patients were more satisfied in the VC group than in the leech group. The authors suggested that VC was an easier, more effective, and safe technique for blood removal with less complications. More studies are needed to evaluate VC effectiveness in different situations and flaps. It may be a good alternative option in flap salvage, especially in patients that cannot use other treatment approaches.

(II). Delay in blood flow reestablishment, and (III). Ischemia/reperfusion injuries

In free flap transfer, a period of inevitable short time global ischemia is present until blood flow is reestablished. However, unexpected intraoperative events may lead to elongation of ischemic time. Moreover, restoring blood flow causes the other type of tissue damage termed reperfusion injury (36-38). In ischemia-reperfusion injury, acute inflammation may occur due to some proinflammatory cytokines and free radicals; consequently, some tissue damages in ischemia-reperfusion injuries are cited to inflammatory cells (39-42). In this case, some anti-inflammatory and anti-oxidative agents are used to reduce the extent of reperfusion injury. In other techniques, the researchers increase the tissue tolerance to the subsequent global ischemia. During tissue ischemia and, in particular, during tissue re-oxygenation, free radical production has a pivotal role in tissue damage and necrosis. In addition to free flaps, this phenomenon is essential in the pathogenesis of some diseases, such as myocardial infarction. In these conditions, the use of free radical scavengers and antioxidant agents, including superoxide dismutase and allopurinol, successfully can reduce tissue damage and necrosis (43-46). Additionally, the use of caffeic acid phenethyl ester (an anti-inflammatory and immunomodulatory agent), fucoidin (a neutrophil rolling Inhibitor), melatonin (an antioxidant and free-radical-scavenger), taurine (with antioxidative properties) for free flaps salvage against ischemia/reperfusion injury is well established (47-50). Leech therapy has direct effects on ischemia/reperfusion injuries because the saliva of medical leeches contains anti-inflammatory agents, such as hirudin (has anti-inflammatory and antioxidant effects), hirustasin (neutrophilic cathepsin G Inhibitor), Bdellins (has anti-inflammatory effects by inhibiting trypsin and plasmin and inhibits the action of the acrosin), tryptase inhibitor (inhibits proteolytic enzymes of host mast cells), and Eglin-c (has anti-inflammatory effects) (9, 51-55). Therefore, hirudotherapy can be an effective treatment for reducing ischemia-reperfusion injuries.

In research conducted on an animal model, leech therapy was applied to decrease ischemia/reperfusion injuries compared to ischemia preconditioning (IPC) (56). In the IPC method, repetitive ischemia-reperfusion is performed before global ischemia. The concept is that this method increases tissue tolerance to the subsequent operative, and then, long-time global ischemia; as a result, it reduces the extent of reperfusion injury after operative time and tissue necrosis after long-time ischemia. Still, its main effect is to prevent reperfusion-type damage and reduce cell death (57). In a separate study, both IPC and hirudotherapy increased the final survival area of cutaneous pedicle flaps after prolonged ischemia. In the mentioned survey, leech therapy was performed after global ischemia. Some researchers have shown that heparin before or during the ischemia period could protect the tissue from ischemia/reperfusion injures (58). Regarding this, the application of leech therapy before global ischemia may also be practical in the survival enhancement of flaps.

(IV). Microthrombus formation

All Virchow criteria of thrombus formation are met in free flap surgery. Thrombus formation in the anastomotic site is one of the most important causes of flap failure. In tissue transfer surgeries, predisposing factors for the local activation of platelet and coagulation cascade and, finally, microthrombus formation (venous and/or arterial thrombosis) include blood stasis, venous congestion, inflammatory pathways due to ischemia/reperfusion injuries, internal elastic lamina, and endothelium injury, the presence of sutures site narrowing, diminished flow sometimes due to kinking of vessels, hematoma, edema, hypovolemia, and hypothermia (59). Microthrombus formation can increase tissue congestion and necrosis. Therefore, it appears that thromboprophylaxis is a useful and essential method that can play a pivotal role in increasing flap success. Some microvascular surgeons use systemic anticoagulant agents, especially flap salvage, after vascular thrombosis (60). However, the employment of anticoagulant agents in microsurgery is highly controversial. Some surgeons refuse the routine application of anticoagulants for uncomplicated flap surgeries. They believe that the use of systemic anticoagulants not only increases the risk of complications, such as heparin-induced thrombocytopenia, systemic bleeding, and hematoma formation, with subsequent compression of the pedicle but also enhances the risk of flap loss, especially in high doses (61, 62). Some surgeons believe that systemic administration of anticoagulants, such as heparin, has no statistically significant effect on the incidence of hematoma formation and even microvascular thrombosis; in this respect, the use of intraoperative anticoagulation agents has no obvious direct or indirect effect on flap survival (63, 64). Although anticoagulant agents in microsurgery are controversial, arterial or venous thrombosis is one of the most common complications of microvascular anastomosis, and microvascular thrombosis may lead to flap failure. Consequently, there is always a tendency to employ anticoagulant agents and thromboprophylaxis in microsurgery, particularly in flap tissue transfer. In this case, one of the most important problems is the lack of a distinct protocol for the use and administration of different pharmacological agents, dosages, and timing for different patients. Based on the literature review, heparin, aspirin, dextran and prostaglandin-E1, nitric oxide and inhibitors of nitric oxide, anesthesia agents, and adenosine-diphosphate receptor inhibitors (e.g., ticlopidine and clopidogrel) are used for thromboprophylaxis in microvascular and flap surgeries (65-70). Nonetheless, according to the results from the literature review, it does not seem that the administration of anticoagulant medications can improve flap survival significantly or reduce the rate of complications (71-74).

Some systemic complications can be caused by some anticoagulant medications (70, 75). Furthermore, some researchers have used hemodilution to provide better microcirculatory blood flow, reduce blood viscosity and cell aggregation, and dilute the coagulation factors. Therefore, they believe that hemodilution is an ideal thromboprophylaxis approach and improves the oxygenation of ischemic and hypoxic flaps (69, 76). The main limitation of this technique is the risk of hematoma formation (64); in this respect, fluid administration must be performed carefully. Leeches excrete numerous bioactive substances during leech therapy, such as prostaglandins, prostacyclin, endorphins, neuropeptides, anesthetics, antibiotics, and especially anticoagulant agents (77)

Biologically active agents in leech saliva that have thromboprophylaxis effects are:

1. Anticoagulant agents, such as hirudin inhibit blood coagulation by thrombin inhibition (54). Calin: Can prevent the Von Willebrand factor from binding to collagen and inhibit blood coagulation. Destabilase: Dissolves fibrin and has thrombolytic effects (54).

Hirustasin: Inhibits kallikrein (55). Bdellins: Inhibits trypsin, plasmin, and acrosin (54), and factor Xa inhibitor (78).
2. Platelet aggregation inhibitor: Apyrase (26).
3. Vasodilators, such as histamine and histamine-like substances (79), acetylcholine (55), and the carboxypeptidase A inhibitors
4. Anesthesia agents: Can decrease stress hormone release, probably secondary to pain attenuation, activate local fibrinolysis, and partially inhibit platelet activation (59).

Hirudin, a 65-aminoacid polypeptide, is the most crucial substance synthesized by the leech salivary gland. Hirudin directly inhibits thrombin and promotes vessel recanalization. Based on the results of some studies, hirudin has been more effective than heparin and it is an appropriate alternative for patients suffering from heparin allergy (59). It has been reported that hirudin can decrease the risk of microthrombus formation and it does not significantly influence activated partial thromboplastin time (APTT) and thrombin time; therefore, hematoma formation is not a severe risk of respective patients, unlike other anticoagulant agents. Some researchers believe that monitoring is unnecessary in patients cured with hirudotherapy (80, 81). The findings of some studies have shown that recombinant hirudin (Lepirudin) can recover platelet counts and APTT in patients with heparin-induced thrombocytopenia, which is a safe and effective anticoagulant strategy in such patients (82). However, some surgeons believe that frequent and skilled hemodynamic assessment is essential for patients with leech therapy because of the large amount of blood loss. This blood loss not only occurs during leech therapy but also continues from bit sites after leech detachment. Douglas et al. (2002) described that the clinical and hematologic evaluation must be performed every 4 hours in patients with leech therapy. In the mentioned study, blood transfusion requirement was the most crucial morbidity related to the leech therapy, and an average of 13 U of packed red blood cells with a range of 5-28 U was necessary.

Complications in leech therapy

One should be ready to manage anemia and infection, as the most common complications, after leech therapy with reported infectious incidence ranging from 4% to 20% (83). Although some researchers believe that leech therapy is a safe approach and has minor morbidity, the risk of infection in leech therapy should not be underestimated, since the occurrence of infection can lead to the loss of flaps partially or entirely (84, 85). The most common cause of infection and septicemia is a Gram-negative, facultative anaerobic rod bacterium called Aeromonas hydrophila (86). This infection can occur after leech use in the first 24 hours (acute onset infection) or the first 26 days (delayed onset infection) (26). The infected tissue is not commonly salvaged; in this regard, after leech therapy, an aggressive prophylaxis regimen by an appropriate antibiotic regimen is highly recommended. Although this infection often responds to antibiotics, it has been reported that it is resistant to accepted prophylactic antibiotics and even broad-spectrum antibiotics, such as ciprofloxacin. In this condition, there is the risk of flap loss and even septicemia. In a recommended prophylactic antibiotic regimen, antibiotic therapy is double coverage during leech therapy and single coverage for 2 weeks after the performance of leech therapy on patients. The results of a study conducted on 21 isolates of Aeromonas species showed that 71.4% of isolates were ciprofloxacin-susceptible and all isolates were sulfamethoxazole-trimethoprim susceptible. It appears that sulfamethoxazole-trimethoprim with a quinolone is an appropriate prophylactic antibiotic regimen of choice for leech therapy (26, 87). Antibiotic susceptibility testing on water collected from leech tanks can be an effective approach to detect resistant Aeromonas species in medical leeches and decrease the infection rate in patients (87). Detachment of leeches by applying salt or pulling them might induce blood regurgitation in leeches, which increases the risk of infection. Therefore, spontaneous detachment is the best method, and it has been suggested that the control of blood volume sucked by leeches should be performed by controlling the number and size of leeches. The other significant complication of leech therapy is the blood transfusion requirement due to blood loss and anemia. As mentioned previously, blood loss occurs during leech therapy and continues from bit sites after leech detachment. In some studies, blood transfusion requirement is the essential morbidity related to leech therapy; in this respect, clinical and hematologic evaluations must be performed every 4 hours (9, 26). Blood transfusion is needed when the hemoglobin concentration is lower than 8 mg/dl. In different studies, approximately 50-100% of patients subjected to leech therapy required blood transfusion (4, 9, 26). A range of 1-28 U of packed red blood cells RBCs was necessary for these patients during the leech therapy. The other rarely reported complications in leech therapy are prerenal azotemia, intensive care unit psychosis, congestive heart failure, pneumonia, decubitus ulcer, non-Aeromonas wound infection, and hematoma (26). Guidelines for the safe use of medical leeches is well described (88, 89).

Contraindication of leech therapy

Contraindications related to hirudotherapy include patient refusal to undergo leech therapy or subsequent blood transfusion, arterial input ischemia, immune-related issues (e.g., immunosuppression by human immunodeficiency virus infection [a risk factor for Aeromonas hydrophila]), or previous exposure to leeches (because of risk for anaphylaxis, allergic reaction or history of allergy to leeches, or severe allergic diathesis), unstable medical status, hematological malignancies, severe anemia, decompensated forms of hepatobiliary diseases, any form of cachexia, during pregnancy and lactation, disposition to keloid scar formation, and in those with recent medication history of anticoagulants, immunosuppressants, and/or vasoactive medications (90).

Leech therapy is an appropriate complement; however, there is no definite approach for flap salvage. Therefore, in some patients, other alternative methods or even flap removal may be a better option. It appears that leech therapy protects free flaps against congestion, thrombus formation, and ischemia/reperfusion injury which are the major complications in flap surgeries. To reduce flap necrosis and loss and increase the flap viability during leech therapy, it is highly recommended to pay attention to the contradictions of leech therapy and the presence of some risk factors in patients, such as obesity, that may increase flap loss. Moreover, since delay in protocol application increases tissue failure, an aggressive application of leech therapy protocol is an essential factor in the effectiveness of leech therapy. It is also suggested that the appropriate number of leeches and the proper application time and frequency be estimated, the leeches be applied according to standard protocols, and enough attention be paid to all details. Furthermore, patients need to be followed and closely examined for flaps, especially in the first days of treatment. Finally, it is recommended that antibiotic prophylaxis, blood transfusion, and other postoperative supports be provided.

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