www.directivepublications.org

Advances in Plastic Surgery

DIRECTIVE PUBLICATIONS

Review Article

A Review Of The Literature On The Evidence And Clinical Uses Of Local Pro- And Anti-Coagulation Therapy In Plastic Surgery Patients.

Jerie D. Olver [1], Imma P. DeLouery [1], Nikitha Guptia [1], Daniel [2], Andriea Sisti [2],Marial [T]. Huayllanoi [2], Davide J. Restreporo [2], Micel S. Hu [3] and Antoniolo J. Fortez [2,*].

Abstract

Although systemic anticoagulation and its reversal carry known dangers, they are sometimes considered required. However, systemic hemostasis changes are frequently unnecessary when local therapy can make the necessary alterations, especially in plastic surgery patients. An overview of the clinical uses of topical anticoagulant and procoagulant therapy in cosmetic and reconstructive surgery was the goal of this review. Hemostats are frequently used to stop bleeding, local anticoagulants like heparin can increase flap survival, and local tranexamic acid (TXA) has demonstrated promise in attaining hemostasis under diverse situations, albeit this research is still in its infancy. Drug delivery is the primary obstacle to the development of local treatment.

Keywords : *coagulation; anti-coagulation; drug delivery; local therapy; flaps; plastic surgery.*

INTRODUCTION

Devastating thrombosis or bleeding may occur when the hemostasis balance is disturbed. There are several treatments that can alter the coagulation system's elements to produce the intended outcome, although they are frequently given systemically. Local medicines that could provide the necessary coagulation changes without the hazards of a systemic therapy would be suitable for the surgical patient in need of pro- or anti-coagulation. Here, we go over the pharmacologic treatments that are accessible as well as circumstances in which a plastic surgery patient would benefit from local hemostasis modification.

A wide range of local pro- and anti-coagulation options exist in the literature, with the earliest documented medical records of ancient Egypt, Greece, and Native America citing the use of agents common in nature such as wax, grease, barley, and animal hide to achieve hemostasis [1]. In the modern era, advances in topical agents have expanded the possibilities to manipulate hemostasis in the surgical patient. These advances include physical (i.e., bone wax and ostene), absorbable (i.e., oxidized cellulose and gelatin foams), and biologic agents (i.e., topical thrombin, fibrin, platelet gel). Synthetic agents, such as cyanoacrylate and polyethylene glycol, have also emerged over the last decade [1].Efficacy,cost, absorption, absence of antigenic characteristics, convenience of use, and delivery methods are all important considerations while looking for the best local agent. Even though no one local agent created to yet has fully utilized each of these characteristics, research into local coagulation agents is still ongoing in an effort to maximize cost and performance and, eventually, the best possible outcome for patients. This review's objective was to present a condensed summary of the clinical uses of topical anticoagulant and procoagulant medications that are pertinent to plastic and reconstructive surgery.

Pro-Coagulants

Reducing blood loss during and after surgery is crucial, and there are numerous techniques to lessen bleeding both during and after surgery. Nonetheless, in some situations, a systemic treatment may be desired, as in the case of a patient receiving anticoagulation for a superficial injury because of a high risk of thrombotic events. Considering the high risk of bleeding during and after surgery Management for these individuals frequently entails using short-acting medications, such as low-molecular-weight heparin (LMWH)

***Corresponding Author:** Antoniolo J. Fortez, University of Health North Carolina, Hill Chapel, NC.
Received: 10-Jan-2025, **; Editor Assigned:** 12-Jan-2025 **; Reviewed:** 31-Jan-2025, **; Published:** 10-Feb-2025,
Citation: Antoniolo J. Fortez. A review of the literature on the evidence and clinical uses of local pro- and anti-coagulation therapy in plastic surgery patients. Advances in Plastic Surgery. 2025 February; 1(1).

or unfractionated heparin, as well as temporarily stopping the anticoagulant before and after surgery (especially when it comes to vitamin K antagonists). Bridging anticoagulation is a technique designed to help maintain a low risk of thrombosis while assisting in obtaining a normal or nearly normal hemostasis at the time of operation.

This is still different from the patient's usual course of treatment, though, and any stoppage in anticoagulant medication could cause a thrombotic event in patients who are especially at risk. On the other hand, a period of too little time between the last anticoagulant dosage and surgery, or between surgery and the start of anticoagulation, may cause bleeding and hematoma formation, which could jeopardize the outcome of the procedure or lead to additional difficulties. A higher incidence of postoperative wound hematoma after pacemaker and implanted defibrillator implantation is linked to the usage of LMWH [2].Warfarin use after surgery also raises the risk of infection and hematoma development in total hip replacements [3]. The risk of rebleeding following surgical evacuation of chronic subdural hematomas is increased when aspirin or warfarin is taken prior to surgery [4]. The three factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban) and one direct thrombin inhibitor (dabigatran) are among the more commonly used direct oral anticoagulants (DOACs). At least in the orthopedic setting, these drugs seem to have comparable intraoperative transfusion needs and post-operative bleeding risks to vitamin K antagonist therapy (warfarin), indicating that hemorrhage will continue to be a concern in anticoagulated patients even as more patients switch off of warfarin [5]. When considering surgery for a patient who is at risk of thromboembolism, a non-pharmacologic approach to avoid thromboembolism would appear ideal, however the available options are not optimal. These choices include different inferior vena cava filters, which can trap the embolus and stop it from getting to the lungs, perhaps preventing pulmonary embolism.

Nevertheless, these filters have a high risk of problems, including as filter-related thrombosis, and they only stop the most fatal side effects of thrombus formation [6]. A local agent that either promotes clot formation or inhibits clot degradation would be advantageous given the risks of bleeding in the anticoagulated patient and the risks of thrombosis if anticoagulation is stopped. This would allow anticoagulation to be reversed at a specific site while preserving anticoagulation systemically. Hemostats, topical thrombin and fibrin, and tranexamic acid (TXA) are a few of these local alternatives.

Topical TXA can be used to treat epistaxis brought on by coagulation abnormalities and anticoagulation, as well as to decrease bleeding after oral surgery [7, 8]. TXA is an anti-fibrinolytic that attaches itself to plasmin to stop fibrin from breaking down. TXA has been demonstrated to lessen postoperative bleeding after heart surgery when given in the pericardial cavity in addition to its topical applications [9]. Although it was less successful at lowering the need for transfusions, it also seemed to be useful at lowering gross hematuria during bladder irrigation when administered intravenously [10]. TXA decreased blood loss and transfusions after total knee replacement when given topically or intra-articularly [11,12]. Although similar outcomes have been observed in other surgical patients, it is uncertain how topical TXA affects thromboembolic risk [13].

Hemostasis can also be accomplished with topical thrombin and fibrin compositions, especially when performing dermatological surgery [14]. In order to achieve hemostasis during laparoscopic surgery, fibrin sealants are also frequently utilized [15,16]. Because fibrin is the final result of the coagulation cascade and does not require biologic activation, fibrin sealants made of fibrinogen and thrombin are especially well-suited for patients who are anticoagulated. Nevertheless, it has been demonstrated that bovine-derived thrombin causes the development of antibodies against cardiolipin, factor V, prothrombin, and thrombin, which could result in a possibly fatal hemorrhagic propensity [1]. Without these immunologic adverse effects, ecombinant human thrombin seems to be just as safe and effective.

To accomplish hemostasis, a large range of hemostats are also available; their composition is dictated by the surgical necessity and each has pros and cons of its own [17]. Hemostats are substances that can be put to a bleeding location to promote coagulation, such as dressings, sponges, meshes, or powders. Bone wax, collagen, and cellulose are examples of physical and absorbable hemostats that work well for controlling low-pressure bleeding, although they can embolize and impede the healing process [18].

Biologic agents, such fibrin sealants or thrombin, can cause an immunologic reaction and are costly, but they can be applied fast and start working right away.

Agents that depend on an intact coagulation route, like those containing collagen, cellulose, or gelatin, are less effective in coagulopathic patients. Generally speaking, fibrin and p-GlcNac-based hemostats have been proven to be more effective at achieving hemostasis than gelatin-based hemostats [17]. Polysaccharide hemostats seem to have the best safety profile for patients and are helpful in trauma situations.

Please see Table 2 for a summary of research examining the use of topical thrombin [22,23] and Table 1 for several references of pro-coagulant TXA in plastic, reconstructive, and craniomaxillofacial surgery [19–21].

Anticoagulants

Since systemic anticoagulation raises the risk of bleeding, local anticoagulants also have a role. Following plastic

and reconstructive surgery, even twice-daily enoxaparin treatment for venous thromboembolism may cause clinically significant bleeding [18].Topical anticoagulants used intraoperatively have been linked to improved flap, skin graft, and replanted finger survival during free-tissue transfer [24]. The leech Hirudo medicinalis, which is arguably the oldest anticoagulant, has demonstrated effectiveness in lowering venous congestion of skin flaps during plastic surgery, preventing flap loss [25, 26]. The leech's release of hirudin, a thrombin inhibitor, is the key to its success.

Excessive bleeding and infection with Aeromonas hydrophilia, a gram-negative bacillus that is indigenous to the leech's digestive tract, are two side effects of leech therapy [26]. Purified and recombinant versions of hirudin are also accessible, and hirudin-containing cream has been demonstrated to enhance mild-to-moderate bruise healing [27]. A number of published research examining the application of H. medicinalis in plastic and reconstructive surgery are listed in Table 3 [28–31]. Heparin, which binds to antithrombin and accelerates the inactivation of thrombin and factor Xa, is probably the most well-known anticoagulant. Heparin has certain surgical uses, despite being a surgeon's worst enemy because it encourages hemorrhage. In a rat model, local unfractionated heparin reduced arterial thrombus size as well as systemic heparin after microsurgery with less change to hemostatic parameters [32]. LMWH, which functions similarly to hirudin by reducing venous congestion, has been demonstrated to enhance free and regional flap survival when administered subcutaneously [33]. Additionally, LMWH has been demonstrated to lessen pain and inflammation and promote skin healing when applied topically to enhance the resorption of skin hematomas [34].

Tissue factor pathway inhibitors, which are naturally occurring protein inhibitors of factor X and the tissue factor-factor VII complex of the extrinsic pathway of coagulation, are among the most effective local anticoagulant drugs. Topical tissue factor pathway inhibitor therapy produced noticeably greater patency rates than heparin, hirudin, or control solutions in a rabbit model of near-total ear avulsion injury [35]. In addition to improving blood flow in the wound bed, its use in chronic wound care aided in the healing process [36].

Catheter-directed thrombolysis, which is less local than targeted, is becoming a more popular therapy option for deep vein thromboses and pulmonary emboli, two frequent and dreaded side effects of several procedures. Catheter-directed thrombolysis enables the administration of lower doses of anticoagulants by concentrating the medication to the clot, potentially lowering the risk of bleeding [37]. Although there is no difference in mortality, catheter-directed thrombolysis seems to carry a little increased risk of bleeding in intermediate-risk pulmonary emboli [38]. Catheter-directed thrombolysis may be less likely to cause bleeding and have a lower death rate than systemic thrombolysis for massive and sub-massive pulmonary emboli [39]. Similar to the majority of local coagulation treatments, further research is required in this area to more precisely determine which individuals and circumstances would benefit most from catheter-directed thrombolysis.

Drug Delivery

Adequate drug transport and targeting are the biggest obstacles to any local therapy, including coagulation manipulation; resolving these obstacles may enable greater value. By delivering strong thrombolytics to the targeted location, catheter-directed thrombolysis is setting the standard in this area.

Collagen sponges with biodegradable thrombin-loaded microspheres and gelatin sponges covered with active coagulation proteins are two examples of innovative targeted techniques; nevertheless, manufacturing and extending shelf life are still challenges [18]. It has been demonstrated that balloon catheters can carry heparin and argatroban to dogs' wounded iliac arteries, with large dosages of the medications preventing thrombus formation [40].

The transport of the medication through the skin, which serves as a barrier to both big and charged molecules, is a significant difficulty with topical therapy in particular. The stratum corneum, the skin's outermost layer, serves as the main obstacle to molecular penetration [41]. Although some absorption may also take place through follicles, the majority of molecules must slip across the lipid bilayers of nearby corneocytes in order to pass through the skin. Drug delivery is improved when the stratum corneum is removed because it is the main barrier to absorption [41]. However, the patient finds such a treatment uncomfortable, and the danger of infection would rise if the skin's natural defenses against the environment were removed.

Lipid-based vesicles, which surround medications in a bubble of variable lipophilicity that more readily penetrates the skin and may also shield the medications from degradation, are a more appealing alternative. Transdermal patches, gels, lotions, and injections are just a few of the ways that these vesicles can be administered [41]. Liposomes seem to enhance the transport of LMWH into the skin when applied to a region of local coagulation [35]. LMWH is a big, negatively charged molecule that has poor skin penetration; however, it seems to be more effective when attached to a positively charged liposome. There should be more alternatives for local coagulation treatment as topical medication delivery techniques advance.

Pros and Cons

Avoiding the systemic effects of impaired coagulation is the primary advantage of local treatment. Locally reversing anticoagulation during and after a minor surgery in an

anticoagulated patient may reduce the risk of deep vein thrombosis, stroke, or other thrombotic events that could happen if the patient's anticoagulant medication were stopped. Similar to this, if a patient just requires local anticoagulation for a skin graft or anastomosis, systemic anticoagulation bears the danger of possibly deadly hemorrhage, which might be avoided.In addition to medication administration and targeting, another challenge with local therapy is the paucity of evidence supporting its application; hemostats are a prominent exception, with the exception of a few specific situations. Currently, the circumstances where such therapy would be helpful are also mostly restricted to minor wounds, although there is room for their use in a broad range of surgical procedures. Even major procedures might be possible using local pro-coagulants, which are administered as a local anesthetic while preserving systemic anticoagulation. Local anticoagulants can help with superficial procedures by reducing venous congestion and promoting healing, but they may also improve blood flow during gastrointestinal anastomosis or increase the survival of vascular grafts.

CONCLUSIONS

Without the hazards of systemic medication, local pro- or anti-coagulation therapy shows significant promise in helping plastic surgery patients achieve the necessary hemostasis changes. Although the scope and usefulness of local therapy are currently rather restricted, there are plenty of chances for further study and advancement in the area. It is hoped that developments in topical medication delivery in particular will enable the growth of this profession, leading to better patient outcomes and treatment.

Funding

The Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery at the Mayo Clinic provided partial funding for this work.

Conflicts of Interest

No conflicts of interest are disclosed by the writers.

REFERENCES

1. Achneck, H.E.; Sileshi., B.; Jamiolkowski, R.M.; Albala, D.M.; Shapiro, M.L.; Lawson, J.H. A comprehensive review of topical hemostatic agents: Efficacy and recommendations for use. Ann. Surg. 2010, 251, 217–228.[CrossRef]

2. Robinson, M.; Healey, J.S.; Eikelboom, J.; Schulman, S.; Morillo, C.A.; Nair, G.M.; Baranchuk, A.; Ribas, S.;Evans, G.; Connolly, S.J.; et al. Postoperative low-molecular weight heparin bridging is associated with an increase in wound hematoma following surgery for pacemakers and implantable defibrillators. PACE 2009,32, 378–382. [CrossRef]

3. McDougall, C.J.; Gray, H.S.; Simpson, P.M.; Whitehouse, S.L.; Crawford, R.W.; Donnelly, W.J. Complications related to therapeutic anticoagulation in total hip arthroplasty. J. Arthroplasty 2013, 28, 187–192. [CrossRef][PubMed].

4. Guha, D.; Macdonald, R.L. Perioperative Management of Anticoagulation. Neurosurg. Clin. N. Am. 2017, 28,287–295. [CrossRef] [PubMed]

5. Bruckbauer, M.; Prexl, O.; Voelckel, W.; Ziegler, B.; Grottke, O.; Maegele, M.; Schöchl, H. Impact of Direct Oral Anticoagulants (DOACs) in Patients with Hip Fractures. J. Orthop. Trauma 2019, 33, e8–e13. [CrossRef][PubMed]

6. Imberti, D.; Ageno, W.; Manfredini, R.; Fabbian, F.; Salmi, R.; Duce, R.; Gallerani, M. Interventional treatment of venous thromboembolism: A review. Thromb. Res.2012, 129, 418–425. [CrossRef] [PubMed]

7. Utkewicz, M.D.; Brunetti, L.; Awad, N.I. Epistaxis complicated by rivaroxaban managed with topical tranexamic acid. Am. J. Emerg. Med. 2015, 33, e5–e7. [CrossRef]Medicina 2019, 55, 208 7 of 8

8. Zirk, M.; Zinser, M.; Buller, J.; Blinsky, V.; Dreiseidler, T.; Zöller, J.E.; Kreppel, M. Supportive topical tranexamic acid application for hemostasis in oral bleeding events–Retrospective cohort study of 542 patients. J. Craniomaxillofac. Surg. 2018, 46, 932–936. [CrossRef] [PubMed]

9. Baric, D.; Biocina, B.; Unic, D.; Sutlic, Z.; Rudez, I.; Vrca, V.B.; Brkic, K.; Ivkovic, M. Topical use of antifibrinolytic agents reduces postoperative bleeding: A double-blind, prospective, randomized study.Eur. J. Cardiothorac. Surg. 2007, 31, 366–371. [CrossRef]

10. Moharamzadeh, P.; Ojaghihaghighi, S.; Amjadi, M.; Rahmani, F.; Farjamnia, A. Effect of tranexamic acid on gross hematuria: A pilot randomized clinical trial study. Am. J. Emerg. Med. 2017, 35, 1922–1925. [CrossRef] [PubMed]

11. Craik, J.D.; Ei Shafie, S.A.; Kidd, A.G.; Twyman, R.S. Can local administration of tranexamic acid during total knee arthroplasty reduce blood loss and transfusion requirements in the absence of surgical drains?Eur.

J. Orthoped. Surg. Traumatol. 2014, 24, 379–384. [CrossRef]

12. Panteli, M.; Papakostidis, C.; Dahabreh, Z.; Giannoudis, P.V. Topical tranexamic acid in total knee replacement: A systematic review and meta-analysis. Knee 2013, 20, 300–309. [CrossRef] [PubMed]

13. Ker, K.; Beecher, D.; Roberts, I. Topical application of tranexamic acid for the reduction of bleeding. Cochrane Database Syst. Rev. 2013, Cd010562.

14. Howe, N.; Cherpelis, B. Obtaining rapid and effective hemostasis: Part, I. Update and review of topical hemostatic agents. J. Am. Acad. Dermatol. 2013, 69, e1–e17. [CrossRef] [PubMed]

15. Dalpiaz, O.; Neururer, R.; Bartsch, G.; Peschel, R. Haemostatic sealants in nephron-sparing surgery: What surgeons need to know. BJU Internat. 2008, 102, 1502–1508. [CrossRef]

16. Saif, R.; Jacob, M.; Robinson, S.; Amer, A.; Kei-Hui, D.; Sen, G.; Manas, D.; White, S. Use of fibrin-based sealants and gelatin-matrix hemostats in laparoscopic liver surgery. Surg. Laparosc. Endosc. Percutan. Tech.2011, 21, 131–141. [CrossRef] [PubMed]

17. Seyednejad, H.; Imani, M.; Jamieson, T.; Seifalian, A.M. Topical haemostatic agents. BJS 2008, 95, 1197–1225. [CrossRef]

18. Pannucci, C.J.; Fleming, K.I.; Agarwal, J.; Rockwell, W.B.; Prazak, A.M.; Momeni, A. The Impact of Onceversus Twice-Daily Enoxaparin Prophylaxis on Risk for Venous Thromboembolism and Clinically Relevant Bleeding. Plast. Reconstr. Surg. 2018, 142, 239–249. [CrossRef]

19. Cansancao, A.L.; Conde-Green, A.; David, J.A.; Cansancao, B.; Vidgal, R.A. Use of tranexamic acid to reduce blood less in liposuction. Plast. Reconstr. Surg. 2018, 141, 1132–1135. [CrossRef]

20. Kurnik, N.M.; Pflibsen, L.R.; Bristol, R.E.; Singh, D.J. Tranexamic acid reduces blood loss in craniosyntosis surgery. J. Craniofac. Surg. 2017, 28, 1325–1329. [CrossRef]

21. Arantes, G.C.; Pereira, R.M.R.; de Melo, D.B.; Alonso, N.; Duarte, M.D.C.M.B. Effectiveness of tranexamic acid for reducing intraoperative bleeding in palatoplasties: A randomized clinical trial. J. Craniomaxillofac.Surg. 2017, 45, 642–648. [CrossRef]

22. Bowman, E.N.; McCabe, M.P.; Cleveland, K.B. Effectiveness of thrombin-collagen and autologous platelet-rich plasma in total hip arthroplasty hemostatis: A prospective, randomized, controlled trial. J. Surg. Orthopaed.Adv. 2018, 27, 136–141.

23. Ofodile, F.A.; Sadana, M.K. The role of topical thrombin in skin grafting. J. Nat. Med. Assoc. 1991, 83, 416–418.

24. Rojas, S.; Pérez Del Caz, M.D.; Esteban Vico, J.R.; Villaverde, E.; Llinas, A.; Martínez, J.R.; Brage, C.; Valero, J.;González Rodríguez, A.; Garcia Barreiro, J.; et al. EHTIC study: Evaluation of a new hemostatic agent based on tissue factor in skin grafting procedures. Burns 2017, 43, 780–788. [CrossRef]

25. Welshhans, J.L.; Hom, D.B. Are leeches effective in local/regional skin flap salvage? Laryngoscope 2016, 126,1271–1272. [CrossRef] [PubMed]

26. Oliver, J.D.; DeLoughery, E.P. Leeches and Plastic Surgery in the Modern Era. Plast.Surg. Nurs. 2018, 38,88–89. [CrossRef] [PubMed]

27. Stamenova, P.K.; Marchetti, T.; Simeonov, I. Efficacy and safety of topical hirudin (Hirudex): A double-blind,placebo-controlled study. Eur. Rev. Med. Pharmacol. Sci. 2001, 5, 37–42.

28. Karino, M.; Okuma, S.; Akutsu, J.; Hattori, M.; Yoshino, A.; Kanno, T.; Sekine, J. A case of medical leech therapy for venous congestion following forearm flap reconstruction. Jpn. J. Cancer Chem. 2018, 45, 2135–2137.

29. Butt, A.M.; Ismail, A.; Lawson-Smith, M.; Shahid, M.; Webb, J.; Chester, D.L. Leech therapy for the treatment of venous congestion in flaps, digital replants and revascularizations–A two year review from a regional centre. J. Ayub Med. Coll. Abbottabad 2016, 28, 219–223. [PubMed]Medicina 2019, 55, 208 8 of 8

30. Moffat, A.D.; Weaver, L.K.; Tettelbach, W.H. Compromised breast flap treated with leech therapy, hyperbaric oxygen, pentoxifylline and topical nitroglycerin: A case report. Undersea Hyperb. Med. Soc. 2015, 42, 281–284.

31. Grobe, A.; Michalsen, A.; Hanken, H.; Schmelzle, R.; Heiland, M.; Blessmann, M. Leech therapy in reconstructive maxillofacial surgery. J. Oral Maxillofac.

Surg. 2012, 70, 221–227. [CrossRef] [PubMed]

32. Andresen, D.M.; Barker, J.H.; Hjortdal, V.E. Local heparin is superior to systemic heparin in preventing arterial thrombosis. Microsurgery 2002, 22, 265–272. [CrossRef]

33. Perez, M.; Sancho, J.; Ferrer, C.E.; Garcia, O.; Barret, J.P. Management of flap venous congestion: The role of heparin local subcutaneous injection. J. Plast. Reconstr. Aesthet. Surg. 2014, 67, 48–55. [CrossRef]

34. Song, Y.K.; Kim, C.K. Topical delivery of low-molecular-weight heparin with surface-charged flexible liposomes. Biomaterials 2006, 27, 271–280. [CrossRef]

35. Lantieri, L.A.; Ozbek, M.R.; Deune, E.G.; Ornberg, R.L.; Brown, D.M.; Chung, S.H.; Wun, T.C.; Cooley, B.C.;Khouri, R.K. Prevention of microvascular thrombosis by topical application of recombinant tissue factor pathway inhibitor. Plast. Reconstr. Surg. 1996, 97, 587–594. [CrossRef]

36. Saba, A.A.; Freedman, B.M.; Gaffield, J.W.; Mackay, D.R.; Ehrlich, H.P. Topical platelet-derived growth factor enhances wound closure in the absence of wound contraction: An experimental and clinical study.Ann. Plast. Surg. 2002, 49, 62–66. [CrossRef] [PubMed]

37. Furfaro, D.; Stephens, R.S.; Streiff, M.B.; Brower, R. Catheter-directed Thrombolysis for Intermediate-Risk Pulmonary Embolism. Ann. Am. Thorac. Soc. 2018, 15, 134–144. [CrossRef]

38. Pollak, J.S. Catheter-Based Therapies for Pulmonary Emboli. Clin. Chest Med. 2018, 39, 651–658. [CrossRef] [PubMed]

39. Tomaru, T.; Kobayakawa, N.; Onitake, A.; Nakamura, F.; Morita, T.; Uchida, Y. Local antithrombotic therapy using a novel porous balloon catheter. Jpn. Heart J. 2000, 41, 87–95. [CrossRef] [PubMed]

40. Akhtar, N. Vesicles: A recently developed novel carrier for enhanced topical drug delivery. Curr. Drug Deliv.2014, 11, 87–97. [CrossRef]

41. Yu, Y.; Gool, E.; Berckmans, R.J.; Coumans, F.A.W.; Barendrecht, A.D.; Maas, C.; van der Wel, N.N.;Altevogt, P.; Sturk, A.; Nieuwland, R. Extracellular vesicles from human saliva promote hemostasis by delivering coagulant tissue factor to activated platelets. J. Thromb. Haemost. 2018, 16, 1153–1163. [CrossRef][PubMed]