Chapter

An Overview of Biosurgical Hemostats in Burn Surgery: Overlooked but Not Forgotten

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Abstract

Management of coagulopathy is a crucial aspect of care for hospitalized burn patients, especially intraoperatively during burn surgery. It is estimated that approximately one-third of blood products utilized during an average burn injury hospitalization are administered intraoperatively during excision of the primary wound and donor sites. Moreover, transfusion of blood products alone during burn surgery does not constitute an adequate method to achieve hemostasis. Biosurgical hemostats should be utilized as adjunctive therapeutic agents to minimize blood loss. Potential options include topical or tumescent epinephrine, fibrin sealants, calcium alginate, platelet rich plasma, topical or intravenous tranexamic acid, NuStat®, recombinant tissue factor, hydrogen peroxide, and oxidized regenerated cellulose. The most abundant clinical evidence is available for the use of topical and tumescent epinephrine and fibrin sealants to achieve hemostasis during burn surgery. The epinephrine technique has been shown to be generally safe, without clinically significant cardiovascular effects from systemic absorption. For fibrin sealants (FS), it is important that surgeons recognize that not all FS are the same, and that different formulations or products may behave in a slightly different fashion. For the other available hemostatic available hemostatic options, further research is needed to fully elucidate their potential roles and utility in minimizing blood loss during burn surgery.

Keywords: biosurgical hemostats, fibrin, hemorrhage control, surgical bleeding, thrombin

1. Introduction

Management of blood loss throughout a burn patient's hospital course is a critical part of global care of those with thermal injuries. Patients suffering major (20–59% Total Body Surface Area (TBSA)) or massive (>60% TBSA) burns experience coagulopathic complications similar to those reported in major trauma or septic shock [1, 2] – a reflection of the systemic impact of such massive injury burden. Burn-related endothelial injury causes the release of tissue factor from a proportionately large surface area, contributing to the generation and consumption of thrombin, fibrin, and other coagulations factors [3–7]. Platelet activation and consumption leads to thrombocytopenia that nadirs between 3 and 5 days

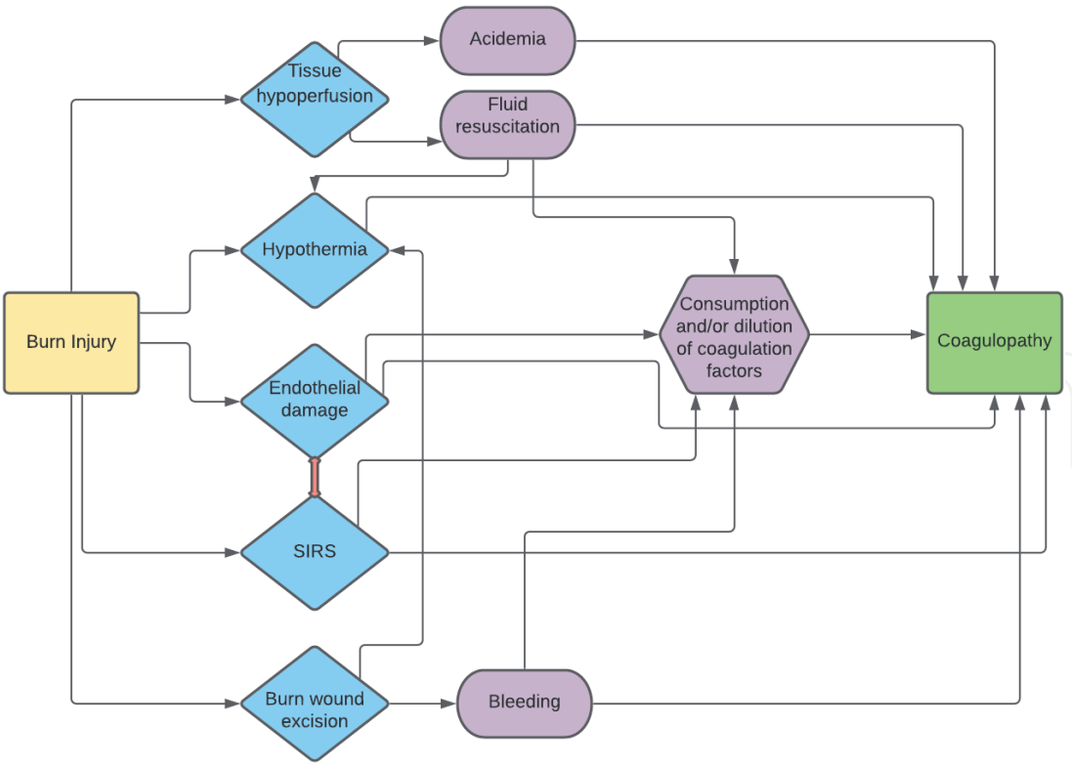

Figure 1.
Schematic presentation of pathophysiologic mechanisms affecting coagulation in patients who sustained severe burn injuries. Legend: SIRS = systemic inflammatory response syndrome. Schematic adopted from Glas, et al. 2016.

Biosurgical hemostat	Application method(s)	Utility in burn surgery
Epinephrine	Topical or tumescent; a typical solution is prepared as 1:1,000,000 epinephrine in normal saline, which constitutes a dilution of 1 mL of 1:1,000 epinephrine into 1 L of normal saline; lidocaine may be added	Long utilized in burn surgery for obtaining hemostasis, decreasing intraoperative blood loss, and substantially reducing rates of blood transfusions; generally safe, without clinically significant cardiovascular effects due to systemic absorption
Fibrin sealants (FS)	A fine spray to create a thin layer resulting in approximately 0.05–0.06 mL/cm^2 material distribution	Benefits include effective graft fixation, decreased hematoma and seroma formation, and shorter operative times; graft-take may be enhanced by the fibrin clot scaffold even when wound bed is infected; can also be used on the donor site to improve the time to hemostasis; excellent safety profile; important that surgeons recognize that not all FS are the same - different formulations or products may behave in a slightly different way
Calcium alginate	Donor-site dressing	In comparison to epinephrine and fibrin-based products, not as effective as hemostatic agent; as donor-site dressing, has been observed to provide superior hemostasis for skin-graft donor sites when compared to plain sterile gauze or paraffin gauze dressings; risk of dermal calcifications
Platelet rich plasma (PRP)	Topical application	Studies on use in burn surgery are scarce; while platelets in burn patients appear to have normal functionality, further studies focusing on the quantitative hemostatic ability of PRP in the setting of thermal injury are needed

Biosurgical hemostat	Application method(s)	Utility in burn surgery
Tranexamic acid (TXA)	Administered topically or intravenously	Few studies exist evaluating the use of TXA in burn patients; however, overall available data is promising; one study demonstrated no difference in mortality or thromboembolic disease, and some improvement of graft survival in the TXA group
NuStat®	Topical dressing	While one RCT showed clinical equivalency of NuStat® compared to historic standard of care, the overall cost of wound care was significantly lower using NuStat®; further studies are needed
Recombinant tissue factor	Topical application	2017 phase II randomized parallel double-blinded study showed promising results without causing adverse events
Hydrogen peroxide	Topical (3% soak applied to the tangential excision site)	Investigators reported no complications related to corrosive damage or lipid peroxidation; needs to be sufficiently irrigated from the wound bed prior to application of the split-thickness skin graft
Oxidized regenerated cellulose (ORC)	Topical application	Limited literature exists on the use of ORC in burn surgery

Abbreviations: RCT = randomized controlled trial.

Table 1.
Summary of biosurgical hemostats in burn surgery.

after injury [8]. In addition, there are important secondary factors that contribute to coagulopathy including hemodilution from resuscitation, hypothermia, and acidosis (**Figure 1**) [1, 9, 10].

In general, greater burn size correlates with increased duration of surgery, number of required operative procedures, and need for blood transfusion [11, 12]. For every 1% of total body surface excised, including surface area of skin graft donor site, a patient can experience as much as 10% loss of their calculated blood volume [13]. Since intraoperative blood loss from both excision of primary wound and donor sites can account for about one-third of blood products administered during an average burn injury hospitalization, minimizing blood loss in the operating room (OR) is vital for minimizing overall transfusion requirements [14, 15]. Blood product resuscitation alone is not sufficient for hemostasis and carries significant associated risks, which opens up an important opportunity for the consideration of topical hemostatic adjuncts in the overall blood management of the burned patient [8, 16, 17]. This chapter focuses on the roles of biosurgical hemostats as they pertain to the transfusion reduction strategy in the setting of thermal injury (**Table 1**).

2. Overview of biosurgical hemostats in burn surgery

There are different types of available biosurgical hemostats, as outlined in **Table 1**. For the purposes of the current chapter, it is important to recognize that a gap exists between provider awareness of this class of adjunctive hemostatic agents and their actual clinical application. Arguably, the latter is much more extensive than one might initially realize or admit. It is therefore important to bring

biosurgical hemostats into focus as increasing emphasis is being placed on reduction in unnecessary blood/blood product transfusions across burn centers and critical care units.

3. Epinephrine

Epinephrine has long been used in burn surgery for obtaining hemostasis at both the wound excision site and donor site, decreasing intraoperative blood loss per area excised, and substantially reducing rates of blood transfusions (in some cases by as much as 50%) [18, 19]. When applying epinephrine to any operative site, a pre-made solution can be applied topically or injected as a tumescent solution [20]. Although exact concentrations and application modality may vary between institutions, a typical solution is prepared as 1:1,000,000 epinephrine in normal saline, which constitutes a dilution of 1 mL of 1:1,000 epinephrine into 1 L of normal saline [21, 22]. Addition of lidocaine to the above solution has also been described to help decrease postoperative pain, duration of surgery, general anesthesia, and potentially accelerate re-epithelialization of the donor site [23].

The tumescent technique significantly decreases intraoperative blood loss and has been shown to be generally safe, without clinically significant cardiovascular effects due to systemic absorption [19, 24, 25]. Typically, the diluted epinephrine is injected subcutaneously with either a long 18-gauge spinal needle or a blunt liposuction cannula with injector. When properly performed, the subcutaneous injection under the desired area causes the area to become firm (tumescent) and the overlying skin to blanch. Whether used at the donor site or the eschar excision site, the firm vasoconstricted surfaces tend to be better prepared for subsequent excision [18], both in terms of technical ease of the operation and decreased blood loss.

The same diluted epinephrine solution can also be used as a topical hemostatic agent at both the donor and wound excision sites. This is most commonly performed by soaking non-adherent gauze, such as specially coated cotton pads, in the epinephrine solution and then applying the pads directly to the freshly excised area. It should be noted that this is performed as a hemostatic maneuver only after any major or brisk surgical bleeding has first been controlled. The epinephrine solution soaked non-adherent gauze can be secured in place by lightly wrapping it with a bandage roll. Typically, these are allowed to stay in place for 10–20 minutes to allow for hemostasis to occur. Careful removal is important for preventing disruption of the newly formed clot. If any residual oozing is present, new gauze can be re-applied until adequate hemostasis is achieved. In the absence of non-adherent gauze, the epinephrine solution can alternatively be applied topically as a spray or gelatinous mixture (e.g., using water-based lubricant as an application medium) [26, 27]. Other vasoactive hemostatic agents utilized in burn surgery include terlipressin and phenylephrine, with associated literature descriptions of reportedly positive effects in terms of blood loss reduction and other operative characteristics [22, 28–32].

4. Fibrin sealants

Fibrin is the hemostatic product of thrombin-mediated cleavage of fibrinogen [33]. Understanding the relationship between fibrinogen and thrombin has allowed for pharmaceutical companies to develop a variety of fibrin-based products, including those designed for hemostatic applications [34, 35]. Although fibrin sealants (FS) have been used since 1909, with reported use on skin grafts as early as 1944,

the first formal U.S. Food and Drug Administration (FDA) approval of a FS for use with skin grafts – including those performed in burn surgery – did not come until 2008 (Artiss®, Baxter, Westlake Village, CA) [36]. Other similar products that fall within the class of "fibrin sealants" have been effectively used in the setting of skin grafts, with similar results [37–39].

Surgeons must recognize that not all FS are the same, and that different formulations or products may not always produce identical results. There are important differences across available products that one must understand in order to optimize clinical outcomes for the burn patient. The products available provide a range of concentration ratios of fibrinogen and thrombin solutions, which are combined and "mixed" during application. For example, Artiss® (Baxter, Westlake Village, CA) contains a ratio of 67–106 mg/mL fibrinogen to 2.5–6.5 units/mL thrombin [40], whereas Tisseel® (Baxter; Deerfield, IL, US) contains a ratio of 67–106 mg/mL fibrinogen to 400–625 units/mL thrombin [41]. Although both products contain similar amount of fibrinogen, the latter has 100-fold more thrombin. Higher concentrations of thrombin will speed up the polymerization process, decreasing clotting and sealing time. With regards to the aforementioned products, increasing the thrombin concentration by 100-fold effectively shortens the polymerization time from minutes to seconds. This difference is so robust that Tisseel® is FDA approved as a hemostatic agent, while Artiss® is not. When hemostasis is less of a concern and the intended use is primarily for sealant/fixation purposes, having a slower polymerization time is better suited for manipulating a skin graft into the desired location and orientation. Similar therapeutic outcomes have been reported using a variety of component concentrations, within a pre-specified range [42].

Benefits of using FS in burn surgery include effective graft fixation, decreased hematoma and seroma formation, and shorter operative times [42–44]. There may also be an added benefit in terms of improved postoperative pain, especially when compared to alternative skin graft fixation modalities such as staples or sutures [36, 45]. When applied correctly, ideally as a fine spray to create a thin layer that is only about 0.05–0.06 mL/cm^2 thick, the graft-take may be enhanced by the fibrin clot scaffold which promotes migration of fibroblasts, epithelial cells, and keratinocytes [42, 46]. Even when the wound bed is infected, FS use may improve graft take by reinforcing graft adherence to the wound bed [47]. FS can also be used on the donor site to improve the time to hemostasis [48].

Taken collectively, FS have an excellent overall safety profile [44, 49, 50]. Historically, complications from exposure to bovine-derived thrombin have been reported, including the subsequent development of anti-bovine thrombin antibodies. Associated morbidity included bleeding, thromboembolisms, hypersensitivity reactions, and prolonged activated partial thromboplastin times (aPTT) [51]. However, most currently available FS are made with recombinant thrombin, which is far less immunogenic [52]. In fact, a meta-analysis of 10 clinical trials showed that at 1 month from surgery, less than 1% of patients exposed to recombinant thrombin will develop antibodies against it [53]. Furthermore, unlike anti-bovine thrombin antibodies, anti-recombinant thrombin antibodies do not neutralize activity of native human thrombin [53, 54]. Lastly, when compared to thrombin alone, FS appear to provide significantly more effective (and generally faster) hemostasis [55].

5. Calcium alginate

The use of calcium alginate (CA) to help control hemorrhage and improve graft take has been described in burn surgery for quite some time [56]. In comparison

to epinephrine applications and fibrin-based products, CA is not as effective as a hemostatic agent [57]. However, as a donor site dressing CA has been observed to provide superior hemostasis for skin-graft harvesting sites when compared to plain sterile gauze or paraffin gauze dressings [58–60]. The alginate dressing also has several other potential advantages, including excellent absorptive properties, biodegradability, ease of postoperative maintenance/wound care, improved healing time, as well as notably lower risk of infection [61]. Still, CA donor site dressings are not without potential complications, including reported instances of dermal calcifications [62].

6. Platelet rich plasma

Investigational studies on the use of platelet-rich plasma (PRP) in burn surgery are scarce overall, with further paucity of data on PRP's hemostatic properties [63, 64]. Nevertheless, there is growing evidence that supports the use of PRP as a promoter of wound bed hemostasis prior to split thickness skin graft (STSG) placement, with the intent of decreasing the rates of hematoma formation under a STSG [65, 66]. Although PRP may have additional benefits, including pain reduction, improved skin graft adherence, and decreased skin graft healing times [67, 68], these findings have not been consistent among all available clinical reports [69]. One case–control study comparing PRP extracted from burn patients to that from matched healthy volunteers demonstrated similar platelet counts and levels of growth factors [70]. It is important to mention that PRP (and its various subcomponents) may also play a role as a regenerative medicine approach due to its rich growth factor content and non-immunogenic properties [71]. For example, this may be important in promoting skin graft donor site healing. Finally, while the platelets in burn patients appear to have normal functionality, further studies focusing on determining the quantitative hemostatic ability of PRP in the setting of thermal injury are needed to fully understand its potential [72].

7. Tranexamic acid

Tranexamic acid (TXA) is an antifibrinolytic agent, whose use topically and intravenously has been shown to decrease traumatic and perioperative blood loss, reducing the need for blood transfusions in multiple surgical applications [73–76]. Despite the promising overall results from the trauma literature, there are very few studies evaluating TXA use in burn patients [77, 78]. Overall, available data show promise; however, there is also evidence of cytotoxicity in the context of wound re-epithelialization, especially with prolonged use/exposure [79]. One retrospective cohort study analyzing the effect of intraoperative intravenous TXA administration in major burn patients (>20% TBSA) undergoing primary wound excision and grafting found that intravenous TXA administration significantly decreased the amount of blood administered during and up to 24 hours after the index operation. The series of patients included in the study received a TXA infusion 15 minutes prior to surgical incision as a loading dose of 10 mg/kg given over 5 minutes, followed by continuous infusion of 1 mg/kg/h until the end of the procedure. Multivariate analysis revealed TXA to be protective against transfusion (Odds Ratio of 0.2) [77]. Secondary findings revealed no difference in mortality or thromboembolic disease, and some improvement of graft survival in the TXA group [77]. A prospective randomized trial of single dose intravenous TXA (15 mg/kg diluted to 25 ml with isotonic saline over 10 min) prior to wound excision in 50 adult patients

with >20% TBSA burns found that the patients who received TXA experienced, on average, about 400 mL less intraoperative blood loss and required significantly less colloid replacement in comparison to those who received an equal volume of only isotonic saline before induction of general anesthesia [78]. Further confirmatory prospective clinical trials will be helpful in clarifying intravenous TXA's place in burn surgery blood management protocols. In terms of TXA use as a topical agent, one case report concluded that such application of TXA, in addition to standard methods, is a safe and effective way of controlling bleeding during burn surgery [80]. Future well-designed, adequately powered comparative studies analyzing blood loss, graft survival, epithelialization rate, and infections are warranted.

8. NuStat topical hemostat: clinical equivalency with lower cost

One prospective randomized control trial compared NuStat® (a product containing patented Hemafiber Technology™ by Beeken Miomedical, Stoughton, MA) to the institutional standard of care for controlling bleeding at both burn and donor sites. Briefly, NuStat® is a two-component product consisting of continuous filament silica and bamboo cellulose, a combination that when used together promotes hemostasis by activating the clotting cascade. Though potentially underpowered, hemostasis provided by the NuStat® dressing was found to be at least comparable to other currently utilized approaches (epinephrine- and thrombin-soaked non-adherent dressings, saline-soaked laparotomy sponges, and elastic bandage wraps) [81]. While the reported results show clinical equivalency of NuStat® compared to historic standard of care, the overall cost of wound care was significantly lower using the novel hemostatic dressing [81]. It is unlikely that these findings alone will change operative practices by most burn surgeons; however, the study does provide an important new treatment option in an area of clinical care that has seen little progress during the past few decades.

9. Recombinant tissue factor

As an initiator of the coagulation cascade, tissue factor is both an intriguing and a promising candidate for use as a topical hemostatic agent. Based on compelling preclinical and clinical data [82–84], a phase II randomized parallel double-blinded study was published in 2017 comparing an investigational topical hemostatic agent "TT-173" that is based on recombinant tissue factor (rTF) to a placebo, for establishing hemostasis at the donor site in burn surgery. The investigational agent "TT-173" reportedly decreased bleeding time from 7 minutes to 3 minutes without causing adverse events, systemic absorption, immunogenic reaction, or perturbance of donor site healing [85]. Further research into rTF as a potential new adjunct in operative hemostasis in burn surgery is clearly warranted based on the above reports.

10. Hydrogen peroxide

Hydrogen peroxide used as a 3% soak applied to the tangential excision site has been reported as a potentially effective and safe means of achieving hemostasis in a burn patient with platelet dysfunction. In one published experience, the investigators reported no apparent morbidity related to corrosive damage or lipid peroxidation, which is a known complication associated with higher concentrations

of hydrogen peroxide. With the hydrogen peroxide sufficiently irrigated from the wound bed prior to application of the STSG, the investigators saw excellent graft take [86]. Other reported uses of hydrogen peroxide as a topical hemostat, either alone or in combination with another agent, have been described in maxillofacial and otolaryngology applications [87, 88]. Benefits of the above approach included less blood loss, shorter procedure times, and fewer surgical ties used [87, 88].

11. Oxidized regenerated cellulose

There is some evidence to suggest that the application of oxidized regenerated cellulose (ORC) products to skin graft donor sites may significantly shorten wound healing and recovery time [89]. The difference between ORC-treated donor sites and fine mesh gauze treated with nitrofurazone (FMN) was substantial, with semiclosed ORC dressing group achieving healing endpoint in 6.5 days (compared to 9.9 days for FMN) and closed ORC dressing group achieving healing in 5.4 days (compared to 8.4 days for FMN) [89]. With limited literature on the use of ORC-based products in burn surgery, further research is warranted to determine safety and efficacy of this topical hemostatic approach.

12. Granular zeolite: a topical hemostatic material capable of causing burns

Although this chapter focuses on topical hemostats in burn surgery, one well-known and highly effective topical hemostat warrants a special mention as a risk-factor for thermal injury [90]. Granular zeolite (GZ, also known as QuikClot®) is a material derived from lava rocks and introduced for field use in the early 2000's [91]. The material is effective via a complex mechanism that involves an exothermic reaction coupled with absorption of water and the ability to concentrate coagulation factors [91–93]. There are multiple reports of GZ causing both cutaneous and internal burns due to excessive heat generation [90, 94, 95]. In fact, the original formulation was deemed sufficiently dangerous – able to reach temperatures up to 65°C (149°F) and cause burns to the operating surgeon – that it was discontinued in 2008 and replaced with a modified QuikClot® ACS and kaolin-containing QuikClot Combat Gauze formulation [91]. Based on the above observations, GZ should not be utilized in burn surgery, at least in its currently available formulation(s).

13. Conclusions

Although their use is certainly not novel in burn surgery, the awareness of biosurgical hemostats appears to be far from adequate. Given the above, the goal of this chapter was to both review published applications of biosurgicals in burn surgery and to increase awareness of these potentially valuable adjuncts. Especially important in this context is the emergence of new research involving novel topical hemostatic agents, such as the Hemafiber Technology™ and recombinant tissue factor. Similar to other surgical specialties, the management of thermal injuries focuses increasingly on optimizing care protocols, maximizing outcomes, and minimizing the need for potentially harmful and costly interventions such as blood and blood product transfusions. The authors believe that the current chapter provides a solid foundation of relevant clinical knowledge in the emerging area of biosurgical hemostasis in burn surgery.

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References

[1] Glas GJ, Levi M, Schultz MJ. *Coagulopathy and its management in patients with severe burns*. J Thromb Haemost. 2016;**14**(5):865-874

[2] Palmieri, T.L., et al., *Restrictive Transfusion Strategy Is More Effective in Massive Burns: Results of the TRIBE Multicenter Prospective Randomized Trial.* Mil Med, 2019. **184**(Suppl 1): p. 11-15.

[3] Kowal-Vern, A., et al., *The effect of burn wound size on hemostasis: a correlation of the hemostatic changes to the clinical state.* J Trauma, 1992. **33**(1): p. 50-6; discussion 56-7.

[4] Lippi, G., L. Ippolito, and G. Cervellin, *Disseminated intravascular coagulation in burn injury.* Semin Thromb Hemost, 2010. **36**(4): p. 429-36.

[5] Mitra, B., et al., *Early coagulopathy of major burns.* Injury, 2013. **44**(1): p. 40-3.

[6] Niemi, T., et al., *Haemostatic disturbances in burned patients during early excision and skin grafting.* Blood Coagul Fibrinolysis, 1998. **9**(1): p. 19-28.

[7] Gibran, N.S. and D.M. Heimbach, *Current status of burn wound pathophysiology.* Clinics in plastic surgery, 2000. **27**(1): p. 11-21.

[8] Pidcoke, H.F., et al., *Acute blood loss during burn and soft tissue excisions: An observational study of blood product resuscitation practices and focused review.* J Trauma Acute Care Surg, 2015. **78**(6 Suppl 1): p. S39-47.

[9] Lavrentieva, A., et al., *Monitoring and treatment of coagulation abnormalities in burn patients. an international survey on current practices.* Ann Burns Fire Disasters, 2016. **29**(3): p. 172-177.

[10] Sherren, P., et al., *Lethal triad in severe burns.* Burns, 2014. **40**(8): p. 1492-1496.

[11] Koljonen, V., et al., *The Use of Blood Products in Adult Patients with Burns.* Scand J Surg, 2016. **105**(3): p. 178-85.

[12] Fuzaylov, G., et al., *Improving burn care and preventing burns by establishing a burn database in Ukraine.* Burns, 2014. **40**(5): p. 1007-1012.

[13] Snelling, C.F. and K. Shaw, *The effect of topical epinephrine hydrochloride in saline on blood loss following tangential excision of burn wounds.* Plast Reconstr Surg, 1983. **72**(6): p. 830-6.

[14] Palmieri, T.L., et al., *Effect of blood transfusion on outcome after major burn injury: a multicenter study.* Crit Care Med, 2006. **34**(6): p. 1602-7.

[15] Sterling, J.P. and D.M. Heimbach, *Hemostasis in burn surgery--a review.* Burns, 2011. **37**(4): p. 559-65.

[16] Graves, T.A., et al., *Relationship of transfusion and infection in a burn population.* J Trauma, 1989. **29**(7): p. 948-52; discussion 952-4.

[17] Welling, H., et al., *Management of bleeding in major burn surgery.* Burns, 2019. **45**(4): p. 755-762.

[18] Gomez, M., S. Logsetty, and J.S. Fish, *Reduced blood loss during burn surgery.* J Burn Care Rehabil, 2001. **22**(2): p. 111-7.

[19] Robertson, R.D., et al., *The tumescent technique to significantly reduce blood loss during burn surgery.* Burns, 2001. **27**(8): p. 835-8.

[20] Robertson, R.D., et al., *The tumescent technique to significantly reduce blood loss during burn surgery.* Burns, 2001. **27**(8): p. 835-838.

[21] Klein, J.A., *The tumescent technique for lipo-suction surgery.* The American Journal of Cosmetic Surgery, 1987. **4**(4): p. 263-267.

[22] Sterling, J.P. and D.M. Heimbach, *Hemostasis in burn surgery—a review.* Burns, 2011. **37**(4): p. 559-565.

[23] Gacto, P., et al., *Haemostatic effects of adrenaline–lidocaine subcutaneous infiltration at donor sites.* Burns, 2009. **35**(3): p. 343-347.

[24] Cartotto, R., et al., *Minimizing blood loss in burn surgery.* J Trauma, 2000. **49**(6): p. 1034-9.

[25] Fujita, K., et al., *The practical procedure of tumescent technique in burn surgery for excision of burn eschar.* J Burn Care Res, 2008. **29**(6): p. 924-6.

[26] Netscher, D.T., et al., *Hemostasis at skin graft donor sites: evaluation of topical agents.* Ann Plast Surg, 1996. **36**(1): p. 7-10.

[27] Smoot, E.C., 3rd and J.O. Kucan, *Epinephrine spray-bottle technique for harvesting skin grafts.* J Burn Care Rehabil, 1992. **13**(2 Pt 1): p. 221-2.

[28] Groenewold, M.D., A.J. Gribnau, and D.T. Ubbink, *Topical haemostatic agents for skin wounds: a systematic review.* BMC surgery, 2011. **11**(1): p. 15.

[29] Mitchell, R.T., et al., *Phenylephrine tumescence in split-thickness skin graft donor sites in surgery for burn injury—a concentration finding study.* Journal of burn care & research, 2011. **32**(1): p. 129-134.

[30] Allorto, N., D. Bishop, and R. Rodseth, *Vasoconstrictor clysis in burn surgery and its impact on outcomes: systematic review and meta-analysis.* Burns, 2015. **41**(6): p. 1140-1146.

[31] Gomez, M., S. Logsetty, and J. Fish, *Reduced blood loss during burn surgery.* The Journal of burn care & rehabilitation, 2001. **22**(2): p. 111-117.

[32] Lawrence, M.B., et al., *Improved Intraoperative Hemodynamics in Burn Surgery: An Institutional Change to Pediatric-Specific Hemostasis Solutions.* Journal of Burn Care & Research, 2020. **41**(2): p. 289-292.

[33] Henley, J. and J.D. Brewer, *Newer hemostatic agents used in the practice of dermatologic surgery.* Dermatol Res Pract, 2013. **2013**: p. 279289.

[34] Seyednejad, H., et al., *Topical haemostatic agents.* British Journal of Surgery, 2008. **95**(10): p. 1197-1225.

[35] Firstenberg, M.S., J.M. Hanna, and S.P. Stawicki, *The Role of Biosurgical Hemostatic Sealants in Cardiac Surgery*, in *Contemporary Applications of Biologic Hemostatic Agents across Surgical Specialties*. 2020, IntechOpen.

[36] Van Kerckhoven, L., et al., *Artiss(R) and burn treatment: a retrospective analysis contributing to current clinical practice.* Int J Burns Trauma, 2020. **10**(2): p. 21-27.

[37] Vibe, P. and J. Pless, *A new method of skin graft adhesion.* Scand J Plast Reconstr Surg, 1983. **17**(3): p. 263-4.

[38] Paw, E., et al., *Effectiveness of fibrin glue in skin graft survival: A systematic review and meta-analysis.* Annals of Medicine and Surgery, 2020.

[39] Grunzweig, K.A., M. Ascha, and A.R. Kumar, *Fibrin tissue sealant and minor skin grafts in burn surgery: A systematic review and meta-analysis.* Journal of Plastic, Reconstructive & Aesthetic Surgery, 2019. **72**(6): p. 871-883.

[40] Boccara, D., et al., *Artiss Sealant®: an alternative to stapling skin grafts on the dorsal side of the hand and fingers.* Journal of Burn Care & Research, 2017. **38**(5): p. 283-289.

[41] Eriksen, J., et al., *Laparoscopic intraperitoneal mesh fixation with fibrin sealant (Tisseel®) vs. titanium tacks: a*

randomised controlled experimental study in pigs. Hernia, 2008. **12**(5): p. 483-491.

[42] Han, H.H., et al., *Fixation of split-thickness skin graft using fast-clotting fibrin glue containing undiluted high-concentration thrombin or sutures: a comparison study.* Springerplus, 2016. **5**(1): p. 1902.

[43] Mullens, C.L., et al., *To Glue or Not to Glue? Analysis of Fibrin Glue for Split-thickness Skin Graft Fixation.* Plast Reconstr Surg Glob Open, 2019. **7**(5): p. e2187.

[44] Reddy, K.S., et al., *Effectiveness of Fibrin Glue in Adherence of Skin Graft.* J Cutan Aesthet Surg, 2017. **10**(2): p. 72-75.

[45] Healy, C., et al., *Prospective randomized controlled trial: fibrin sealant reduces split skin graft donor-site pain.* Plast Reconstr Surg, 2013. **132**(1): p. 139e-46e.

[46] Mittermayr, R., et al., *Skin graft fixation by slow clotting fibrin sealant applied as a thin layer.* Burns, 2006. **32**(3): p. 305-11.

[47] Jabs, A.D., Jr., et al., *The effect of fibrin glue on skin grafts in infected sites.* Plast Reconstr Surg, 1992. **89**(2): p. 268-71.

[48] Nervi, C., et al., *A multicenter clinical trial to evaluate the topical hemostatic efficacy of fibrin sealant in burn patients.* J Burn Care Rehabil, 2001. **22**(2): p. 99-103.

[49] Greenhalgh, D.G., et al., *Multicenter trial to evaluate the safety and potential efficacy of pooled human fibrin sealant for the treatment of burn wounds.* J Trauma, 1999. **46**(3): p. 433-40.

[50] Mandell, S.P. and N.S. Gibran, *Fibrin sealants: surgical hemostat, sealant and adhesive.* Expert Opin Biol Ther, 2014. **14**(6): p. 821-30.

[51] Chapman, W.C., et al., *A phase 3, randomized, double-blind comparative study of the efficacy and safety of topical recombinant human thrombin and bovine thrombin in surgical hemostasis.* Journal of the American College of Surgeons, 2007. **205**(2): p. 256-265.

[52] Ham, S.W., W.K. Lew, and F.A. Weaver, *Thrombin use in surgery: an evidence-based review of its clinical use.* J Blood Med, 2010. **1**: p. 135-42.

[53] Singla, N.K., et al., *Safety and immunogenicity of recombinant human thrombin: a pooled analysis of results from 10 clinical trials.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2012. **32**(11): p. 998-1005.

[54] Zhu, W., et al., *Thrombin induces endothelial arginase through AP-1 activation.* Am J Physiol Cell Physiol, 2010. **298**(4): p. C952-60.

[55] Drake, D.B. and L.G. Wong, *Hemostatic effect of Vivostat patient-derived fibrin sealant on split-thickness skin graft donor sites.* Ann Plast Surg, 2003. **50**(4): p. 367-72.

[56] Kneafsey, B., M. O'Shaughnessy, and K. Condon, *The use of calcium alginate dressings in deep hand burns.* Burns, 1996. **22**(1): p. 40-43.

[57] Groenewold, M.D., A.J. Gribnau, and D.T. Ubbink, *Topical haemostatic agents for skin wounds: a systematic review.* BMC Surg, 2011. **11**: p. 15.

[58] Basse, P., E. Siim, and M. Lohmann, *Treatment of donor sites--calcium alginate versus paraffin gauze.* Acta Chir Plast, 1992. **34**(2): p. 92-8.

[59] Groves, A.R. and J.C. Lawrence, *Alginate dressing as a donor site haemostat.* Ann R Coll Surg Engl, 1986. **68**(1): p. 27-8.

[60] Steenfos, H.H. and M.S. Agren, *A fibre-free alginate dressing in the treatment of split thickness skin graft donor sites.* J Eur Acad Dermatol Venereol, 1998. **11**(3): p. 252-6.

[61] Brenner, M., et al., *Management of pediatric skin-graft donor sites: a randomized controlled trial of three wound care products.* J Burn Care Res, 2015. **36**(1): p. 159-66.

[62] Davey, R.B., A. Sparnon, and R.W. Byard, *Unusual donor site reactions to calcium alginate dressings.* Burns, 2000. **26**(4): p. 393-398.

[63] Marck, R.E., E. Middelkoop, and R.S. Breederveld, *Considerations on the use of platelet-rich plasma, specifically for burn treatment.* J Burn Care Res, 2014. **35**(3): p. 219-27.

[64] Pallua, N., T. Wolter, and M. Markowicz, *Platelet-rich plasma in burns.* Burns, 2010. **36**(1): p. 4-8.

[65] Chen, J., et al., *The application of platelet-rich plasma for skin graft enrichment: A meta-analysis.* Int Wound J, 2020.

[66] Dhua, S., T.R. Suhas, and B.G. Tilak, *The Effectiveness of Autologous Platelet Rich Plasma Application in the Wound Bed Prior to Resurfacing with Split Thickness Skin Graft vs. Conventional Mechanical Fixation Using Sutures and Staples.* World J Plast Surg, 2019. **8**(2): p. 185-194.

[67] Gupta, S., P. Goil, and S. Thakurani, *Autologous Platelet Rich Plasma As A Preparative for Resurfacing Burn Wounds with Split Thickness Skin Grafts.* World J Plast Surg, 2020. **9**(1): p. 29-32.

[68] Miller, J.D., et al., *Reduction of pain via platelet-rich plasma in split-thickness skin graft donor sites: a series of matched pairs.* Diabet Foot Ankle, 2015. **6**: p. 24972.

[69] Marck, R.E., et al., *The application of platelet-rich plasma in the treatment of deep dermal burns: A randomized, double-blind, intra-patient controlled study.* Wound Repair Regen, 2016. **24**(4): p. 712-20.

[70] Marck, R.E., et al., *Growth Factor Quantification of Platelet-Rich Plasma in Burn Patients Compared to Matched Healthy Volunteers.* Int J Mol Sci, 2019. **20**(2).

[71] Mashiko, T., et al., *Platelet-derived factor concentrates with hyaluronic acid scaffolds for treatment of deep burn wounds.* Plastic and Reconstructive Surgery Global Open, 2016. **4**(10).

[72] Marck, R.E., et al., *Activation, function and content of platelets in burn patients.* Platelets, 2019. **30**(3): p. 396-402.

[73] Hunt, B.J., *The current place of tranexamic acid in the management of bleeding.* Anaesthesia, 2015. **70 Suppl 1**: p. 50-3, e18.

[74] Kamhieh, Y. and H. Fox, *Tranexamic acid in epistaxis: a systematic review.* Clin Otolaryngol, 2016. **41**(6): p. 771-776.

[75] Montroy, J., et al., *The efficacy and safety of topical tranexamic acid: A systematic review and meta-analysis.* Transfus Med Rev, 2018.

[76] Xie, J., et al., *Comparison of intravenous versus topical tranexamic acid in primary total hip and knee arthroplasty: An updated meta-analysis.* Thromb Res, 2017. **153**: p. 28-36.

[77] Dominguez, A., et al., *Transfusion requirements in burn patients undergoing primary wound excision: effect of tranexamic acid.* Minerva Anestesiol, 2017. **83**(4): p. 353-360.

[78] Bhatia, N., et al., *Impact of single dose intravenous tranexamic acid*

on peri-operative blood transfusion requirements in burn patients: A prospective, randomized trial. Egyptian Journal of Anaesthesia, 2017. **33**(3): p. 251-255.

[79] Eikebrokk, T., et al., *Cytotoxicity and effect on wound re-epithelialization after topical administration of tranexamic acid.* BJS open, 2019.

[80] Tang, Y.M., T.W. Chapman, and P. Brooks, *Use of tranexamic acid to reduce bleeding in burns surgery.* J Plast Reconstr Aesthet Surg, 2012. **65**(5): p. 684-6.

[81] Butts, C.C., et al., *Controlling intraoperative hemorrhage during burn surgery: A prospective, randomized trial comparing NuStat((R)) hemostatic dressing to the historic standard of care.* Burns, 2017. **43**(2): p. 374-378.

[82] Rojas, S., et al., *Characterization of the biodistribution and systemic absorption of TT-173, a new hemostatic agent of recombinant human tissue factor, using radiolabeling with 18F.* European Journal of Drug Metabolism and Pharmacokinetics, 2017. **42**(4): p. 583-592.

[83] Centeno, A., et al., *Experimental evaluation of a new tissue factor-based topical hemostat (TT-173) for treatment of hepatic bleeding.* Journal of Investigative Surgery, 2018.

[84] López-López, J., et al., *TETIS study: evaluation of new topical hemostatic agent TT-173 in tooth extraction.* Clinical oral investigations, 2016. **20**(5): p. 1055-1063.

[85] Rojas, S., et al., *EHTIC study: Evaluation of a new hemostatic agent based on tissue factor in skin grafting procedures.* Burns, 2017. **43**(4): p. 780-788.

[86] Potyondy, L., et al., *The use of hydrogen peroxide for achieving dermal hemostasis after burn excision in a patient with platelet dysfunction.* J Burn Care Res, 2006. **27**(1): p. 99-101.

[87] Arakeri, G. and P.A. Brennan, *Povidone-iodine and hydrogen peroxide mixture soaked gauze pack: a novel hemostatic technique.* Journal of Oral and Maxillofacial Surgery, 2013. **71**(11): p. 1833. e1-1833. e3.

[88] Al-Abbasi, A.M. and Z.K. Saeed, *Hydrogen Peroxide 3%: Is it Beneficial in Tonsillectomy?* Sultan Qaboos University Medical Journal, 2008. **8**(2): p. 201.

[89] Uysal, A.C., et al., *An alternative dressing material for the split-thickness skin graft donor site: oxidized regenerated cellulose.* Annals of plastic surgery, 2006. **57**(1): p. 60-64.

[90] Rhee, P., et al., *QuikClot use in trauma for hemorrhage control: case series of 103 documented uses.* Journal of Trauma and Acute Care Surgery, 2008. **64**(4): p. 1093-1099.

[91] Schreiber, M.A. and D.J. Neveleff, *Achieving hemostasis with topical hemostats: making clinically and economically appropriate decisions in the surgical and trauma settings.* AORN journal, 2011. **94**(5): p. S1-S20.

[92] Arnaud, F., et al., *Exothermic reaction in zeolite hemostatic dressings: QuikClot ACS and ACS+®.* Annals of biomedical engineering, 2008. **36**(10): p. 1708.

[93] Arnaud, F., et al., *Comparative efficacy of granular and bagged formulations of the hemostatic agent QuikClot.* Journal of Trauma and Acute Care Surgery, 2007. **63**(4): p. 775-782.

[94] Khan, M., et al., *An iatrogenic burn from the use of a topical haemostatic agent.* Emergency Medicine Journal, 2010. **27**(12): p. 950-951.

[95] Wright, J.K., et al., *Thermal injury resulting from application of a granular mineral hemostatic agent.* Journal of Trauma and Acute Care Surgery, 2004. **57**(2): p. 224-230.