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Fracture blisters: pathophysiology and management

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ABSTRACT

Open fractures are considered an orthopaedic emergency due to the severe soft tissue disruption that might potentially lead to devastating complications. On the other hand, closed fractures, and especially those resulting from high-energy mechanisms, are also often accompanied by severe soft tissue trauma. Soft tissue envelope compromise can have a detrimental effect on the final outcome of the patients. Fracture blisters in particular, develop as a sign of significant local tissue trauma and appear in a time period between 6 to 72 hours post-injury. They can delay the definitive fracture treatment for a considerable amount of time and at the same time they also increase the risk for post-operative wound complications. Awareness of fracture blisters pathophysiology and their management options are crucial for orthopaedic surgeons, in order to achieve a favorable clinical outcome. In the herein study we present a concise synopsis of the pathophysiology pathways and management options of fracture blisters.

Introduction

Fracture treatment should ideally take into account two major considerations, the treatment of the bone injury and the management of the associated soft tissue trauma. Successful management of soft tissue injuries is of paramount importance for a favorable clinical outcome. Open fractures constitute a well-recognised orthopedic emergency, often described with the original Gustilo and Anderson classification [1]. However, closed fractures are also frequently accompanied by severe soft tissue trauma [2]. Soft-tissue envelope compromise may result in a number of significant complications, such as soft tissue loss, protracted course of treatment, deep infection, pain, stiffness, reflex sympathetic dystrophy and even amputation [3]. Fractures in body areas with limited tissue coverage such as the foot, the ankle and the knee are prone to the development of blisters [4]. Awareness of the soft-tissue injury pathophysiology and management options is of paramount importance for orthopedic surgeons treating these injuries. In the herein study we present a concise synopsis of the pathophysiology pathways and management options of fracture blisters.

Pathophysiology

Fracture blisters have originally been described by Shelton and Anderson in 1986, as “areas of epidermal necrosis with separation of the stratified squamous cell layer from the underlying vascular dermal layer by edema fluid” [5]. The initial blister definition of Shelton and Anderson [5] was confirmed histologically only in 2 out of 15 specimens in the subsequent study of Varela et al. [6] in 1993. In these specimens, the blisters were subepidermal, characterized by full-thickness epidermal necrosis that formed the blister roof [6]. In the rest of the specimens subcorneal blisters were evident, located superficial to the granular layer [6]. Therefore, Varela et al. [6] proposed a new definition of fracture blisters that described them as “tense vesicles or bullae that arise in markedly swollen skin over a fracture”. The pathophysiology of fracture blister formation should be conceptualized within the context of two basic pillars: the injury of the soft tissue in molecular level and the formation of blisters as a consequence of the injury.

The cascade of events that take place in closed soft-tissue injuries can be divided in three phases: inflammatory, proliferative and reparative [7,8]. The inflammatory phase of the cascade mainly refers to changes in microcirculation, which is disrupted due to soft tissue breakdown at the time of injury [7]. Thereafter, the exposure of subendothelial collagen due to trauma, triggers further response. Platelets and leukocytes are activated and aggregated. The clotting cascade, kinin system, and complement cascade are also activated. Vasoconstriction, platelet aggregation, and acti-

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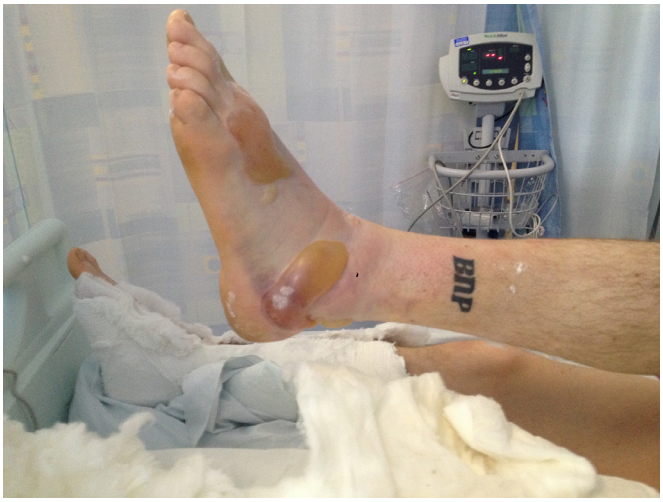

Fig. 1. Clear-fluid blisters in a patient who suffered a calcaneus fracture.

vation of the clotting and complement cascade take place so that hemostasis occurs. At the same time, there is an increase of the capillary system endothelial permeability, as a result of the action of kallikrein, prostaglandin, and histamine from mast cells. Consequently, soft tissue edema and hypoxia are deteriorated [7,8]. During this stage, there is "total microvascular perfusion failure combined with maximum microvascular leakage in the compromised tissue" on the injury site [7]. In addition to the microcirculation disruption, a large number of cytokinesis are released such as serotonin, epinephrine, thromboxane- A2, platelet-derived growth factor. As a result, a localized inflammatory reaction is triggered [7]. Neutrophils and macrophages are transferred to the injured tissue. Phagocytosis of necrotic tissue stimulates the release of additional cytokines, which attract significant numbers of leucocytes and platelets [7,8]. The inflammatory process then spreads to the surrounding healthy tissues. The peak of capillary permeability and tissue edema takes place between 24 and 72 hours after the initial injury [8]. When the inflammatory response starts to subside, the proliferative phase begins. Fibroblasts and endothelial cells are transported to the injured tissue. They subsequently proliferate and construct the collagenous proteins of the extracellular matrix [7]. Formation of new extracellular matrix stimulates endothelial cell ingrowth and increase of the tissue vascular supply [7]. Finally, during the reparative phase, scarring and fibrosis occur as collagenous proteins cross-link, leading to a decrease of the tissue water content and vascularity [7].

Blister formation is directed by two parameters [9]. Soft tissue edema during the inflammatory phase leads to increase of the interstitial pressure. As a result, filtration pressure increases and subsequently leads to diminished cohesion between epidermal cells which results to transport of fluid into the blister [5]. Another parameter that leads to blister formation is the increased colloid pressure in an epidermal or subepidermal cleft, that leads to fluid transfer into the cleft [6]. It seems that the former of the two plays the most important role in blister formation [6]. As a result of the aforementioned parameters, when a critical level of stress is reached, separation of the dermal-epidermal junction occurs due the differing elasticity and viscoelastic properties of the two layers [10,11]. The potential space fills in with fluid, leading to blister formation.

According to their gross and histologic appearance, two distinct subtypes of blisters have been identified, the clear-filled and the blood-filled [12]. Clear-filled blisters contain serous fluid (Fig. 1), while blood-filled are characterized by hemorrhagic content (Fig. 2) [6]. Clear and hemorrhagic blisters can coexist in an injured area (Fig. 3). Histologically, the main difference between them is the presence of some epidermal cells in clear-filled blisters, while blood-filled are completely devoid of epidermal cells [11]. The presence of epidermal cells can lead to faster reepithelization of the blister bed and therefore decreased morbidity of clear-filled blisters [12]. Haemmorhagic blisters represent a more severe injury of the dermal-epidermal junction [13]. In a biomechanical study [13], uniaxial strain was applied on cadaveric ankle-skin specimens in order to reproduce the mechanism of fracture blister formation. In specimens strained to 152%, complete separation of the dermis and epidermis was found along with scattered areas of retained epidermis on the dermis. This is a similar histologic picture to that of clear-filled blisters. In specimens strained to 167%, complete separation of the dermis and epidermis was identified, analogous to blood-filled blister development [13].

Patients who suffer high-energy fractures are more prone to the development of blisters. Higher amounts of energy absorbed by the fracture site at the time of the injury exacerbate the inflammatory reaction at the first phase of the above-mentioned cascade. Other factors suggested to play an important role in fracture blister formation are hypertension, smoking, alcohol abuse, peripheral vascular disease, lymphatic obstruction, and diabetes, as they cause impairment of the skin microvasulature [14]. Scott [15] also published 2 case reports of patients on sodium valproate that developed extensive blistering after low energy ankle fractures. In both patients there was reduced activation response of platelets to stimulation by collagen. Alterations of platelet function are a known side effect of sodium valproate [16]. However, association of sodium valproate and fracture blisters has not been investigated and/or substantiated in other studies.

Locations

Skin blisters have been reported at an incidence of 2,9% in an analysis of 1.468 fractures requiring hospital admission [6]. Straus et al. reported the presence fracture blisters at an incidence of 7.2% in 655 patients with isolated or multiple lower extremity trauma [17]. The most common anatomic area of development of blisters is the ankle and hindfoot followed by the proximal tibia [17,18]. Injuries associated with higher incidence of blister formation were pilon fractures, calcaneus fractures and ankle fractures [17,18]. Distal humerus fractures also were accompanied by a significant development of blisters.

Soft tissue anatomy around the ankle places the area in higher risk of blister formation compared to other fracture sites. In this anatomic area, there are smaller amounts of adipose and muscular tissues, which could offer local skin protection [9]. In addition, at the skin of the ankle there are smaller numbers of hair follicles, which hold together the dermo-epidermal junction [4]. Hair follicles are also major sources of epithelial cells and may assist in wound reepithilialization [19]. Finally, decreased skin thickness around the ankle is another factor predisposing to blister formation. Skin over the medial malleolus is usually 1.5 to 2.5 mm [20] and can be as thin as 0.4 to 0.8 mm in patients with collagen disease [21], in comparison to 5 mm skin thickness of the soles and palms [19].

Management of fracture blisters

Initial management

The first step of fracture-related soft tissue injury management is immobilization of the fractured limb as soon as possible, preferably on the site of the accident, in order to prevent further soft tissue injury [22]. After examining limb perfusion, neurologic status

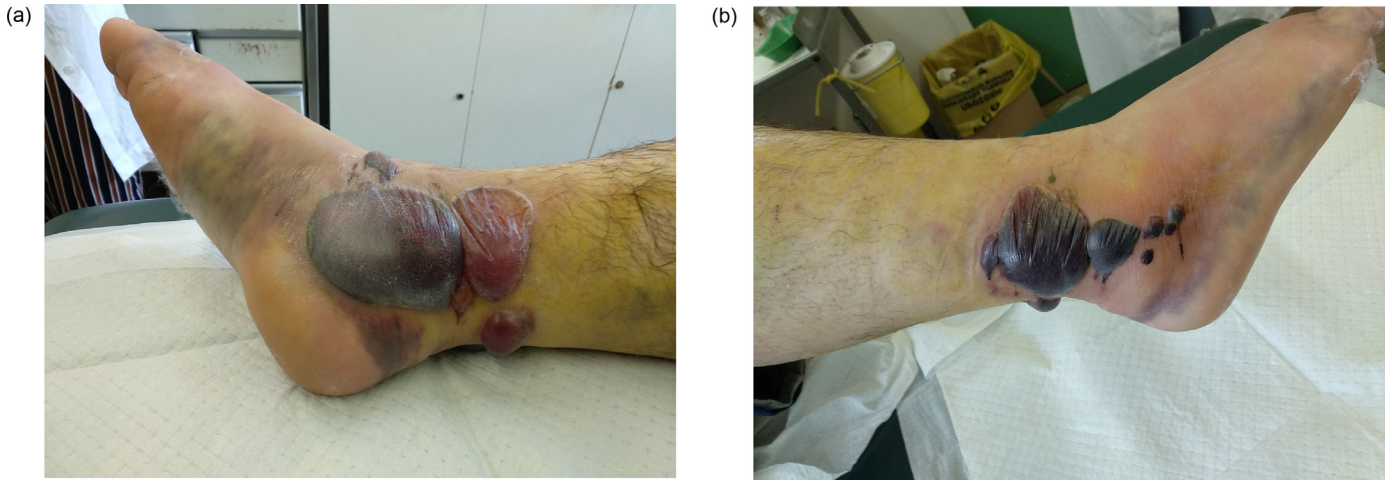

Fig. 2. Hemorrhagic blisters at the a) medial aspect of the ankle and b) lateral aspect of the hindfoot in a patient who suffered a calcaneus fracture.

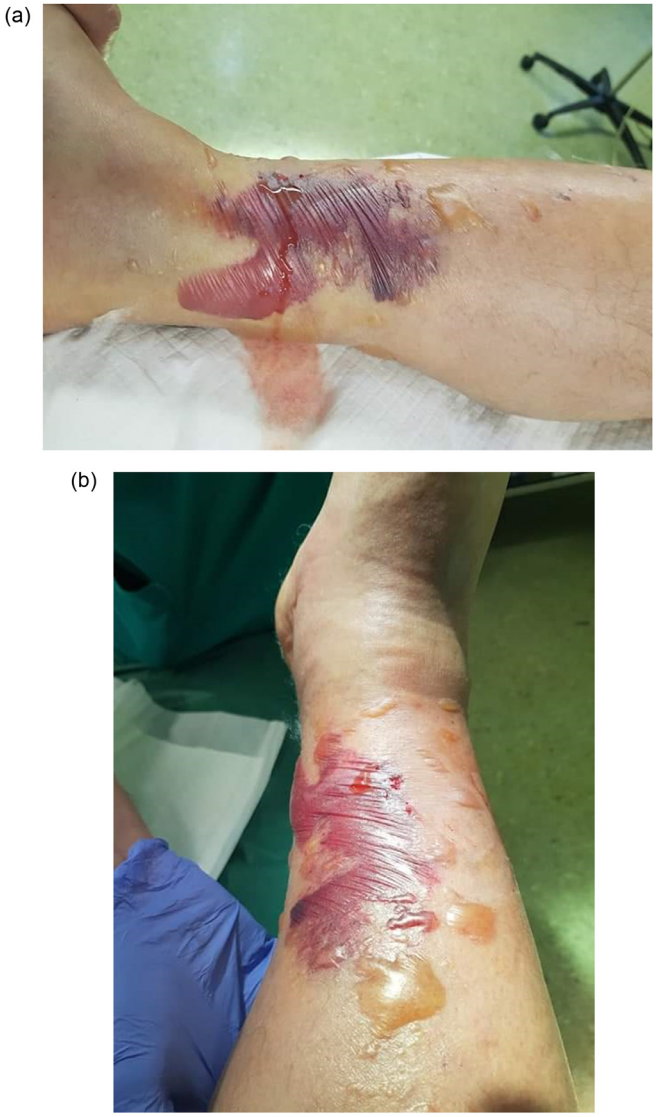

Fig. 3. Hemorrhagic and clear-fluid blisters coexisting in the a) anterior and b) medial aspect of the tibia in a patient who suffered a distal tibia fracture.

and signs of compartment syndrome, closed reduction and splinting of the extremity should be performed. Well padded-splints can reduce soft tissue edema by supporting the limb in a physiologic position [23]. It is important to apply the splint properly and with caution, as it is to possible, if the splint is applied incorrectly to act as a constricting agent and therefore resulting in further injury of the soft-tissue envelope [24].

As already stated, during the inflammatory phase of soft tissue injury, capillary permeability and edema peak at the interval between 24 and 72 hours postinjury [18]. Control of the inflammatory process especially during the first 24 to 72 hours could have a beneficial effect in preventing further soft tissue injury and therefore blister formation. A number of strategies have been proposed for achieving that goal, namely passive (elevation, cryotherapy) and active (intermittent pneumatic compression devices) [25–27]. Elevation of the limb decreases soft tissue edema as venous and lymphatic drainage is assisted by gravity [18]. Additionally, elevation decreases limb perfusion pressure [25], therefore it must be applied with caution in cases where arterial supply compromise is suspected. Cryotherapy can also be of use in edema control [26]. Ice can inhibit the inflammatory response by decreasing soft tissue temperature and therefore decreasing soft tissue edema [28]. Cryotherapy duration up to 20 minutes has shown effectiveness in reducing blood volume of the limb without causing reactive vasodilation [29]. Care must be taken to avoid skin burns and nerve injuries [30], while cryotherapy should be avoided in patients with cryoglobulinemia, cold allergy, or Raynaud's phenomenon [29]. Intermittent pneumatic pedal compression devices can reduce edema in ankle [31] and calcaneus [32] fractures through intermittent compression of the plantar venous plexus, resulting in an increase of venous flow from the limb [33]. Pooling of blood in the ankle is prevented and also there is improvement in the lymphatic flow [34]. Additionally, all the abovementioned measures can potentially assist in the prevention of compartment syndrome. However, it is worth noting that in a study by Varella et al. [6] in the patients with extreme swelling and pain of the ankle or foot, significant reduction of compartment interstitial pressure was noted after the formation of blisters [6]. Improvement of clinical symptoms was noted as well [6].

Blister aspiration and unroofing

Orthopaedic literature about the management of fracture blisters is rather sparse. Besides leaving the blisters intact until the time of surgery, surgeons have two additional options regarding

blister management: blister aspiration and unroofing. However, there are few studies analysing these two interventions and their outcomes. As a result, information is limited about the blister management prior to surgery. It is unclear whether such interventions are necessary, and their exact timing prior to definitive fracture fixation. In the study of Varela et al., [5] 6 random, intact blisters were aspirated. The aspirated fluid was identified as sterile. However, multiple microbiology cultures from ruptured blister beds revealed that they were colonized with multiple organisms, most of them consistent with opportunistic skin flora, such as Staphylococcus aureus and Staphylococcus epidermidis. The majority of the blisters (47 of 53) were left intact or were allowed to rupture spontaneously. Debridement was performed in the rest. There were no notable differences regarding blister healing between the two groups. Giordano et al. [35] applied a protocol of blister treatment that included three management strategies: aspiration, deroofing, or leaving the blister intact. In 46 out of 53 patients (87%), blisters were re-epitheliased without complications. There was no difference regarding blister healing between the three above-mentioned techniques. In both studies there were postoperative infections in the cases where the surgical incision crossed the blister site [6,35]. Strauss et al. [17] studied a treatment algorithm of blisters that included sharp unroofing of the overlying epithelium in a sterile fashion. Silver sulfadiazine (Silvadene, King Pharmaceuticals Inc., Bristol, TN) was then applied to the blister bed and covered with a clean dressing. Dressing change and sulfadiazine application was carried out twice daily until complete blister healing. Two significant complications related to blisters occurred [17]. One major complication involved an ankle fracture-dislocation in an elderly diabetic female, with an associated blood-filled blister present medially. Full-thickness skin breakdown occurred at the base of a blood-filled fracture blister 0.5 cm proximal to a surgical incision. On the 5th postoperative day deep infection occurred and the patient eventually required ankle fusion. The second complication occurred in an ankle fracture in another diabetic patient. Postoperatively, he presented with persistent medial-ankle skin breakdown in the area of a clear-filled blister, requiring hardware removal. In the rest of the patients blister healing was uneventful, even though the scarring that developed in 21% of the patients influenced their satisfaction [16]. Table 1 provides a synopsis of the main studies reporting on the preoperative blister management.

The fluid within the blisters is sterile and contains activated neutrophils and opsonins that prevent infection [36,37]. Additionally, it contains epidermal growth factors that assist in faster wound epithelization. Once ruptured, the blisters are no longer sterile and the blisters beds are quickly colonized by pathogens [38]. The blister roof acts as mechanical barrier against microorganisms and provides a sterile dressing for wound healing [6,36]. For these reasons, some authors advocated towards leaving all blisters intact and applying soft dressings until surgery [5,34]. During the operation however, it is important that skin incisions are placed away from blister beds. Incisions crossing blister beds can increase the risk of infection [6,17,35]. Strebel et al. [39] confirmed that the majority of fracture blisters contains sterile fluid. 64 blisters were aspirated in a sterile fashion, with 57 of them (89.1%) being identified as sterile. 7 blisters (10,9%) were found to be colonized [39]. 4 of the colonized blisters were blood-filled [38]. However, the authors were not able to identify predicting factors for a positive aspirate. Also, no evidence was found that positive aspirates lead to postoperative infections.

Two case reports have been published in which negative wound pressure therapy was used for the treatment of fracture blisters [40,41]. The first case report [40] included two patients with combined ankle and foot fractures. The mechanism of injury was high energy and in both patients there was significant soft tissue edema and blistering. Dermal fenestration of the blisters with multiple stab incisions was performed in the operation theatre. A negative wound pressure therapy device was applied. In both patients, soft tissue appeared healthy on the removal of NWPT, with minimal scarring. The second case report [41] involved one ankle fracture and one tibial plateau fracture. Blisters were drained with scalpel incisions and negative wound pressure devices with instillation and dwell (NWPT-id) were applied. Complete reepithelization of blister bed was observed in both patients 7 days post-injury. Negative wound pressure therapy showed promising results in these 4 cases, however the small number of cases indicates that further research is required to include this technique in the everyday orthopaedic practice.

Wound complications and risk of infection

Wound healing complications were observed in 7 out of 53 patients (13.2%) in the study of Giordano et al. [32]. Five of them had injuries around the ankle (ankle and distal tibia fractures). In one of them the knee was involved (distal femur fracture) and one complication occurred following fixation of a Lisfranc injury. All cases had blood-filled blisters. In 2 of them, skin incisions went through or near blood-filled blisters beds. In the study of Strauss et al., [17] 40 of 45 patients with fracture blisters followed an uneventful postoperative course. Blister associated soft-tissue complications occurred in 5 cases (11.1%). Two patients required reoperation, therefore these complications were classified as major. The rest of them were treated conservatively, with these complications being classified as minor. Both major complications occurred in patients with diabetes mellitus. The authors concluded that blood-blisters potentially result in a higher rate of complications [17,35]. They also noted that it is safe to place incisions around intact blisters. It also safe for the incision to go through a clear-filled blister, while it is advised to avoid blood-filled blisters due to their greater morbidity [17,35]. It was also confirmed that the presence of blisters is a factor that delays definitive treatment for significant amount of time [17,35].

The study of Strebel et al. [39] provided more evidence, after aspirating a significantly larger number of blisters, that the majority of blisters contains sterile fluid. The results of the study showed that 7 of 64 (10.9%) of the aspirated blisters were colonized, with 4 of them being blood-filled. Postoperative infection occurred in 4 patients, in whom however the aspirate was negative. The authors were not able to identify predicting factors for neither positive aspirate or postoperative infection. The only predicting factor of infection risk that has been identified is the placement of skin incision through or near haemorrhagic blisters [17,35].

In order to avoid wound complications, authors have suggested delayed [42,43] or 2-staged [44–46] fixation for fractures in areas susceptible to severe soft tissue edema and blisters such as the knee and ankle. Regarding ankle fractures, literature shows that early definitive fixation within 8 hours from the injury can decrease the rate of postoperative wound complications [47]. It needs to be stated that meticulous technique and soft tissue handling are an absolute necessity in order to achieve favorable outcomes [48]. However, in cases where definitive fixation is not possible in that short amount of time post-injury, it is recommended that the fracture is closely reduced and immobilized in a plaster splint. Definitive fixation is carried out after a minimum of 5-7 days observation of the soft tissue envelope [48].

In high energy fractures, such as tibial plateau or pilon fractures, early definitive fixation can lead to devastating soft tissue complications [49,50], that may result even in the amputation of the limb [50]. Therefore, staged fixation protocols are recommended in these types of fractures [49,50]. Staged management protocols are a well-recognized method of treatment of complex, high energy fractures of the ankle, [51,52] foot [53,54], and prox-

Table 1
Synopsis of the main studies reporting on the preoperative blister management

AUTHORS	DATE	TYPE OF STUDY	TYPE OF INJURY	TYPE OF BLISTERS	MANAGEMENT	COMPLICATIONS	OUTCOMES
Strauss et al.	2006	Prospective	• 17 ankle fractures (9.8%) • 13 tibial-plateau fractures (11.8%) • 5 tibial-shaft fractures (3.0%) • 8 calcaneus fractures (21.1%) • 4 pilon fractures (10.8%).	• blood-filled: 22 patients (47%) • clear-filled: 20 patients (43%) • combination: 5 patients (10%)	• Blister unroofing and silver • Sulfadiazine application twice daily	• deep infection following an ankle fracture fixation requiring fusion • medial skin breakdown following an ankle fracture fixation requiring hardware removal	• 43 of 45 cases (95.6%): uncomplicated fracture union • 2 major complications (4.4%) • Scarring: 6 patients (21%) at 51.3 months follow-up
Giordano et al.	1994	Prospective	• 13 ankle fractures	• blood-filled: 3 patients (23%) • clear-filled: 8 patients (61%) combination: 2 patients (15%)	• Observation until fracture fixation • Intraoperative blister biopsy	1 case of delayed wound healing	12 of 13 cases(92%): uncomplicated healing
Giordano et al.	1995	Prospective	• 29 ankle fractures • calcaneus fractures • foot fractures • distal femur fractures • tibial plateau fractures • tibia/fibula fractures • supracondylar humerus fractures	• blood-filled: 21 patients (40%) • clear-filled: 17 patients (32%) • combination: 15 patients (28%)	• Aspiration • Unroofing • Observation-leaving the blisters intact	7 cases of postoperative infection	46 of 73 cases: uncomplicated healing
Strebel et al.	2019	Retrospective	• 33 ankle fractures • 13 foot fractures • 15 other lower limb fractures • 3 upper limb fractures	• blood-filled: 29 patients (40%) • clear-filled: 17 patients (32%)	• Aspiration	4 cases of postoperative infection	60 of 64 cases: uncomplicated healing
Varela et al.	1993	Prospective	• 10 ankle fractures • 9 tibial shaft fractures • 7 calcaneus fractures • 4 tibial plateau fractures • 3 elbow dislocations • 2 distal humerus fractures • 2 radius fractures • 1 humeral shaft fracture	NA	• Observation • Aspiration	2 cases of postoperative infecion	49 of 51 cases: uncomplicated healing

Table 2
Fracture Blister Management Recommendations

1. Early soft-tissue edema control measures are of great importance in order to prevent blister formation.
2. Application of an external fixator when fracture blisters development is anticipated adds to better soft tissue management and blisters follow up.
3. Fracture blisters should be left intact and covered with soft dressings until the time of definitive fracture fixation.
4. Surgical incisions should be placed away from hemorrhagic blister beds due to the increased risk of soft tissue complications.

imal[43,55] or distal tibia.[56,57] The first stage of treatment involves application of a spanning fixation system that offers temporary stabilization of the fracture, allowing the soft tissue envelope to recover [39]. After soft tissue resuscitation, which might take 10-21 days, internal fixation can be performed [46]. Temporary external fixation offers the benefits of early soft tissue and bone stabilization in combination with avoidance of the risk of local complications in severely compromised soft tissues and also systemic risks in polytrauma patients [58–60]. Furthermore, a provisional external fixation offers the advantage of inspecting the soft tissue condition on a daily basis avoiding the necessity of changing the extremity splint, which poses additional stress to the soft tissues. The two-stage surgical treatment protocol does not negatively affect the functional outcome of patients with ankle fractures [61] and it currently considered the standard of care in injuries with severe soft tissue compromise such as the tibial pilon fractures [50,51].

Summary

Fracture blisters develop in areas such as the ankle, the foot, the knee and the elbow as a result of a significant soft tissue trauma and subsequent edema. Increased filtration pressure due to soft tissue edema which occurs as result of direct trauma and inflammation that peaks 24 hours post-injury, results in formation of subepidermal clefts. Fluid transfer into the clefts leads to blister formation. They can delay definitive treatment for significant amount of time and increase the risk for wound complications. Temporary external fixation as part of a two-stage treatment protocol is advisable for soft tissue resuscitation and regular follow up of blisters and soft tissue edema, (Table 2). Blister aspiration and/or unroofing has not been substantiated by the sparse contemporary literature. Surgical incisions for definitive management should avoid areas of hemorrhagic blisters. Further research with high quality prospective randomized trials is advisable in order to shed light to the best clinical management of fracture blisters.

Conflict of interest

All authors declare no conflict of interest in relation to the content of this manuscript.

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