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ORIGINAL ARTICLE

Management of extravasation injuries: A retrospective study

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Abstract

The extravasation of many agents during administration by way of the peripheral veins can produce severe necrosis of the skin and subcutaneous tissue. The incidence of an extravasation injury is elevated in the populations prone to complications, including the younger age groups. The severity of the necrosis depends on properties of the extravasated agent (vinca alkaloids, antracyclines, catecholamines, cationic solutions, osmotically active chemicals) including the type, concentration, and the quantity injected. In general, the primary diseases were chronic diseases such as hepatic or ischaemic encephalopathies, cardiac or pulmonary diseases, diabetes mellitus, and oncological diseases. The aim of this article was to explore the prevention, diagnosis, and treatment of extravasation injuries with a review of the literature. From January 2009 to August 2011, 22 patients were reviewed. Ten patients were children, and the others were adults. The surgical interventions were delayed until the development of the necrosis. A topical boric acid 3% solution was applied to all wounds with repetitive debridement. Debridement was performed once every 2 days and was continued until healthy tissue was obtained. The wounds of eight patients were repaired with split-thickness skin grafts, the wounds of six patients were reconstructed with randomised fasciocutaneous flaps, and the wounds of five patients healed by secondary intention. The wounds of three patients with massive swelling of the forearms were treated with only conservative modalities and limb elevation for 24–48 hours. Boric acid was found to promote granulation tissue in the wounds. The extravasation injuries can be prevented by using appropriate measures, such as the avoidance of perfusion under pressure, patient participation in pain follow-up, wound management by experienced health professionals, and preference for large and suitable veins.

Key Words: Extravasation injuries, extravasation management, prevention, boric acid

Introduction

Extravasation is the process by which a solution that is administered intravenously leaks into the surrounding tissue [1]. The extravasation of cytotoxic drugs may cause an excessive necrosis in the cutaneous and subcutaneous tissues [2]. Many agents, including calcium, potassium, bicarbonate, hypertonic dextrose, cytotoxic drugs, and antibiotics, could cause tissue necrosis after the intravenous infusions have extravasated [3]. The incidence of extravasation injuries has increased from 11% to 58% in children [4]. The patients with significant risk factors should be followed more closely. Therefore, these factors facilitate the progression of extravasation injuries (Table I). Initially, the extravasation injury manifests as inflammatory symptoms, including indurations, swelling, blistering, and pain (Figure 1) [5].

In published reports, the mechanism of the damage is thought to include the direct cellular toxicity of the drug, the vasoconstriction that leads to ischaemic necrosis, the osmotic damage, the ischaemic effect of the extrinsic mechanic compression of the large volumes of the extravasated solutions, and all factors causing the superimposed infections and skin defects [3,5]. The most common extravasated agents are cationic solutions (Ca++, K+, and HCO^{3-}), osmotically active chemicals (total parenteral nutrition and hypertonic dextrose), cytotoxic drugs, and antibiotics (Figure 2) [6].

The degree of the tissue damage and the adverse events caused by the injury generally remain unclear during the time period ranging from several hours to days [7]. The chosen management course depends on the surgical expertise employed. In this study, we aimed to present our clinical findings in the context of a literature review regarding the mechanisms, prevention, diagnosis, treatment, follow-up, and squeal of extravasation injuries. We wanted to emphasise that prevention of the injury is better than the cure.

Patients and methods

All cases of extravasation injuries from January 2009 to August 2011 were reviewed retrospectively via a computer database. Twenty-two hospitalised cases were reviewed for this study. The project was approved by the institutional ethics committee. The patients' sex, age, localisation of the injury, agents implicated in the extravasation injury, treatment methods and diagnosis of primary disease were determined from the reviewed medical records (Table II). In the children, patients' ages ranged from 6 days to 14 months. In this group, the extravasation injuries localised to all extremities as well as the scalp, whereas the lesions in the adults were generally situated on the forearms and hands. Most of the children were in the early infantile range (0–1 years), and the majority of the adult patients had chronic diseases.

All patients were treated with topical modalities until necrosis or spontaneous healing occurred. A topical boric acid 3% solution was applied to the wounds with repetitive debridement.

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Table I. Risk factors for development of extravasation injuries.

- Endothelial dysfunction (elder patients, diabetes mellitus, hypertension, dyslipidemia, atherosclerosis, chronic renal failure)
- Vasoconstrictive agents (ephinephrine, phenylephrine, dopamine)
- DNA binding vesicants (Doxorubicin, Dactinomicin, Daunorubicin, Mitomycin C)
- Radiotherapy (previously radiotherapy executed patients, Recall Phenomenon)
- Decreased elasticity of veins (atherosclerosis, elder)
- Compromised blood flow
- High pressure infusion (paediatrics or altered sensory perception)
- Patients unable to describe the pain (paediatrics, compromised sensory perception, intubated patients in intensive care units)
- Inexperienced staff (lack of knowledge or experience)
- Multiple use of same vein
- Type of catheter (length, gauge, metal needle, fibrin sheath development)
- Viscosity of administered fluid (pH, concentration of fluid)
- Undesirable site location (hand dorsum, antecubital fossa, ankle)

Debridement was performed until the healthy bleeding tissue once in 2 days and was continued until healthy tissue was obtained. During follow-up, eight patients received repetitive debridement and boric acid treatment before repairing the wound with the split-thickness skin grafts, six patients received randomised fasciocutaneous flaps, and secondary healing occurred in five patients. The wounds of three of the six patients were treated with fasciocutaneous flaps with the tendon exposure that localised to the dorsa of the right hand, left hand, and left ankle (Figure 3).

Three patients with massive swelling on the forearms and hands were treated conservatively with limb elevation for 24–48 hours (Figure 4). Compartment pressures in all suspected patients for compartment syndrome were measured with an intra-compartmental pressure monitor (Stryker®) to decide which treatment protocol to initiate. The follow-up period ranged from 1–10 months.

Results

The conservative modalities, including the anti-inflammatory, hirudin, antibiotic, oily, and moisturising pomades as well as hot-cold packs, had not been observed to prevent the development of necrosis in many cases. Improvement of the necrosis interval ranged from 24 hours to 2 weeks. As soon as the tissue became necrotic, the treatment was continued with the boric acid 3% solution application and repetitive surgical debridement.

Varying degrees of necrosis involving the skin and subcutaneous tissues developed in 19 patients. The wide removal of the necrotic debris was performed until a healthy layer of tissue was revealed. All wounds were debrided and dressed with the topical boric acid solution before repair. The boric acid was found to promote granulation tissue of the wounds.

In another adult patient, the extravasation of a radio-opaque medium caused a massive oedema on his forearm. Blisters on the patient's forearm were also noted. Similarly, the massive oedema was observed in two patients as a result of the mechanical compression of large amounts of extravasated saline (Figure 5). These three patients were successfully treated with limb elevation and conservative modalities (cold pack, anti-inflammatory treatment, and hirudin pomade).

Finally, all patients recovered well. Scar development was observed in four patients. A minor functional loss in the hands or feet as a result of scar formation was managed by physiotherapy and pressure garments.

Discussion

In this study, 2 years of retrospective data of patients with extravasation injuries were analysed. The most common

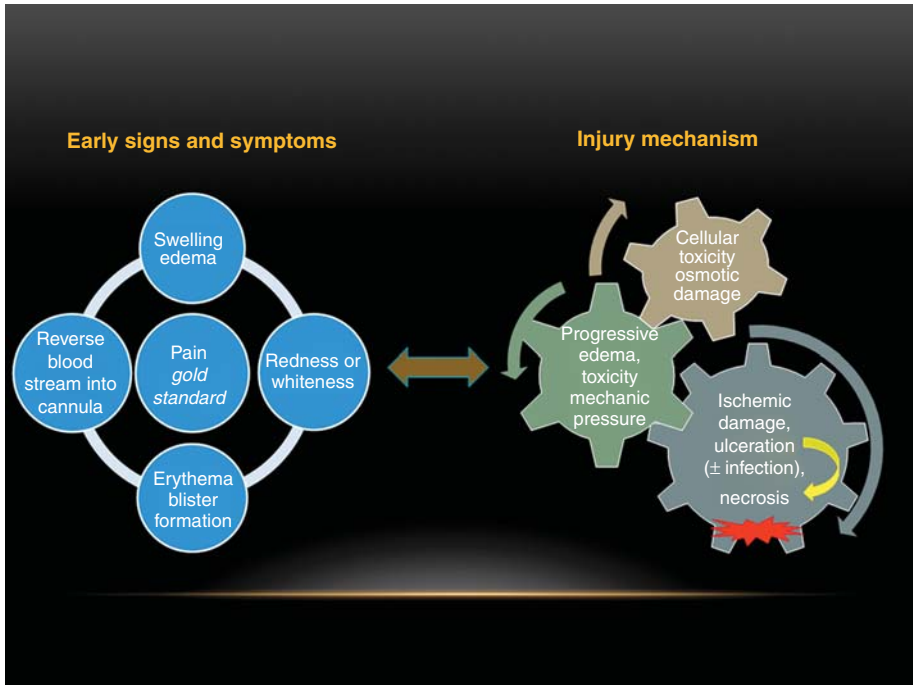

Figure 1. Early symptoms and mechanism of the extravasation injury.

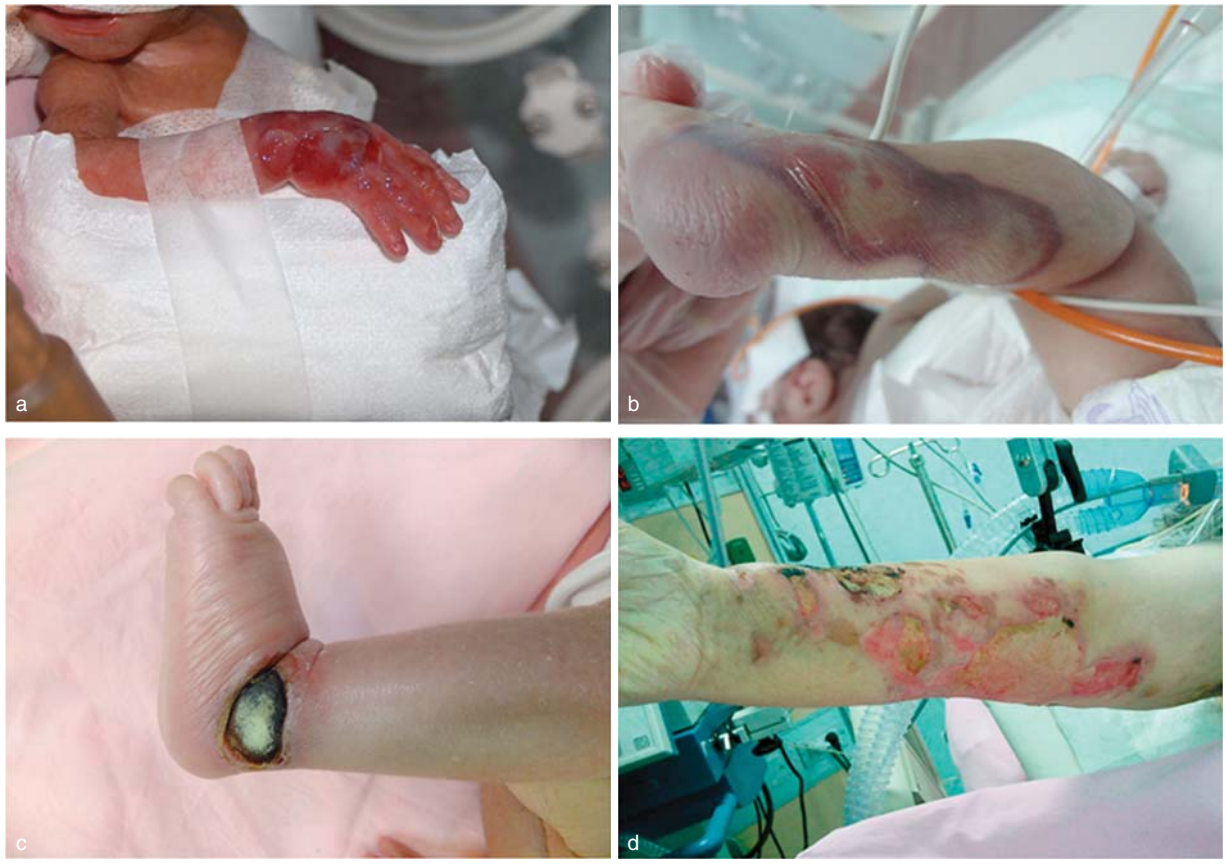

Figure 2. (*a*) Bicarbonate extravasation injury after 6 hours on the dorsum of the hand of a premature baby. (*b*) An extensive HCO3-extravasation injury after 10 hours on the ankle and posterior tibial region of a premature baby. (*c*) Ca^{++} extravasation injury after 6 days. (*d*) Doxorubicin extravasation injury after 4 days.

Table II. Patients with extravasation injuries according to age, sex, localisation of injury, kind of extravasated agent, and treatment method.

Case No.	Age/sex	Localisation	Agent	Treatment	Diagnosis
1	1 m/M	Wrist (volar)	Cephalosporin	Skin graft	Down syndrome, cardiac failure
2	49 y/F	Dorsum of hand	Radio-opaque media	Skin graft	Hepatic encephalopathy
3	21 d/M	Lateral malleol	Phenytoin	Skin graft	Hypoxic encephalopathy
4	20 y/M	Right forearm	Adriamycin	Flap	ALL (Leukemia)
5	1 y/M	Pretibial	Calcium	Secondary healing	Protein enteropathy
6	2 m/M	Scalp (frontal)	Calcium	Skin graft	Nephrotic syndrome
7	1 y/M	Scalp (temporal)	Calcium	Secondary healing	Pericardial effusion
8	1 m/M	Lateral malleol	Sodium bicarbonate	Skin graft	Pyloric stenosis
9	9 m/M	Wrist (volar)	Cephalosporin	Skin graft	Pneumonia
10	57 y/F	Dorsum of hand	Daunorubicin	Secondary healing	AML (Leukemia)
11	17 y/M	Left forearm	Adriamycin	Flap	ALL (Leukemia)
12	6 d/F	Left forearm	Sodium bicarbonate	Secondary healing	Respiratory distress syndrome
13	43 y/M	Left forearm	Salin	Conservative	Chronic hepatic failure
14	25 d/M	Scalp (temporal)	Dextrose	Skin graft	Respiratory distress syndrome
15	55 y/M	Dorsum of hand	Doxorubicine	Flap	Lung adenocarcinoma
16	37 y/F	Left forearm	Radio-opaque media	Conservative	Hodgkin lymphoma
17	17 y/M	Dorsum of hand	Cephalosporin	Skin graft	Electrical burn, renal failure
18	76 y/F	Left forearm	Sodium bicarbonate	Flap	Diabetes mellitus
19	67 y/M	Right forearm	Dopamine	Flap	Chronic hepatic failure
20	56 y/F	Right forearm	Salin	Conservative	Chronic hepatic failure
21	5 y/F	Ankle	Potassium	Flap	Diabetes mellitus
22	13 y/F	Dorsum of hand	Sodium bicarbonate	Secondary healing	Cerebral palsy, pneumonia

d = day; m = month; y = year; flap = fasciocutaneous flap.

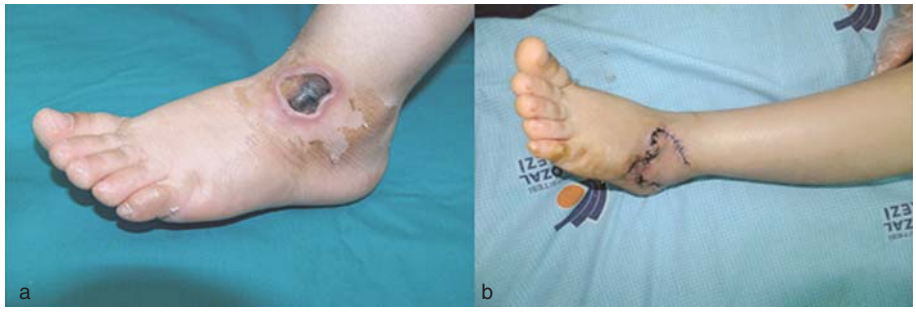

Figure 3. (*a*) K^+ extravasation injury after 8 days. (*b*) Repairing with fasciocutaneous flap.

extravasated agents in the children and elder groups were cationic solutions (Ca++, K+, HCO^{3-}) and chemotherapeutic drugs, respectively [6]. The incidence of extravasation injuries varied between 11%–58% in children [4].

The dorsum of the hand was the most common site of the injury, causing extensor tendon exposure. The scalp and dorsum of the foot were the most common sites in the neonatal patients [8]. In our series, the extravasation injuries often occurred at uncommon sites, including the pretibial area, ankle, and scalp. The newborns carried the most risk factors due to the small calibre of their veins and their inability to localise pain.

In many departments of our hospital, fluid infusions have been given to children with pumps. Pump use represents another disadvantage. The fluids flow under pressure, which leads to the leakage of fluids from the punctured site of the vein. The related extravasation causes extensive tissue damage.

In most cases, the tissue necrosis is initially underestimated. Therefore, early diagnosis is the most critical step in preventing extensive tissue damage. The symptoms range from irritation and indurations to darkening of the skin. The duration of the pain indicates the severity of the injury [9]. Fundamentally, the prevention of extravasation is easier than the treatment [3]. It is important to stop the infusion and administer the saline infusion from the same point (if the cannula is in the vein), as this dilutes the extravasated drug. It is also necessary to elevate the affected extremity. The potent parenteral analgesics (NSAIDs such as nimesulid) must be administered to prevent extravasation injuries [2,10].

Initially, we managed all the patients with conservative treatment methods, including anti-inflammatory, hirudin, antibiotic, oily, and moisturising pomades as well as hot-cold packs, until the tissue became necrotic. Improvement of the necrosis time from injection to appearance of necrosis ranged from 24 hours to 2 weeks. As soon as the necrosis occurred, the tissue was debrided. After debridement, the boric acid was applied to all open wounds to improve granulation tissue formation. The debridement procedures and boric acid dressing provided excellent wound granulation, which facilitated and accelerated the primary or secondary wound healing. The 3% boric acid solution was recommended by Blech et al. [11] as an efficient treatment of wounds with loss of substance. Jaiyeoba and Spring [12] reported that boric acid and a lactose mixture provided a strong granulation in the treatment of deep wounds with loss of substance.

In this study, three patients presented with massive swelling that we called "client compartment syndrome" due to the extensive amount of saline extravasation and radio-opaque media extravasation in one patient. We proposed that the client compartment syndrome may develop by several mechanisms, including a systemic or local inflammatory reaction of extravasated agent, displacement or malposition of the intravenous line that increases the propensity for fluid leakage, increased vascular permeability, and external mechanical compression of the fascia. Although the compartment pressure was 20 mm Hg, we considered performing fasciotomies or skin relaxation incisions. Notably, clinical symptoms, including pain with passive and active movements, paralysis, tingling, and firm swelling, were similar to those observed in the compartment syndrome. Massive swelling with pain has been accepted as an indication for compartment syndrome [3]. We have treated three patients with massive swelling of the forearms with limb elevation and conservative modalities (cold pack, anti-inflammatory treatment, and hirudin pomade) without any surgical intervention.

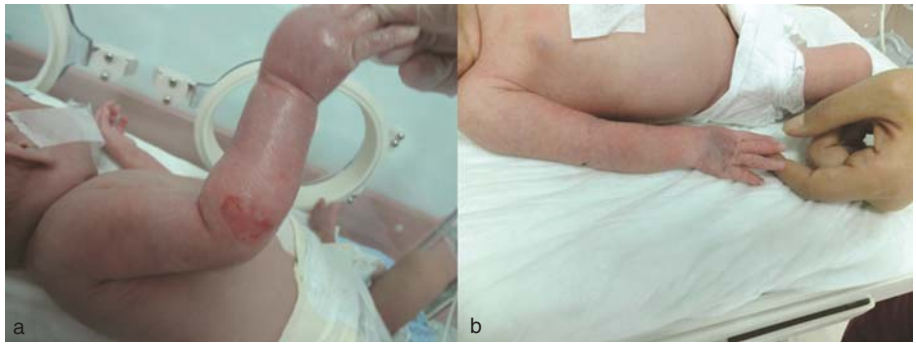

Figure 4. (*a*) Extravasation of Isolyte P in 5% Dextrose after 4 hours. (*b*) The view of the injury, 24 hours after alcohol (ethyl alcohol 70%) application and limb elevation.

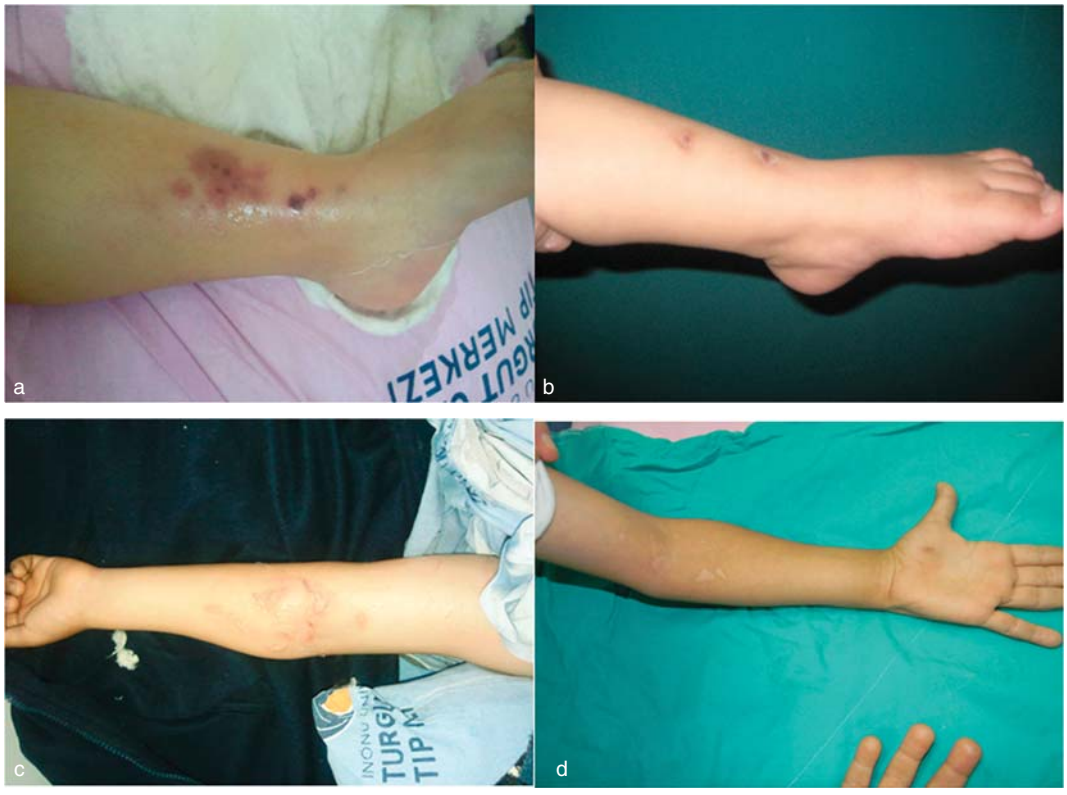

Figure 5. (*a*) Saline extravasation after 6 hours, treated with alcohol dressing. (*b*) View of the injury after 10 months with minimal scar. (*c*) Saline extravasation after 10 hours, treated with alcohol dressing. (*d*) View of the injury after 9 months with hypopigmented areas.

The pharmacological approach with specific antidotes and the injury mechanism of extravasated agents are summarised in Tables III and IV [3,11–16]. The antidotes have been discussed controversially and are not considered standard methods for treatment. In the pharmacological management of extravasation injuries, several drugs have been reported to be ineffective, including antihistamines, heparin, sodium bicarbonate, hydrocortisone, and glucocorticoids [15,16]. In contrast, heparin has been found to be successful in doxorubicin-related extravasation ulcers in experimental studies [17].

Napoli et al. [18] reported their surgical approach in four steps: saline, local anaesthetic, and hyaluronidase infiltration; aspiration through subcutaneous tunnels; washout/irrigation with saline solution (300–500 ml); and reaspiration [18]. Gault [19] was an innovator of this surgical technique, reporting an 86% success rate in his series. We initially employed the local treatment methods for all patients, and the surgical procedure was delayed until the end of the wound-healing period, complete healing, or necrosis. Langstein et al. [20] reported that a few cases (23.8%) required an operation to achieve wound

Table III. Mechanisms and treatment of the extravasated agents.

Agents	Injury mechanism	Antidotes	Type of temperature
Vinca alkaloids (vinblastine, vincristine)	Vesicant agents, direct cellular toxicity	Hyaluronidase*, dexamethasone, hydrocortisone	Warm pack
Carmustine	Direct cellular toxicity, ischemic necrosis	Sodium bicarbonate*	Cold pack
Antracyclines (doxorubicin, daunorubicin, epirubicin)	DNA binding vesicants, direct cellular toxicity	Dimethylsulfoxide (DMSO)*, dextrazoxane, dexamethasone	Cold pack
Cisplatin, Actinomycin D, Dacarbazine, Mitomycin-C	Direct cellular toxicity, ischemic necrosis	Sodium thiosulfate*	Cold pack
Etoposide, Teniposide	Direct cellular toxicity, ischemic necrosis	Hyaluronidase	Warm pack
Calcium, Potassium, Nafcilline, Radiocontrast media, dextrose 10%	Hyperosmotic damage, ischemic necrosis, mechanical compression	Hyaluronidase	Cold pack
Dopamine, Dobutamine, Epinephrine, Norepinephrine, Phenylephrine	Vasoconstriction, ischemic necrosis	Phentolamine*, nitroglycerin, terbutaline	No pressure; warm pack
Fluorouracil, Ifosfamide, Mitoxantrone	Direct cellular toxicity, (vesicant agents) ischemic necrosis	DMSO*, dexamethasone, hydrocortisone	Cold pack

*Most specific antidote.

Table IV. Dose and usage of antidotes.

Antidotes	Dose	Usage
Hyaluronidase	1–6 times of 150-U/mL	Subcutaneously into the affected area
Dimethylsulfoxide (DMSO)	1–2 mL of mM 50–99% DMSO solution	Topical application, every 4–8 hours for 14 days
Dextrazoxane	First 2 days 1000 mg/m^2, 3rd day 500 mg/m^2	Intravenous
Dexamethasone, Hydrocortisone	Twice daily as long as the erythema persists	Cream forms, apply to affected area
Sodium thiosulfate	1/6 molar solution, mix 4 mL of 10% 6 mL of sterile water for injection	2 mL subcutaneously into affected area for each mg extravasated agent
Phentolamine, nitroglycerin, terbutaline	1–2 dose for 1 day after extravasation of vasoconstrictive agents	Orally (terbutalin tablets), topical pomade (nitrogliserin)

healing; the remaining patients could be managed without an operation.

Elevation of the injured site, warm/cold treatments, and anti-inflammatory modalities are crucial to reducing oedema as initial management methods. The application of a cold pack to the injured area is beneficial by decreasing the metabolism and so inactivating the destructive capacity of the extravasated agent [3,20]. In contrast, cold packs are contraindicated in vasoconstrictive agents such as vinca alkaloids (vincristine, etoposide, vinblastine, teniposide) and catecholamines (dopamine, dobutamine, epinephrine, norepinephrine, phenylephrine), so that warm packs should be applied in such agents [3,16,20].

In conclusion, repetitive debridement and boric acid treatment accelerate secondary wound healing or preparation of the wound bed for coverage with flaps or grafts. The boric acid treatment with repetitive debridement is very effective to improve granulation tissue for reconstruction. Extravasation injuries are often encountered. However, morbidity can be reduced by early diagnosis and treatment. Moreover, these injuries can be prevented with the appropriate measures, such as the avoidance of perfusion under pressure, patient participation in pain follow-up, wound management by experienced health professionals, and preference for large and suitable veins.

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The authors have no financial or proprietary interest in any instrument or product used in this study. The project was approved by the institutional ethics committee (05.07.2011, 2011/98).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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