



## Extravasation injuries

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**SUMMARY.** The leakage of cytotoxic drugs, intravenous nutrition, solutions of calcium, potassium, bicarbonate and even 10% dextrose outside the vein into which they are delivered is known not only to cause skin necrosis but also to precipitate significant scarring around tendons, nerves and joints.

In this review of 96 patients with extravasation injuries seen between 1987 and 1992 at St Thomas' Hospital, Mount Vernon Hospital and The Hospital for Sick Children, Great Ormond Street, several patients required extensive reconstruction and in some, despite this, extravasation injury has rendered a limb virtually useless.

Two techniques, liposuction and saline flushout, are described to remove extravasated material while conserving the overlying skin. Analysis of flushout material confirmed that the extravasated material was actually being removed. Forty four of the study group in whom noxious materials were known to have extravasated underwent such early treatment. The results in this group were quite striking—the majority (86%) healed without any soft tissue loss at all. The early referral and treatment of extravasation injuries is, therefore, recommended.

The extravasation of normal saline or 5% dextrose may cause minor discomfort but no long term tissue damage ensues. An extraveneous leak of cytotoxic drugs, calcium, potassium or bicarbonate solutions, however, is known to cause significant tissue necrosis<sup>1</sup>. The extravasation injury and its sequelae can prove more serious than the condition which originally brought the patient to hospital; amputation, for example, has been known to ensue<sup>1</sup>.

Peripheral veins used in the administration of drugs lie beneath the dermis in subcutaneous fat. Extravasation may cause full thickness skin loss above the affected area, but where there is little subcutaneous fat, as on the dorsum of the hand and in the antecubital fossa, the agent may also cause severe damage to the underlying nerves, tendons and joints.

Cancer patients receiving intravenous chemotherapy are particularly prone to extravasation as their veins are often fragile, mobile and difficult to cannulate. Courses of injections may thrombose vessels and limit the number of accessible veins. One girl in the series presented with exposed extensor tendons on her hand 3 months after an extravasation of doxorubicin. Once extravasation has occurred it may be difficult to predict whether a serious soft tissue complication will occur or whether the leak will dissipate without problems. The toxicity of the drug, the site of the extravasation, the amount of the agent that has leaked outside the vein, and the general nutrition of the patient all influence the outcome.

The many papers on the management of extravasation injuries present a diversity of views. Some advocate specific antidotes as the mainstay of treatment<sup>2,3</sup>. Hyaluronidase has been injected to promote drug absorption<sup>4</sup>, and injections of saline have been used to dilute the drug (clysis)<sup>5</sup>. Ice or steroid creams have been recommended to minimise the inflammatory reaction<sup>2,6-9</sup>. Some authors have recommended early

surgical debridement and skin grafting<sup>10</sup>, while others feel that this is excessive and think a "wait and see" policy is more appropriate<sup>7</sup>.

Any technique which allows extravasated material to remain, whether diluted, cooled or treated with an antidote, is less than ideal. The extent of the tissue damage observed in the early patients of this series prompted a search for an alternative treatment—one which would physically remove extravasated material while conserving the overlying skin. This paper presents two such techniques: liposuction and saline flushout.

### Incidence

Extravasation is a common problem, occurring in 0.1-0.7% of cytotoxic drug administrations<sup>2,6,11,12</sup>. Patients receiving a course of cytotoxic injections run a 4.65% risk of extravasation injury<sup>13</sup>. In children, the number of intravenous lines which tissue is high (11-58%)<sup>14,15</sup>. The number of extravasations involving potentially harmful agents is, however, small. In a large series of children, Brown *et al.*<sup>15</sup> reported that extravasation caused skin loss in 0.24% of the peripheral lines sited. These injuries usually follow the extravasation of intravenous hyperalimentation but bicarbonate, calcium and antibiotic solutions may also be responsible<sup>15-17</sup>.

### Materials and method

In all, 96 patients (37 female/59 male), referred to a plastic surgery unit, were reviewed. In each case, a substance capable of causing necrosis had leaked into the subcutaneous tissues.

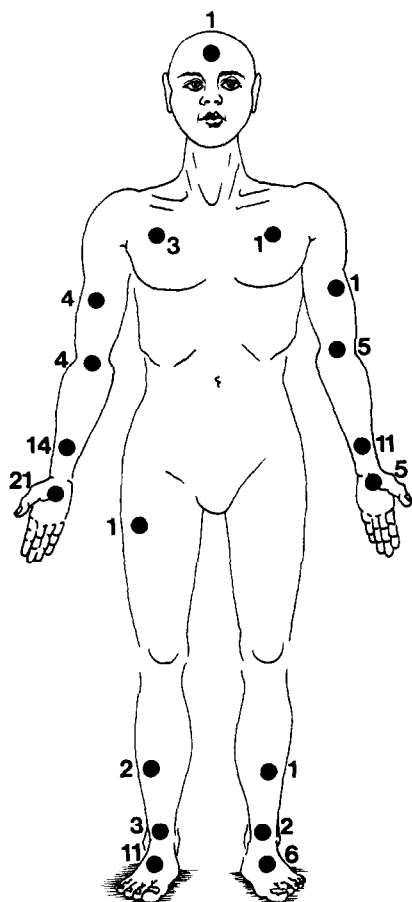


Fig. 1

Figure 1—The location of the extravasation injury in the 96 patients studied.

Forty four of the patients were seen within 24 hours of the extravasation incident and before the overlying skin had become overtly necrotic. In 6 of the patients, liposuction and saline flushout were used in combination to remove the material while conserving the overlying skin. In one liposuction alone was used and in 37 saline flushout alone was used.

#### Liposuction

A small incision is made alongside the area of extravasation under local or general anaesthesia. A blunt-ended liposuction cannula with side holes is then inserted and used to aspirate extravasated material and subcutaneous fat. Vigorous manipulation of the cannula within subcutaneous tunnels is used, as in conventional liposuction.

#### Saline flushout

Where there is little subcutaneous fat, as in pre-term infants, the area of extravasation is infiltrated with hyaluronidase (1 vial = 1500 units) to break down or hydrolyse the hyaluronic acid of the connective tissues. This depolymerisation process results in a decrease in the viscosity of the matrix of connective tissue,

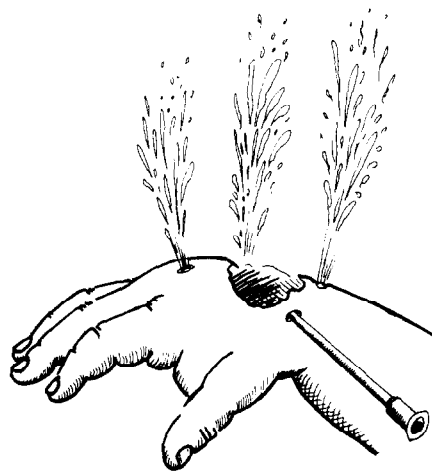


Fig. 2

Figure 2—The saline flushout technique.

rendering it more permeable to injected fluid. Four small exit stab incisions are then made around the periphery of the area of extravasation, and a large volume of normal saline (500 ml) is flushed through the subcutaneous space to cleanse it. The saline is injected through each of the stab wounds in turn and exits through the remainder, a sort of subcutaneous shower (Fig. 2).

To prevent damage to the underlying nerves, tendons or joints, a blunt-ended cannula with side holes is employed to instil the saline. The central component of a "Verres" needle (used to insufflate the abdomen during laparoscopy) has proved ideal for the process.

The saline is injected in 20 or 50 cc aliquots and even in pre-term infants the full 500 cc can be flushed through the zone of extravasation. It is important to check that the flushout fluid does not collect in the surrounding subcutaneous tissues. Should this occur, the fluid can be manipulated down to the exit holes and expressed. In some cases, the flushout fluid has been analysed to confirm that extravasated material is actually being removed.

A sterile technique is important. In those who are immunosuppressed after receiving chemotherapy, for example, prophylactic antibiotic treatment is recommended. After flushout, a layer of jelonet and betadine soaked gauze is applied to the wound and the limb elevated for 24 hours. The stab incisions are never sutured and are allowed to close spontaneously.

Fifty one of the patients were referred late. Some of these patients healed without tissue damage but in 15 cases extensive reconstruction was required.

#### Results

The patients ranged in age from new born and premature infants to 70 years. The mean age of the group was 10 years. The site of injury is recorded in Figure 1. The most common location was the dorsum of the hand. The forearm, cubital fossa and dorsum of the foot were also commonly involved. The agents extravasating are listed in Table 1. Some injuries

**Table 1** The agents extravasating in this review

<i>Metabolic</i>	Calcium	20
	Parenteral nutrition	14
	Dextrose 10–20%	6
	Potassium	3
	Bicarbonate	4
<i>Chemotherapy</i>	Vincristine	17
	Daunorubicin	11
	Doxorubicin	8
	Cisplatinum	1
	VP16	1
	VM26	1
<i>Other</i>	Thiopentone	3
	Flucloxacillin	2
	Blood	1
	X-ray contrast	1
	Heroin	2
	Dobutamine	1
	Total	96

**Table 2** Results

<i>Outcome</i>	<i>Late referral</i>	<i>Flushout</i>
No tissue damage	8	39
Minor skin necrosis or delayed healing	17	5
Scar revision	5	
Skin graft	6	
Contractures	6	
Radial forearm flap	2	
Groin flap	2	
Abdominal flap	1	
Free flap	1	
Amputation	3	
Infection	1	
Total	52	44

The outcome in both the late referral and flushout groups is listed. Where flaps and grafts were required the skin loss was extensive.

followed an urgent infusion to treat metabolic disorders; in this group, calcium, 10% dextrose, potassium and bicarbonate caused particular damage. Of the chemotherapeutic agents, doxorubicin and daunorubicin are particularly worrying as they interfere with the replication of cells involved in the healing process. Their extravasation can present late with ulcers<sup>18</sup> resembling the late ulceration which may follow radiotherapy.

The range of agents extravasating was very similar in the two groups (early and delayed referral). Of the 52 patients referred late, 8 (15%) healed without any tissue necrosis and 17 (33%) suffered only minor sloughing of the skin, so that delayed healing of the area resulted. In the other 27 (52%) patients, extensive damage to the soft tissues was observed (see Table 2). Six patients required flap coverage and 6 needed split skin grafting. Several complications were also seen in this group.

In 2 of the patients, the extent of the extravasation damage was underestimated and the initial excision proved to be inadequate. In these patients, a second flap was required to achieve soft tissue cover. In another patient, the damage to the dorsum of his hand was so extensive that despite tenolysis, joint capsulo-

tomies and flap coverage on two occasions, little useful hand function was regained. Three babies in the group had toes or fingers amputated following the extravasation of bicarbonate or dobutamine shortly after birth.

In the other 44 patients, in whom an attempt was made to remove the extravasated material, 39 (88.5%) showed no signs of soft tissue damage at all and the other 5 (11.4%) exhibited minor skin blistering or delayed healing only. One patient in the flushout group, who was neutropenic and receiving treatment for leukaemia, developed a transient cellulitis in the treatment zone which rapidly responded to antibiotic therapy. Immunocompromised patients treated later in the study were given prophylactic antibiotics at the time of flushout.

In 5 patients with an extravasation of chemotherapeutic agents, the presence of doxorubicin or daunorubicin was confirmed in the flushout fluid when this was analysed using a radioimmuno assay technique. (The flushout fluid was stored at  $-20^{\circ}\text{C}$  until the assay was carried out.)

## Discussion

Extravasation is usually due to leakage around the original puncture site at which the cannula enters the vein<sup>19</sup>. In such cases flow proximal and distal to the infusion site becomes occluded and the rise in intraluminal pressure causes the leak. Phlebitis induced by the acidity of the infusate<sup>20</sup> may lead to eventual vasoconstriction. Commonly used crystalloid solutions are mildly acidic and dextrose solutions have a pH of 4.3 or lower<sup>21, 22</sup>.

Early aggressive treatment of extravasation injuries is clearly of benefit; the key question is where to draw the line on what merits treatment. The nature and amount of the extravasated substance is important. For each drug the pathology may vary considerably. Damage may be due to a direct toxic effect, pressure of the accumulated drug causing collapse of small vessels, changes in the osmotic equilibrium between the extracellular and intracellular fluids, adverse changes in pH or induced vasospasm.

Cytotoxic drugs cause pain, erythema, discolouration of the overlying dermis and tissue necrosis when they leak outside a vein. Local hypothermia is known to prevent alopecia when therapeutic doses of doxorubicin are given<sup>23</sup> and has been reported to help in treating doxorubicin extravasation<sup>7</sup>. Leaving such material in the subcutaneous space, however, would run the risk of the material being incorporated into cell nuclei and gradually destroying tissue to cause late ulceration<sup>18, 24</sup>. Doxorubicin is lipophilic and if not removed quickly will fix to subcutaneous tissues<sup>25</sup>.

When extravasation occurs there is no sure way of knowing which cases will cause significant tissue damage or whether the onset of damage will be delayed. Moreover, it is difficult to compare series from different authors as the amount of a drug extravasated in individual cases is rarely precisely known. Reilly *et al.*<sup>8</sup> found that 7 cases in a series of 10 doxorubicin extravasations progressed to ulcer-



Fig. 3

Fig. 4



Fig. 5



Fig. 6

Figures 3-6. For legend see opposite.

ation while Larson<sup>7</sup>, who recommended the application of ice, noted such problems were less common. Figure 3 shows a patient from the present series. Even when the overlying skin remains intact, significant scarring around tendons, nerves and joints can occur (Fig. 4). One child in this review has the metacarpophalangeal joints of the fingers of his left hand fixed in extension following the extravasation of daunorubicin without associated skin loss.

The extravasation of the hypertonic or acidic solutions used for peripheral intravenous nutrition can cause serious skin sloughs and limb contractures, especially in the premature infant<sup>15,16</sup> and 10% dextrose alone caused extensive soft tissue loss in two patients in this series (Fig. 5).

Calcium and potassium solutions may also cause extensive damage. These salts are slightly acidic<sup>1,16</sup>, hypertonic and capable of precipitating proteins to produce cell death directly<sup>26</sup>. Both 4.2% and 8.4% solutions of sodium bicarbonate cause extensive subcutaneous damage soon after the material leaks out<sup>17</sup> and in such instances urgent removal of the drug is needed. Four patients with bicarbonate injuries are included in this review. The two treated by early flushout conserved their skin while the other two had digits amputated. Ischaemic necrosis can follow the extravasation of vasoactive drugs such as adrenaline, noradrenaline and dopamine<sup>1,15,27</sup>.

The promotion of vasodilation using hot towels prior to cannulation and the maintenance of vein dilation after cannulation with Glyceryl Trinitrate paste are useful tips to mitigate against extravasation<sup>2,28</sup>. The occlusion alarms of positive pressure pumps may help to detect small rises in pressure suggesting an extravasation but such devices are not totally reliable<sup>14</sup>. Special vigilance is needed in patients who may not experience the pain of extravasation, such as diabetic patients with peripheral neuropathy<sup>1</sup> and patients undergoing resuscitation or general anaesthesia.

There will always be patients who, despite meticulous precautions, will sustain soft tissue injuries from tissue drips, just as some surgical patients develop infections and some develop hypertrophic scars. Stopping the infusion is common sense. Aspiration through the cannula in an attempt to remove some of the retained material has been recommended<sup>2,29</sup> but, in practice, achieves little as subcutaneous fat usually clogs the cannula and distresses the patient needlessly<sup>30</sup>.

Hyaluronidase is an enzymic spreading factor which acts by temporarily breaking down the hyaluronic acid which holds tissue planes together. This has proved useful in preventing soft tissue necrosis after extravasation of parenteral nutrition solutions<sup>4</sup> or the vinca alkaloids, vincristine or vinblastine<sup>30,31</sup>. The injection

of hyaluronidase has also been combined with small volumes of saline to disperse and dilute extravasated material<sup>5</sup>.

Introduced to try and avoid the complications of extravasation injury, early flushout and liposuction seems so far to have been successful. It must be undertaken before extensive skin necrosis occurs, and a limit of 24 hours after the injury has been used as the cut off time in this series. When the skin is merely swollen and discoloured with perhaps superficial blistering, the early effects of extravasation may appear quite innocuous. But adoption of a "wait and see" policy runs a great risk of soft tissue damage. Where such patients with definite skin changes have undergone a rigorous saline flushout of the extravasation zone there has often been an immediate improvement in skin colour (Fig. 6).

While in both the early and late referral groups the mix of types of agents extravasating was similar, it is not strictly possible to claim one series as a control for the other, as in each case the amount extravasated is not quantified. Accepting this, however, tissue loss was often extensive in those cases in which the flushout technique was not used. Many of the early patients in this series had already been treated with ice, steroids, or hyaluronidase injections and yet, despite this, problems occurred. Twelve cases required flaps or skin grafts to repair the damage and eleven cases required secondary surgery to revise scars or treat contractures. In three cases, toes or fingers were amputated. In each case treated with flushout or liposuction or both, the overlying skin was conserved and only one complication—a transient cellulitis—was seen in this series.

Patients referred late often present with well demarcated areas of slough. They should have a generous debridement including a margin of normal skin to ensure that a satisfactory bed is created for flap or graft reconstruction. Non viable doxorubicin laden tissue glows reddish/orange under UV light<sup>32</sup> and this may prove useful in ensuring that these wounds are adequately debrided. Skin grafts are known to take poorly in the presence of doxorubicin<sup>33</sup>.

A number of authors have found the soft tissue damage caused by extravasation injuries to be so extensive that they have recommended early excision of the involved area<sup>12,34,35</sup>. The techniques of saline flushout and liposuction offer an alternative treatment which removes material while conserving the overlying skin.

Tissue damage after careful injection of intravenous drugs is more sensibly regarded as a complication of treatment rather than actual negligence. When an agent likely to cause problems does extravasate, referral for flushout at the earliest opportunity can save tissue, since the drug can be removed or its effects minimised. Unfortunately, there is often a natural

**Figure 3**—(A) This 4-year-old girl has had an extravasation of doxorubicin. Redness and swelling developed over 4 days and then settled gradually. (B) Two months later the skin broke down exposing the extensor tendons. (C) A local radial forearm flap was used to reconstruct the defect and hand function was preserved. **Figure 4**—This 9-year-old girl had an extravasation of daunorubicin in her left cubital fossa 5 years ago. A significant contracture developed and extensive calcification is seen on the X-ray. The calcified plaque was excised to restore elbow motion. **Figure 5**—This 2½-year-old child had an extravasation of 10% dextrose to the dorsum of her foot. One month later, a split thickness skin graft was used to heal the wound. **Figure 6**—(A) This newborn infant developed a blue swollen arm shortly after birth. A drip in the arm had been used to deliver a variety of drugs during neonatal resuscitation. (B) Liposuction and the saline flushout technique were used. The arm pinked up immediately.

reluctance to seek an urgent surgical consultation for these patients who have already "suffered enough". The complications of an extravasation injury may, however, be more disabling in the long term than the primary disease. The patient may go into remission, while extensive soft tissue scars will remain a permanent legacy.

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