Extravasation injuries and accidental intra-arterial injection

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Key points

Accidental extravasation and intra-arterial (IA) injection may cause significant permanent tissue injury.

Saline washout is an effective treatment after accidental extravasation.

Early anticoagulation is an important intervention in accidental IA injection with tissue ischaemia.

Prompt management improves outcome, and early referral to a plastic surgeon may be appropriate.

Specific management strategies reduce long-term damage.

Extravasation

Extravasation is the accidental injection or leakage of fluid into the subcutaneous (s.c.) or perivascular tissues. It has been estimated that between 10% and 30% of patients receiving i.v. therapy may experience this complication. Most extravasations have only minor sequelae. However, some drugs can cause serious injury such as necrosis, soft tissue loss, and scarring around nerves, joints, and tendons leading to contractures and deformity. Severe tissue injuries may require extensive surgical debridement, tissue grafting, surgical release of contractures to restore function, or amputation.

Extravasation injury has been frequently described from cytotoxic drugs used in cancer chemotherapy. Personnel working in this field are well aware of the potentially serious consequences of extravasation, and guidelines for its management are generally available in most units. It would be expected that anaesthetists would also see this complication relatively frequently, given the large number of i.v. drugs used. However, there are surprisingly few reports of the management of drug extravasation in the perioperative and intensive care settings, perhaps because the drugs used are not associated with serious consequences when extravasated. However, the tissue damaging effects of many drugs used in these areas are not well known, and those administering them may underestimate the consequences of their extravasation.

Risk factors

Patient factors

The elderly have fragile skin and veins which may rupture on injection. Neonates, infants, and especially ex-premature babies have small veins that may be difficult to cannulate, and the unavoidable use of small cannulae increases the injection pressure. Cannulation of scalp veins in neonates is associated with a high incidence of extravasation, and these should be avoided for induction of anaesthesia. Children and unconscious or sedated patients may be unable to communicate pain at the injection site. Patients who have received multiple i.v. therapies have thrombosed veins, increasing the risk of leakage, while obesity or oedematous tissue may make siting cannulae and detection of misplacement difficult. Patients with concurrent disease causing decreased peripheral sensation or circulation such as peripheral neuropathies, diabetes, Raynaud's disease, and peripheral vascular disease may not be aware of any discomfort when drugs leak into the tissues.

Administration methods

Many drugs in the critical care setting are administered as infusions driven by automated syringe drivers. These may allow a drug to be infused under pressure into the perivascular tissues when a cannula has been misplaced. Such devices should have a pressure-limiting mechanism that triggers an alarm when the resistance to injection becomes elevated. However, a significant volume of fluid is likely to have extravasated before such a pressure increase will occur. With gravity infusions, the pressure generated relates to the height of the bag above the venous access point. The use of pressure bags increases the risk of high volume extravasation.

With bolus injections administered by hand, the pressure required to inject depends on the cannula diameter and length, syringe size, and the viscosity of the solution being injected according to the Hagen–Poiseuille equation. Anaesthetists become familiar with the anticipated resistance to injection, and an alteration in the perceived pressure required to inject should raise the suspicion of cannula misplacement.

Multi-lumen central lines are frequently used in intensive care and during major surgery. The location of the orifices of the

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individual lumens is spaced over the distal few centimetres of the catheter. If central venous catheter insertion depth is insufficient or the catheter migrates towards the skin after insertion, one or more of the proximal orifices of the catheter may be left outside the vessel lumen, with any drugs administered via these lumina entering the perivascular tissues. Extravasation via this route is potentially dangerous because of vulnerable neighbouring anatomical structures, and also it may easily escape early detection.[1]

Drug and formulation factors

All i.v. medications and fluids can cause tissue damage, but certain substances are associated with a greater risk of tissue necrosis and these are shown in Table 1. Vesicants are substances capable of causing inflammation, pain, and blistering of tissues leading to tissue death and necrosis. Exfoliants can cause inflammation and shedding of the skin but are less likely to result in loss of tissue viability. Irritants cause inflammation and irritation but rarely lead to tissue breakdown. Cytotoxic drugs by their very nature damage tissues but are rarely administered by anaesthetists. However, anaesthetists regularly use a number of i.v. agents with vesicant potential. Hyperosmolar substances such as parenteral nutrition solutions or any solution with osmolarity greater than plasma (290 mmol litre^{-1}) cause damage by exerting an osmotic pressure leading to a compartment syndrome. Highly acid or alkaline solutions with pH outside the range 5.5–8.5 can injure tissues. Vasoconstrictor drugs cause local ischaemia and tissue death, and drugs may be prepared in formulations containing alcohol or polyethylene glycol that can precipitate resulting in tissue necrosis. Other formulation factors such as the volume of fluid to be injected and the concentration of drug in the fluid give rise to conflicting risks. The smaller the volume of fluid to be injected the lower the likelihood of extravasation, but a stronger concentration of drug in a small volume increases the risk of damage if leakage does occur. Volume itself is a factor, as extravasation of large volumes may cause localized mechanical compression of tissues leading to ischaemia.

Table 1 Drugs used in anaesthesia/intensive care unit with potential to cause tissue damage

Hyperosmolar agents	Acids/alkalis	Vascular regulators
Calcium chloride	Aminophylline	Epinephrine
Calcium gluconate	Amiodarone	Dobutamine
Glucose >10%	Amphotericin	Dopamine
Magnesium sulphate 20%	Co-trimoxazole	Metaraminol
Mannitol 10% and 20%	Diazepam	Norepinephrine
Parenteral nutrition	Erythromycin	Prostaglandin
Potassium chloride	Phenytoin	Vasopressin
Sodium bicarbonate	Thiopental	
Sodium chloride >0.9%	Vancomycin	
X-ray contrast media		

Table 2 Side-effects of specific anaesthetic drugs

Drug	Side-effects when	
	Extravasated	Injected intraarterially[7]
Amiodarone	Tissue necrosis	Ischaemia
Atracurium	Ischaemia, necrosis	Ischaemia
Atropine	None reported	None reported
Fentanyl	None reported	None reported
Ketamine	Ischaemia, necrosis	Necrosis
Midazolam	None reported	None reported
Morphine	None reported	None reported
Pancuronium	None reported	None reported
Phenytoin	Cellulitis, ischaemia, necrosis	Ischaemia, necrosis, tissue death
Propofol	Usually none	Hyperaemia, distal 'blanching'
Rocuronium	Local irritation	Ischaemia
Succinylcholine	None reported	None reported
Thiopental	Ischaemia, necrosis	Ischaemia, necrosis, tissue death

Pathophysiology

Tissue damage results from one or more of the following pathophysiological mechanisms:[2]

(i) Vasoconstriction and ischaemic necrosis.
(ii) Direct toxicity.
(iii) Osmotic damage.
(iv) Extrinsic mechanical compression by large volumes of solution.
(v) Superimposed infection.

The degree of damage caused by extravasation is related to the nature (Table 2) and amount of drug extravasated, and the speed with which extravasation is recognized. Tissue damage may not become apparent until 1–4 weeks later by which time it is irreversible.

Recognition of extravasation

Careful observation during injection of drugs will help identify extravasation early. No 'flashback' of blood returning from a cannula on insertion suggests that it may not be in the vessel lumen, but flashback is not always seen with very small cannulae and these should be flushed before use. Peripheral cannulae should ideally be visible to the anaesthetist and be directly observed during administration of the drug. Resistance to injection greater than expected for cannula size is suspicious, and an i.v. gravity infusion that fails to run or drips very slowly relative to its expected rate also suggests misplacement of the cannula.

Pain on injection may be due to the nature of the drug (such as propofol) or may be a symptom of extravasation. Swelling of the tissues around the cannula on injection suggests fluid leakage, and blanching may result from either an increase in tissue pressure due to fluid volume or vasoconstriction due to extravasation of a vasoactive drug. Inflammation, erythema, or blistering around the cannula site after injection are all signs that tissue injury may be occurring.

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Differential diagnosis

Certain drugs are known to cause localized reactions that do not necessarily result in tissue injury. Propofol, ondansetron, rocuronium and cyclizine can all cause discomfort or pain on injection which is thought to be due to vessel wall irritation. Venous spasm can also occur due to rapid administration of a cold drug or vasoconstrictors, producing localized skin blanching.

Minimizing the risk of extravasation

Site your own cannulae or check placement of *in situ* lines before use. Avoid siting cannulae in the antecubital fossa or over joints if possible, as patient movement may cause displacement. Use an appropriately sized cannula for the vein to minimize trauma to the vessel walls. Flush the cannula with saline before use to check for ease of injection and absence of tissue swelling, or attach an i.v. infusion and check the flow rate. If in doubt, take it out and recannulate. Ensure the dressing is secure and prevents cannula movement. Use a clear dressing and do not cover the cannula site with bandage to allow direct observation. Check for swelling or inflammation around cannulae at frequent intervals during injection and ask the patient to report any pain, stinging, or burning sensations during injection. I.V. infusion sites must be observed regularly. Check the pressure settings on infusion pumps and do not override them without good reason. With central lines, aspirate from the lumen you are about to use to ensure that proximal lumens have not migrated out of the vessel. Be aware of the extravasation policy/kit (if there is one) in your department.

Management of extravasation

Prompt, appropriate management will minimize subsequent injury. Management should follow local guidelines and will generally fall into the following phases (summarized in Table 3).

Early management

Stop drug administration and if possible aspirate from the cannula to reduce the amount of drug present in the tissues. The potential for serious injury should be identified and subsequent management determined according to this risk; the cannula should be left in place until this has been determined and then removed to prevent further use and injury.

Table 3 Management of extravasation injury

Stop the injection/stop and disconnect the infusion immediately
Aspirate as much drug as possible from the cannula
Leave the cannula in place until advice sought regarding further treatment. When no longer required, remove immediately to prevent further use and injury
If visible, mark the area of extravasation with a pen or take photographs
Elevate the limb
Consider specific treatments if appropriate
Consider referral to plastic surgery
Ensure documentation is complete

General management

For most extravasations, general treatments aimed at minimizing the concentration of drug at the site will be enough to allow healing and prevent further injury—the 'spread and dilute' approach; only in the case of extravasation of cytotoxic agents is a 'localise and neutralise' policy applicable. The limb should be elevated to reduce swelling and promote venous drainage. Heat may be used via warm compresses to promote vasodilatation and increase drug reabsorption and distribution. The application of moist heat can lead to maceration and necrosis of the already delicate tissues, and care must be taken to avoid this by monitoring the site regularly.[3]

Secondary management including specific antidotes

For drugs that are associated with a high risk of tissue damage, further treatments can be used to minimize the risk of permanent injury.

Saline washout

This is probably the most effective way of removing drug from the site of extravasation and has been shown to reduce tissue injury. Under sterile conditions with local or general anaesthesia, four to six stab incisions are made around the area of extravasation. A blunt-ended cannula is inserted through one of the incisions and a large volume of saline flushed through the s.c. tissues, exiting through the other incisions.

Liposuction

A blunt-ended liposuction cannula is inserted into the area of extravasation and used to aspirate fat and extravasated material. This is less effective than saline washout.[1]

Steroids

Hydrocortisone and dexamethasone have both been used for their anti-inflammatory action, usually by injection into the cannula through which the extravasation occurred. There is, however, little evidence that the use of steroids by topical, s.c., or i.v. routes alters outcome.

Hyaluronidase

This enzyme has a temporary and reversible depolymerizing effect on the polysaccharide hyaluronic acid, which forms the intercellular matrix of connective tissue. Depolymerization makes the tissues more permeable, aiding the dispersion or flushing out of extravasated material. 1500 units are dissolved in 1–2 ml of saline and injected into the area of extravasation. There is no clear evidence that this method is of benefit when used alone without a washout procedure.

Phentolamine

Infiltration of this α-adrenergic blocking agent will relax vascular smooth muscle and produce vasodilatation. Early use may be of benefit after extravasation of vasopressors; 5–10 mg is prepared in

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10 ml of normal saline and given by multiple s.c. injections into the affected area.

Regional sympathetic block

Stellate ganglion block has been reported to relieve the tissue ischaemia caused by extravasation of vasopressors and thiopental. Lumbar sympathetic blocks are used in the management of sympathetically mediated pain syndromes and ischaemic pain, but there have been no reports of their use in lower limb ischaemia.

Documentation and follow-up

Although extravasation injury after careful injection through an i.v. cannula could be viewed as an unfortunate complication of a necessary therapy, medicolegal proceedings are not uncommon. The scarring, loss of function, and need for multiple reconstructive surgical procedures resulting from an iatrogenic injury can cause significant psychological stress. Events and their management must be clearly documented in the patient's notes, with photographs if possible. Immediate referral to a plastic surgeon is warranted for high-risk extravasations to allow early washout. If conservative management is used, patients must have follow-up arrangements in place and be counselled to report any tissue changes immediately.

Intra-arterial drug injection

Intra-arterial (IA) injection of drugs may cause acute, severe extremity ischaemia and gangrene. Fortunately, this is a rare event, and because of this, the actual incidence is difficult to quantify. Historically, accidental IA injection occurred when drugs were given via a 'butterfly' or even simply a needle; the most common error now is the administration of drugs via an arterial line, but accidental arterial cannulation does still occur.

Risk factors

An early symptom is discomfort and pain on injection, and so unconscious or sedated patients and trauma patients with distracting injuries are at risk. The morbidly obese and those with darkly pigmented skin are also at risk, as are hypotensive patients when the arterial pulsatile flashback into a cannula may be difficult to see. In both anaesthesia and critical care, indwelling arterial cannulae are commonly inserted. Patients are often sedated, ventilated, and receiving multiple infusions through lines with numerous ports and it is easy to see how a drug can be inadvertently given IA.

Most cases of accidental IA cannulation involve radial artery branches of the forearm and hand and are often due to vascular anomalies. The most common are a 'high-rising' radial artery resulting in a superficial branch in the forearm, and the *antebrachialis superficialis dorsalis* artery which crosses underneath the terminal branch of the cephalic vein just superficial to the radial styloid process.[4] The antecubital fossa and groin are also sites for error, simply because of the proximity of the arteries and veins in these sites.

The drugs which cause the most severe injury are barbiturates (Table 2), and drug formulations have changed over the years to reflect this; the notorious 5% thiopental which caused damage by precipitation of crystals which formed when the alkaline drug reached arterial pH is no longer available.

Pathophysiology

Many processes are thought to be responsible for the common presentation of tissue ischaemia distal to the injection site.[4] In summary, these include:

- arterial spasm, either caused by the local release of norepinephrine or directly mediated by the drug;
- direct tissue destruction by the drug;
- subsequent chemical arteritis leading to endothelial destruction;
- release of endogenous substances that mediate deleterious effects themselves, for example, thromboxane;
- drug precipitation and crystal formation within the distal microcirculation leading to ischaemia and thrombosis.

Recognition

The first sign may be that the drug fails to have the expected effect. Patients usually complain of immediate severe discomfort distal to the site of injection. Pallor, paraesthesia, hyperaemia, and cyanosis of the affected limb develop and severe cases may progress to develop profound oedema and gangrene.

Management

There is no universally accepted treatment protocol; most interventions attempt to maintain perfusion distal to the site of injury. The affected extremity should be elevated to improve venous and lymphatic drainage, and analgesia given as a priority. The extent of the injury should be identified and documented carefully and plastic surgery advice sought. As thrombosis is ultimately the cause of the tissue injury, anticoagulation with heparin should be considered in an attempt to limit the extent of the ischaemia. Other specific interventions include:

Local anaesthetic injection

IA injection of lidocaine through the implicated cannula may prevent reflex vasospasm. However, this procedure may actually damage the artery and compromise the blood supply to the already affected limb.[5]

Extremity sympatholysis

Stellate ganglion blocks and lower-extremity sympathetic blocks will produce sustained arterial and venous vasodilatation, but the

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potential benefit must be weighed against the risks of the procedure.

Other pharmacological therapies[4]

Calcium channel blockers have been tested with varying results. Thromboxane promotes vasoconstriction, and drugs which inhibit thromboxane (aspirin, methylprednisolone) may help to reverse the tissue ischaemia. Iloprost is a prostacycline analogue with vasodilatory and platelet-inhibiting properties and IA papaverine facilitates vascular smooth muscle relaxation; both these have been used as part of a multimodal approach to treatment with varying success.

Prevention

Inadvertent IA cannulation and injection may be hard to detect as the classic signs of cannula misplacement may not be apparent and the drug may inject easily with few local signs. Warning signs include:

- The cannula 'flashback' appears pulsatile.
- The flashback blood appears redder than expected.
- It is possible to palpate a pulse proximal to the cannula.
- There are distal signs of ischaemia.
- Inserting the cannula was more painful than expected.

If there is doubt as to the accurate placement of a cannula, it could be transduced for an arterial waveform or blood sampled for blood gas analysis. However, by far the safest approach is to remove the cannula if there is any doubt that it is placed in an artery. In the case of arterial lines, a protocol should exist for the management of arterial cannulae which aims to minimize the likelihood of accidental drug administration.[6]

Conflict of interest

None declared.

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Please see multiple choice questions 9–12.

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