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REVIEW ARTICLE/BRIEF REVIEW

The incidence, significance, and management of accidental intra-arterial injection: a narrative review

Incidence, importance et prise en charge des injections intra-artérielles accidentelles: un compte rendu narratif

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Abstract *This narrative review discusses the incidence, risk factors, mechanisms of injury, complications, and treatment regimens for accidental intra-arterial injection of medications. Despite awareness of the issue and the establishment of safety recommendations by national agencies, accidental iatrogenic intra-arterial injection of medications continues to occur. Most of these injuries are caused by accidental injection into an established arterial cannula or the inadvertent and unrecognized cannulation of an artery instead of a vein. Although many medications have been injected into arteries without significant consequence, a number of drugs are consistently associated with severe morbidity, including the need for amputation, making early incident recognition and treatment vital. Accidental intra-arterial injection of medications has also been increasingly reported in those who use illicit drugs, as these intravenous injection attempts can be misdirected into an artery. These reports have improved understanding of these injuries and possible treatment modalities. While the characteristics of injuries from illicit injections are diverse and the optimal treatment modalities are still uncertain, a regimen that includes anticoagulation and intra-arterial injection of thrombolytics and prostaglandins may improve outcomes. Steroids, vasodilators, and sympathetic blocks do not appear to influence amputation rates. Owing to the small and sporadic number of cases, no definitive clinical trial evidence exists, but the treatment modalities found to be useful in the illicit intra-arterial injection group may benefit treatment of similar iatrogenic injuries.*

Résumé *Ce compte rendu narratif traite de l'incidence, des facteurs de risque, des mécanismes de lésion, des complications et des régimes thérapeutiques lors de l'injection intra-artérielle accidentelle de médicaments. Malgré la reconnaissance de ce problème et la mise en place de recommandations de sécurité par les organismes nationaux, les injections intra-artérielles iatrogéniques accidentelles de médicaments surviennent encore. La plupart de ces lésions sont provoquées par l'injection accidentelle dans une canule artérielle déjà en place ou la canulation par inadvertance et non reconnue d'une artère au lieu d'une veine. Bien que de nombreux médicaments aient été injectés dans des artères sans conséquence importante, plusieurs médicaments sont régulièrement associés à une morbidité grave, notamment au recours à l'amputation, ce qui rend essentiels tant l'identification que le traitement rapides de l'incident. L'injection intra-artérielle accidentelle de médicaments est également rapportée de manière plus fréquente chez les personnes utilisant des drogues illicites, étant donné que ces tentatives d'injection intraveineuse peuvent accidentellement se retrouver en intra-artériel. Ces comptes rendus ont amélioré la compréhension de ces lésions et les modalités de traitement possibles. Alors que les caractéristiques des lésions provoquées par des injections illicites varient beaucoup et que les modalités optimales de traitement demeurent incertaines, un régime thérapeutique incluant une anticoagulation et l'injection intra-artérielle d'agents thrombolytiques et de prostaglandines pourrait améliorer les pronostics. Les stéroïdes, les vasodilatateurs et les blocs sympathiques ne semblent pas avoir d'impact sur les taux d'amputation. En raison du petit nombre de cas et de leur aspect sporadique,*

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aucune donnée probante définitive tirée d'une étude clinique n'existe, mais les modalités de traitement qui se sont avérées utiles dans le groupe d'injection intra-artérielle illicite pourraient également être bénéfiques pour traiter des lésions iatrogéniques semblables.

Accidental intra-arterial drug injection is an uncommon complication of anesthetic and critical care practice, and is associated with serious morbidity, including chronic pain and tissue necrosis, often necessitating amputation. These morbid events have been documented in the anesthetic literature for over 70 years, often related to the injection of thiopental.[1] The replacement of thiopental with propofol in contemporary anesthetic practice has clearly reduced thiopental-related complications but iatrogenic intra-arterial injection-related injuries still occur. Given the broad characteristics and formulations of available drugs, it is not surprising that some accidental injections are associated with significant complications and morbidity, while others have little to no sequelae. This makes treatment regimens difficult to evaluate and standardize, given the low number of occurrences for each individual medication.

Historically, most intra-arterial injections occur in hospital settings, including the operating room (OR) and intensive care unit (ICU). In the past two decades, however, there has been a significant increase in the number of accidental intra-arterial injections outside of the hospital setting. These involve the use of recreational drugs, some of which are also often medications in common anesthetic use (e.g., opiates and benzodiazepines). In particular, the oral form of many benzodiazepines is inexpensive, readily available, and the tablets can be ground into a paste and injected, making their reported intra-arterial injection more frequent. These cases can be complex, given the tablets may contain binding agents that were not intended for injection; in addition, the time to presentation can be extended and variable. Nevertheless, they provide important outcome, mechanistic, and potential treatment information.[2,3]

The aim of this narrative review article is to discuss the risk factors, pathophysiology, and recently developed treatment modalities for accidental intra-arterial drug injections encountered in anesthetic, critical care, and emergency department practice.

A literature review utilizing PubMed, EMBASE, and Cochrane databases from inception to April 1, 2018 was performed. English language articles were identified using the search terms, "accidental intra-arterial injection" and "inadvertent intra-arterial injection" as well as "intra-arterial injection [drug]" for drugs commonly used in anesthetic practice (propofol, fentanyl, vecuronium, rocuronium, atracurium, thiopental, midazolam, diazepam, penicillin, cefazolin, clindamycin, succinylcholine, epinephrine, ephedrine, dopamine, and atropine). The references from these articles were also checked for additional relevant articles. In addition to articles concerning drugs relevant to anesthetic and critical care practice, those describing illicitly injected medications were also included.

Incidence

As shown in Fig. 1, of the 1,825 articles initially identified, 78 were selected for more detailed review. These included 30 articles describing iatrogenic injuries involving 35 patients, 17 articles pertaining to the injection of illicit medications in 93 patients, as well as a number of articles relating to the science of endothelial injury, pharmacology, and related review articles. In the group of patients suffering iatrogenic injuries, benzodiazepines and penicillin-based drugs were the most commonly identified drugs associated with severe complications such as gangrene. In these patients, the most frequent causative error was the accidental cannulation of an artery, which occurred in 21 patients. Accidental injection into an *in situ* arterial monitoring system occurred in 13 patients. Of the 93 patients who suffered injuries related to the injection of illicit medications, 24 required amputation. The most commonly injected illicit medications were crushed benzodiazepines (most commonly flunitrazepam), and the majority of these were accidentally injected into an upper extremity artery.

There are approximately 60 reported cases of severe ischemia (in 70 years of literature) resulting from accidental iatrogenic injection.[4] The incidence of iatrogenic inadvertent intra-arterial injection has been estimated to be between 1:3,440 and 1:56,000, based primarily upon decades old data, and during the more common use of thiopental.[5] The true incidence in today's practice is difficult to evaluate because of significant underreporting due to lack of recognition (especially in anesthetized or sedated patients who may not verbalize a painful injection) and the fear of potential professional and medico-legal consequences. For example, in a survey of 56 ICU directors in the United Kingdom in 2014, 16 respondents (28.5%) reported they had personally witnessed an accidental injection into a pre-existing arterial monitoring cannula in the previous five years, yet few were actually reported, suggesting a much higher incidence rate than that in the published literature.[6] It is possible that new anesthesia incident reporting systems

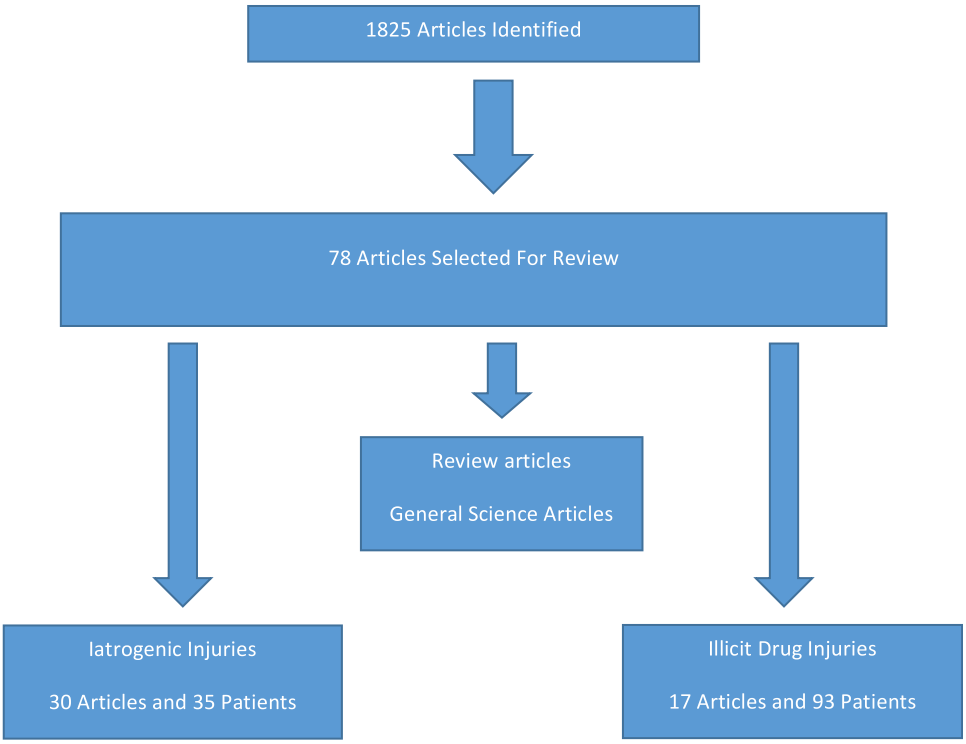

Fig. 1 Study selection

will make it easier to confidentially report these types of patient safety issues.[7]

Risk factors for iatrogenic intra-arterial injection

In the clinical setting, iatrogenic intra-arterial injection of medications most often occurs because of inadvertent cannulation of an artery instead of the intended vein, or the accidental injection of medications into an *in situ* arterial monitoring system. Table 1 summarizes the medications injected, site of injection, and the treatment and outcomes that have been reported in the literature. A number of risk factors for the accidental cannulation of an artery have been described, including the recent introduction of a new cannula, which incorporates a feature to prevent backflow of blood. This feature makes recognizing accidental arterial cannulation more difficult.[38] The attempted cannulation of a vein in close proximity to an artery is also an important risk factor for inadvertent arterial cannulation.[20] For example, the proximity of the brachial artery to the basilic vein in the antecubital fossa was the location of the most frequent accidental cannulation and occurred in nine of 21 described incidences (Table 1). Eight cases occurred in the forearm, one on the dorsum of the hand, and one in the femoral artery. No incorrect vessel cannulations were noted at the time of the puncture, nor was an ultrasound used to identify deeper vessels.

An aberrantly located radial artery in the lateral aspect of the forearm is an anatomic anomaly, which occurs in 0.8-1% of individuals. This artery has been accidentally cannulated instead of the intended target, the cephalic vein.[39,40] The cannulation of the radial artery in this location was described in two separate case reports. In both instances, the arterial cannulation was noticed prior to drug administration and there were no significant complications.[39,40] Another anatomical anomaly that predisposes accidental cannulation occurs when the radial artery runs a superficial course through the anatomic snuff box (occurring in 0.5-1% of individuals).[41] The cannulation of this artery, the antebrachialis superficialis dorsalis artery, has been described.[41] Promethazine was injected, and despite surgical exploration, two digits had to be amputated. Although seemingly unlikely, arterial cannulation has also been reported on the dorsal surface of the hand in an anesthetized three-year-old. Propofol was injected and there were no permanent sequelae.[19] Signs suggestive of an inadvertent cannulation include a bright red flashback into the cannula, pulsatile backflow, and an intravenous catheter that runs poorly or not at all.[5]

Accidental injection into an *in situ* arterial monitoring system was responsible for 13 of 34 iatrogenic events in this review. Suggestions to minimize this type of cognitive error include better labelling, colour-coded tubing, minimizing the number of injection ports, and locating sampling ports nearer to the insertion site.[14] Lack of staff training and workload are often cited when these errors occur.[42]

Table 1 Reports of iatrogenic intra-arterial injections including the drug involved, treatment, and outcomes

Author (year)	Number of cases	Site of injection	Drug involved	Treatment	Outcome
Fell[1] (1953)	1	Lateral forearm	Curare	Procaine	No deficit
Mazumder *et al.*[8] (1980)	1	Lateral forearm	Thiopental 2cc	Heparinized saline	No deficit
Rees and Dormandy[9] (1980)	1 of 2	Lateral forearm	Diazepam	3 days post injury heparin and streptokinase	Amputation
Rees and Dormandy[9] (1980)	2 of 2	Ventral forearm	Diazepam	Block Heparinized saline	Chronic pain
Chong and Davis[10] (1987)	1	Anticubital	Propofol	None	Brief hyperaemia and no deficit
Marsch and Schafer[11] (1990)	1	Arterial cannula	Midazolam	None	No deficit
Holley and Cuthrell[12] (1990)	1	Arterial cannula	Propofol	None	No deficit
Andreev *et al.*[13] (1995)	1	Anticubital	Azlocillin (extended spectrum penicillin)	Heparin Streptokinase Iloprost (Prostacyclin)	No deficit
Jones[14] (1995)	1 of 2	Arterial cannula	Phenytoin	Papavarine and stellate ganglion block	Gangrene and death by other causes
Jones[14] (1995)	2 of 2	Arterial cannula	Dopamine infusion	None	No deficit
Ozel *et al.*[15] (1995)	1	Lower limb (attempted intramuscular injection)	Penicillin		Amputation
Kessell[16] (1996)	1	Femoral	Atracurium	Caudal block	No deficit
Joist[17] (1999)	1	Anticubital	Diazepam	Heparin and surgical exploration	Amputation
Ohana *et al.*[18] (1999)	1	Lateral forearm	Propofol	None	No deficit
Duggan and Braude[19] (2004)	1	Dorsum hand	Propofol	None	No deficit
Saad and Horn[20] (2007)	1	Anticubital	Midazolam and Demerol	Heparin	No deficit
Mirzatolooei and Afshar[21] (2008)	1	Anticubital	Diazepam	Heparin and surgical exploration	Amputation
Mitani *et al.*[22] (2009)	1	Arterial cannula	Propofol	None	No deficit
Kjaergaard and Rovsing[23] (2010)	1	Lateral forearm	Propofol	None	No deficit
Aghoutane *et al.*[24] (2010)	1	Anticubital	Floxacillin	Surgical exploration and heparin	Amputation
Iblher *et al.*[25] (2011)	1	Forearm	Diazepam	3 days after injury urokinase, heparin, and prostaglandin	Amputation
Lehavi *et al.*[26] (2011)	1	Arterial cannula	Clindamycin	Papavarine, block, dexamethasone, and heparin	Chronic pain
Jain *et al.*[27] (2012)	1 of 2	Arterial cannula	Neostigmine and glycopyrrolate	None	No deficit
Jain *et al.*[27] (2012)	2 of 2	Arterial cannula	Neostigmine and atropine	None	No deficit
Dutton[28] (2013)	1	Arterial cannula	Aminocaproic acid	None	No deficit
Prabhu *et al.*[29] (2014)	1	Lateral forearm	Pentazocin	Heparin	Amputation

Table 1 continued

Author (year)	Number of cases	Site of injection	Drug involved	Treatment	Outcome
Shenoi *et al.*[30] (2014)	1	Arterial cannula	Propofol	None	No deficit
Shukla *et al.*[31] (2014)	1	Anticubital	Rocuronium and fentanyl	Heparinized saline	No deficit
Samanta *et al.*[32] (2014)	1 of 2	Arterial cannula	Paracetamol in benzyl alcohol	Heparin and lidocaine	Amputation
Samanta *et al.*[32] (2014)	2 of 2	Arterial cannula	Paracetamol aqueous solution	None	No deficit
Kozar and Kurnik[33] (2015)	1	Arterial cannula	Ephedrine	Nitroglycerine and heparin	No deficit
Singh *et al.*[34] (2015)	1 of 2	Anticubital	Benzyl penicillin	Heparin	Amputation
Singh *et al.*[34] (2015)	2 of 2	Lateral forearm	Benzyl penicillin	Heparin, ASA, and clopidogrel	Distal finger necrosis
Witkowski *et al.*[35] (2016)	1	Anticubital	Amiodarone	Heparin, ticagrelor, tirofiban thrombus aspiration	Compartment syndrome
Ghatak *et al.*[36] (2013)	1	Arterial cannula ulnar	Dexmedetomidine	None	No deficit
Hanci *et al.*[37] (2016)	Animal study	Intra-arterial rabbit ear injection	Sugammadex	None	Histologic arterial damage

ASA = American Society of Anesthesiologists

Proposed mechanisms of injury

A number of mechanisms of injury have been reported, and these include direct endothelial injury, vasospasm, drug crystallization, and thrombosis.[6] How an inadvertent arterial injection damages a vessel is not completely understood and is probably complex given the wide variety of pharmaceuticals and formulations available. A number of drugs used in anesthetic practice (fentanyl, succinylcholine, pancuronium, atropine, rocuronium) have been injected intra-arterially without causing serious damage to vessels, while others (thiopental, diazepam) have caused significant morbidity.[9,31,43,44] Early studies noted that drugs that caused necrosis, such as thiopental, were more lipophilic, which may have caused the tissue damage. More recently, however, a number of cases studies have shown that propofol, which is also lipophilic, causes severe pain upon intra-arterial injection, but no necrosis.[12,44] Similarly, midazolam (another highly lipophilic drug, though not supplied in a lipid formulation) has been injected intra-arterially without significant complications compared with its class partner (and less lipophilic drug) diazepam, where arterial injection has been associated with significant morbidity, including the need for amputation.[9,11,20,25]

The potential for damage depends on the drug injected, and also its formulation. For example, in the case of inadvertent intra-arterial injections of paracetamol, one preparation utilizing a benzyl alcohol formulation was reported to cause gangrene, while injection of an aqueous paracetamol formulation was benign.[32] Similarly, diclofenac in a benzyl alcohol-based preparation caused necrosis and gangrene, while the aqueous version caused no significant damage.[45] Benzyl alcohol, studied primarily as a preservative agent, induces the intracellular production of reactive oxygen species in endothelial cells, and activates caspase-driven apoptotic pathways.[46,47] In a dose and time dependent pattern, benzyl alcohol disrupts the integrity of endothelial layers and promotes cell death through the activation of apoptotic pathways and non-specific tissue necrosis.[47,48]

Illicit drugs, in the form of crushed tablets, often are contaminated with binding agents, including cellulose. These binding agents may exert their own effects, in addition to those of the drug itself. Although the lack of understanding of a distinct pathway or mechanism complicates the evaluation of proposed treatment regimens, there are likely candidates that can be targeted to mitigate potential damage from most substances.

Direct endothelial injury

As stated above, many pharmaceuticals used in an OR or ICU setting are lipophilic, so can rapidly cross tissue barriers (i.e., the blood-brain barrier) and exert effects directly on cellular membranes or cell membrane receptors.

In humans, lipid soluble drugs such as thiopental and diazepam induce tissue necrosis after arterial injection compared with more hydrophilic drugs such as ketamine, fentanyl, rocuronium, and pancuronium.[43,44] In an animal model of injection into rabbit ear arteries, thiopental (unrelated to preparation, pH, or preservatives) crystalized downstream in arterioles and had a direct cytotoxic effect on endothelial cells (see text below).[49] Interestingly, the drug did not damage smooth muscle cells, suggesting a cell-specific mechanism that is distinct from direct ischemia or physical damage.[44,47] Diazepam, in the same rabbit ear model, induced gangrene, but did not crystalize. Within minutes of injection, the ears appeared dusky and endothelial cells began to swell (shown by electron microscopy).[44] Four hours after injection, electron microscopy revealed endothelial cell swelling and cellular membrane disruption. Seven to ten days after injection, intra-arterial thrombosis was observed.[44]

Although the intra-arterial injection of propofol causes severe pain on injection, no severe permanent damage, such as gangrene, has been reported.[10,22] In the rabbit ear model, propofol did not damage endothelial or smooth muscle cells, and the vessels remained responsive to acetylcholine-mediated dilatation and noradrenalin-mediated constriction.[50] Although propofol is lipophilic, it does not damage endothelial cells in a manner similar to other lipophilic drugs, indicating that the lipophilicity model of injury on its own does not account for vessel and tissue injury. Propofol also activates endothelial nitric oxide synthase, increasing nitric oxide (NO) levels and protecting cells from oxidative stress through decreased caspase-3 activation.[51,52] Propofol improved endothelial barrier function.[53] Whether these factors are protective of endothelial cells and subsequent distal ischemia during intra-arterial injection has not been fully investigated.

Endothelial cells have a complex role involved in the maintenance of vascular tone, platelet activation, and the coagulation cascade. Intact endothelial cells release NO, which serves as a vasodilator and prevents platelet activation. Endothelial cell destruction prevents local NO release, resulting in vasoconstriction and platelet activation.[54] Endothelial cells also produce prostacyclin (PGI_2) and thromboxane (TXA_2), which cause vasodilatation and constriction, respectively.[54] Thromboxane is released after intra-arterial injection of thiopental in a rabbit ear model.[49] Endothelial cells can release mediators of vessel tone, including endothelin-1 and endothelium-derived hyperpolarizing factor. Damage to endothelial cells promotes clotting through platelet activation via the release of Von Willebrand factor and activation of the intrinsic and extrinsic coagulation pathways.[54,55] In summary, endothelial cell damage causes vasoconstriction, platelet activation, and thrombosis, which likely contribute to the adverse effects of a drug that is injected into an artery.

Vasospasm

Vasospasm occurs in two phases after intra-arterial injection. The first phase begins almost immediately after injection and can last up to 15 min. The second usually occurs 24-48 hr after the injury. In a rabbit femoral artery injection model, the initial phase was not thought to contribute to gangrene based on its timing, brevity, and rapid return of blood vessel diameter to baseline.[56] In a rabbit ear model, pretreatment with the rapidly acting vasodilator tolazoline (an alpha adrenergic blocker) had no effect on outcome, confirming that early, direct vasospasm does not contribute to damage.[57] Clinically, this initial phase of vasospasm is consistent with the intense pain awake patients experience upon intra-arterial injection of drugs and may be accompanied with localized blanching. The pain usually subsides within 15 min and the blanching is often followed by hyperemia..9,10[23] Consistent with this, direct intra-arterial injection of vasoconstrictors or compounds that exacerbate vasospasm (i.e., epinephrine, ephedrine, and cocaine) causes intense pain in awake patients. This is usually accompanied by discolouration, but the effect is transient and without permanent sequelae.[33,58,59]

The second phase of vasospasm can contribute to ischemic injury once endothelial cell damage occurs. As outlined above, the mechanism by which this occurs includes diminished levels of NO and the release of TXA_2.[50,54] The net result of these is tissue ischemia caused by vasoconstriction and promotion of thrombosis by reduced flow.[50,54] This is consistent with the timing of ischemic changes seen after arterial injection (i.e., usually occurring one to two days after the inciting event in both human and animal models).[44,57] Interestingly, despite reduction of vessel diameter in the rabbit ear model, the degree of gangrene was unchanged by pretreatment with the vasodilator reserpine (an antihypertensive that blocks catecholamine reuptake from sympathetic nerve endings in the peripheral vasculature that is effective up to three days).[49,57]

Drug crystallization

Thiopental has a pKa of 7.2, but is clinically available in a highly alkaline solution (i.e., pH = 10.5) and crystallizes when mixed in high concentrations with blood at a physiologic pH (crystallizing as thiopentone with hemoglobin).[58] This is not observed when the drug is

injected intravenously as the concentration is significantly reduced in the venous circulation by rapid dilution.[60] In arterial injections, thiopental crystallizes in the narrowing vessels approaching the distal capillary bed. In animal models of intra-arterial injection, crystals are formed and are carried distally where they obstruct the vessels causing endothelial cell damage.[44] The mechanism and importance of crystallization in selective thiopental-mediated endothelial cell damage is not known.[44] Importantly, the injection of a strongly alkaline solvent does not mimic the toxic effects of thiopental, indicating that the pH is not the cause of pathology.[60]

The role of crystallization as a mechanism of injury was further tested by experimental femoral artery cocaine injections in a dog.[61] In this model, injection of purified cocaine had no permanent detrimental effect on the distal vasculature, but addition of micro-crystalline cellulose to the solution caused gangrene. Similarly, accidental intra-arterial injection of zolpidem powder, which also contains cellulose, suggested that micro-crystalline cellulose may act as a thromboembolic nidus in (or immediately proximal to) the capillary bed.[62,63] Finally, drug crystallization was reported in the intravenous tubing when thiopental and rocuronium were injected one directly after the other. The intravenous line became occluded and the cannula had to be re-positioned.[64] This reaction was thought to be the result of the large difference in pH between the two drugs (pH 10.5 and 4). Although the drugs did not crystallize in arterial circulation, this case highlights the potential complications of injecting different medications in close temporal proximity to one other.

Thrombosis

Initial vascular injury can occur after drug injection through a combination of endothelial injury, vasospasm, and drug crystallization. Nevertheless, the final common pathway that leads to tissue damage and limb ischemia is thrombosis.[65] As early as 1959, thrombosis was recognized as an important mechanism of injury after the intra-arterial injection of thiopental, and improved outcomes were observed with early heparinization.[56] Endothelial cell damage can cause platelet surface adherence, swelling, and release of mediators that reduce vessel diameter.[49,54] Similarly, crystal formation can block blood flow.[44] These factors promote thrombosis through stasis, endothelial injury, and hypercoaguability (i.e., Virchow's triad). Anticoagulation with heparin reduced the extent of thiopental induced necrosis in the rabbit ear model.[56] As a result, heparin has been the cornerstone of treatment protocols for many years. The promising results utilizing thrombolysis as a treatment modality for illicit drug-induced ischemia support thrombosis as a key mechanism of injury.[3,62,66,67]

Evaluating injury severity

In a clinical setting (i.e., iatrogenic injection-related injury), the offending drug is often known. Nevertheless, even with this knowledge, determining treatment based on the literature can be challenging because there are not many reports for a given drug and the severity of reported injuries are highly variable. Additionally, multiple treatments or interventions are often undertaken simultaneously, and started at different intervals after the injury, making efficacy challenging to delineate.

In 1990, the Tissue Ischemia Score (TIS) was developed to clinically evaluate injury severity and predict outcomes in patients with arterially injected illicit drugs.[2] The original study evaluated 48 patients over a 17-year period. All patients received a similar treatment protocol, consisting of heparin (10,000 unit *iv* bolus, followed by an infusion to maintain the partial thromboplastin time (PTT) at 1.5-2.5 times normal), dexamethasone (4 mg *iv* q6hr), a platelet inhibitor (low molecular weight dextran 20 $mL{\cdot}hr^{-1}$, opioids for pain control, and elevation of the extremity. The investigators determined that (upon presentation) cyanotic colour, capillary refill $>$ 3 sec, cool temperature, and sensory deficits were the greatest predictors of prolonged/permanent tissue damage and adverse outcome. Pulse deficit, motor deficit, weakness, numbness, and time to evaluation were not predictive in their evaluations. From this data, the authors developed the TIS, where each predictive factor is scored as a 1 if present and 0 if absent. When utilizing the treatment regimen described, patients with a maximal score of 2 or less had more favourable outcomes and 3 required a limited amputation. Those that had a maximal score of 3 or 4 had a 46% chance of requiring amputation. In this study, the drugs most commonly injected were Ritalin (methylphenidate Hcl) and barbiturates, and their effects on outcome were not independently evaluated.

In a separate study, a smaller ($n = 7$) group was assessed and followed up clinically after the self-injection of illicit medications (including benzodiazepines, opioids, and zolpidem). In this study, angiography was also performed on each patient.[68] Patients with abnormal skin sensation and delayed capillary filling (and therefore a high TIS if calculated) also had absent blood flow distal to the site of injury, and eventually required amputation. Those patients with normal sensation generally had some distal blood flow, and did not require amputation. This study validates the TIS and illustrates the potential predictive capacity of angiography.

Clinical course

We identified nine separate publications that detailed the clinical evolution of serious injuries caused by the iatrogenic injection of drugs that are relevant to OR or ICU settings. Eleven patients were involved. Five cases involved diazepam, four involved penicillin or its analogues, and one each involved clindamycin or paracetamol in benzyl alcohol.[9,15,17,21,24-26,32,34] The typical clinical courses from these reports are shown in Table 2. Of the 11 patients in these publications, eight required amputation, two suffered from chronic pain, and one developed distal necrosis of the fingers. Of note is the extreme variability in time taken to develop signs of ischemia (from four to 72 hr), even in patients injected with the same drug. Although not strictly limited to arterial injection, short-lived but severe pain on injection is common, and may be used as a warning of potential arterial injection. Pain more typically reappears a few hours post-injection, and this delayed pain is often the first sign that a significant injury will result. The delayed pain is typically followed by other signs of ischemia, including delayed capillary refill, limb discolouration, and abnormal sensation. It is important to note that since these signs take several hours to appear, their initial absence does not rule out a subsequent significant injury. Likewise, the early presence of peripheral pulses does not predict positive outcomes, as vascular impairment occurs distally in the microvasculature.[9]

Illicit drug injection

Although the above-described clinical course is typical for iatrogenic intra-arterial injection of conventionally prepared medications, the sequence of events is similar to that observed when illicit medications are injected.[2,9,17] The initial complaint is often severe pain upon injection, which quickly subsides. Pain reappears and other signs of ischemia develop over the next few hours but often take 24-48 hr to fully manifest. It is at this later time point that these patients usually seek medical attention. The similarity in the signs, symptoms, and time frame in which they occur suggests a similar mechanism of injury, which includes initial vasospasm, possible crystallization, followed by endothelial injury and thrombosis.

Treatment modalities

Historically, proposed treatment regimens were based on the results of case reports (often of a single patient) and animal experimentation, which, combined with the variety of injected drugs and formulations, has made establishing protocols challenging. The intravenous injection of illicit medications has increased and the consequences of accidental intra-arterial injections of these drugs may be useful in improving the outcomes of iatrogenic injuries. The following treatment options were obtained from 17 studies of illicit drug injection, the largest of which contained 48 patients. Table 3 summarizes these studies, including the drugs injected, treatment undertaken, and outcomes.

General measures

Initial and delayed pain are common, resulting from vasospasm, edema, and subsequent ischemia. Pain relief, utilizing intravenous and/or oral analgesics and elevation of the extremity have been suggested, although these do not modulate the outcome.[62] The largest study, which included 48 patients who injected illicit medications, did not include antibiotic administration in its protocol and no cases of cellulitis, sepsis, or gangrene were reported.[2] A smaller study, which included five patients who accidentally injected illicit mediations, developed a treatment protocol that included administration of antibiotics only if there were signs of infection.[65] The protocol for initiating antibiotic therapy was not defined in the article.

Vasodilators

Despite the role of vasospasm and arterial obstruction in adverse outcomes, animal studies have failed to show

Table 2 Time course after intra-arterial injection

Time	Clinical features	Angiography
At time of injection	Severe pain	
4-24 hr	Peripheral pulses palpable	
	Pain: mild burning to severe	
	Normal sensation and colour	
4-72 hr	Swelling	Abnormal distal flow
	Severe pain	
	Deceased sensation	
	Poor capillary refill	
	Discolouration	
	Peripheral pulses palpable	
3-14 days	Necrosis	

Note: Based upon Rees 1980, Ibhler 2011, Lehavi 2011, Mirzatolooei 2008, Joist 1999, Aghoutane 2011, Singh 2015, Ozel 1995, Sumanta 2014

Table 3 Illicit drug injections: site, drug, treatment, and outcomes

Author (year)	Number of cases	Site of injection	Drug involved	Treatment	Outcome
Righini[4] (2005)	1	Forearm	Crushed midazolam	Heparin Tissue plasminogen activator (tPA) Axillary block	Distal amputation
Treiman *et al.*[2] (1990)	48	Various	Various but most commonly Ritalin and barbiturates	Heparin Dextran 40 Elevation	22 of 24 with low Tissue Ischemia Score normal, 2 distal amputations 10 of 24 with high Tissue Ischemia Score normal 11 amputations 3 functional deficits
Ipaktchi *et al.*[3] (2008)	1	Ulnar artery	Crushed zolpidem	Urokinase then heparin	Normal
Simon *et al.*[59] (2008)	1	Upper extremity	Flunitrazepam and cocaine	Nitroglycerine Tolazolin Urokinase Iloprost (prostacyclin)	Compartment syndrome distal amputation
Rohn[62] *et al.* (2013)	16	Various	Flunitrazepam	Heparin tPA	13 normal 1 minor amputation 1 leg amputation 1 neurologic dysfunction
Chang[63] *et al.* (2003)	1	Radial artery	Crushed zolpidem	Heparin Hyperbaric O_2 Vasodilators Prostacyclin	Amputation
Breguet[65] *et al.* (2014)	5	Upper extremity	Crushed midazolam x3 Cocaine x1 Antiseptic x1	Heparin tPA	3 normal 1 distal necrosis 1 septic arthritis
Hering[66] *et al.* (2006)	3	Brachial x2 Radial x1	Flunitrazepam	Prostaglandin E1 tPA	2 normal 1 distal ischemia after late presentation
Silverman[67] *et al.* (1991)	3	Upper extremity	Heroin Methamphetamine Meparidine	Streptokinase Tolazoline Heparin	Normal
Rautio[68] *et al.* (2006)	7	Upper extremity	Crushed benzodiazepines and/or buprenorphine	#1 heparin and vasodilators #2 heparin, vasodilators, thrombolysis #3 antibiotics #4 nifedipine, block, then heparin #5 thrombolysis, heparin, block #6 heparin, nifedipine #7 heparin	#1 amputation #2 amputation #3 normal #4 distal amputation #5 distal amputation #6 normal #7 normal
Bittner[69] *et al.* (2002)	1	Brachial	Crushed benzodiazepines	Urokinase, heparin, axillary block	Normal
Leifert[70] *et al.* (2008)	1	Femoral	Crushed flunitrazepam	Urokinase Prostaglandin Heparin	Normal

Table 3 continued

Author (year)	Number of cases	Site of injection	Drug involved	Treatment	Outcome
Radeleff[71] *et al.* (2011)	1	Femoral	Flunitrazepam	Lidocaine Prostaglandin E1 Urokinase tPA	Normal
Hohenstein[72] *et al.* (2014)	1	Femoral	Crushed diazepam	Heparin Nitroglycerine Prostaglandin E1 Femoral nerve block	Normal
Gouny[73] *et al.* (1999)	1	Ulnar artery	Crushed buprenorphine	Iloprost (protacylclin) Dextran 40 Nifedipine Nadroparine (anti Xa)	Normal
Samuel[74] *et al.* (1993)	1	Femoral artery	Adulterated heroin	Iloprost	Normal
Seak[75] *et al.* (2012)	1	Upper extremity	Crushed meprobamate	Heparin Dextran Steroids Hyperbaric O_2	Distal amputation

improved outcomes after thiopental injection with the use of vasodilators such as reserpine and tolazoline.[57] Nevertheless, intra-arterial, intravenous, and oral administration of vasodilators have been used to treat a small number of patients after accidental intra-arterial injection, often in combination with other treatment modalities. The most obvious use of vasodilators is after the accidental injection of vasoconstrictors. The short half-life of most vasoconstrictors, however, often negates the need for vasodilators, and short-term accidental injection of medications such as dopamine generally have favourable outcomes.[20] Nevertheless, nitroglycerine, in combination with heparin and acetylsalicylic acid, was used to treat an intra-arterial injection of ephedrine with a good outcome.[33]

In cases of non-vasoconstrictor injection, vasodilators such as nitroglycerine, calcium channel blockers, tolazoline, and papavarine have also been reported. These medications have had mixed results. Benefits have been observed and no harm has been noted from vasodilator medication itself. A single article reported successful treatment of a patient after an illicit drug injection using nifedipine combined with prostaglandins, and failed treatment in a similar patient with a combination of nifedipine and heparin.[68] Recently, Devulapalli *et al.*, published a multivariable regression analysis looking at the relationship between treatment modalities and amputation rates.[76] All patients in the study suffered injuries from the inadvertent injection of illicit medications. The review analyzed 25 studies including 209 patients and showed no relationship between vasodilator treatment and amputation rates. The limitations of this study included a small sample size ($n = 39$) of patients who actually received vasodilators, and that those patients who did get vasodilators usually got combination therapy, making the isolation of vasodilator efficacy challenging. Therefore, the use of vasodilators as part of a standard treatment regimen could not be recommended.[76]

Steroids

Drug-induced damage to endothelial cells and the release of inflammatory mediators suggest a potential role for steroids in therapeutic protocols. Treatment with steroids has been reported in a number of case reports, always in combination with other treatment modalities, again with mixed results.[13,34] Devulapalli *et al.*,[76] analyzed the relationship between steroid treatment and amputation rates. The steroids and their method of delivery were not stated, and the study was limited by the fact that the steroids were always administered in combination with other treatments. In the initial analysis, steroid administration was associated with lower amputation rates, but adjustment for potential confounding variables such as severity of injury revealed that this association was no longer statistically significant.[76] As such, there is no definitive evidence of benefit from steroid administration.

Sympathetic block

Surgical sympathectomy was used to decrease the severity of thiopental-induced necrosis in a rabbit ear model.[56] Similar results were not shown after an iatrogenic injection of clindamycin was treated with papavarine, heparin, dexamethasone, and an axillary nerve block; this resulted in an ischemic extremity and chronic pain.[26] Chronic pain was also reported after an iatrogenic diazepam injury was treated three days after the injury with intra-arterial procaine, heparinized saline, and a brachial plexus block.[9] In one patient, a caudal block successfully treated a femoral arterial atracurium injection, but other atracurium-related injuries have not been reported.[15] Brachial plexus or stellate ganglion blocks did not improve amputation rates after the injection of illicit medications.[76] Nevertheless, the evaluation of block efficacy was limited by the small number of patients who received this treatment, the heterogeneity of the patient population, and the variable delay in time of presentation.[76] Importantly, the use of nerve blocks (in particular neuraxial) is limited in patients who receive anticoagulants or thrombolytics.

Anticoagulation

Anticoagulants have been advocated by early animal studies in which tissue damage was diminished by heparin pretreatment (primarily for barbiturates). Almost all case reports have used anticoagulants to prevent thrombosis and to maintain blood flow. Nevertheless, Devulapalli *et al.*'s recent systematic review suggested anticoagulation made no difference to outcome.[76] Given the lack of any controlled trials in the literature, it is difficult to truly ascertain whether patient outcome is improved by anticoagulant treatment, despite the reasonable link to disease pathology. Recently published regimens, based on studies involving patients using illicit medications, continue to recommend immediate heparin treatment combined with thrombolytics and prostaglandins. A bolus dose of 5,000 IU *iv* and an infusion to maintain the PTT in the range of 2.0-2.5 times control is suggested.[39,65] In these studies, the heparin infusion is continued for at least 72 hr (and for as long as eight days), although there are no known benefits of continuing beyond the three-day period when most pathology manifests. Radiology has also yielded conflicting results as to whether heparin improves outcomes when using thrombolytic agents to treat ischemic limbs affected by atherosclerosis and whether any incremental bleeding risk justifies its use.[77]

Thrombolysis

Thrombosis is an important mechanism of tissue injury in patients who suffer accidental intra-arterial injection of illicit medications, therefore thrombolytics have been used to treat patients with these injuries.[65] All thrombolytic medications work in a similar fashion, as plasminogen activators. Treatment with streptokinase and urokinase was common in the past. Now, these drugs have been replaced by recombinant tissue plasminogen activator (rt-PA).[77] The complications of accidental intra-arterial injection of illicit medications are treated by thrombolytics, infused via an arterial catheter placed proximal to the site of injury. The rationale for intra-arterial infusion is increased efficacy and reduced systemic bleeding complications compared with systemic intravenous infusions.[4] A number of regimens have been described. Urokinase, for example, has been used with an initial bolus of 250,000 IU followed by an infusion of 60,000 IU over 12 hr.[69] Recombinant tissue plasminogen activator has been used with an initial bolus of 8 mg followed by an infusion of 1 $mg{\cdot}hr^{-1}$ as well as 5 mg infused over four hours alternating every four hours with an infusion of prostaglandin PGE_1 5 ug for 48 hr.[62,65]

Case reports of clinical improvement of ischemic extremities after injection of crushed and dissolved tablets and re-establishment of distal blood flow (shown angiographically) suggest a role for thrombolysis.[3,66,67,69-71] The most compelling evidence is a report of 16 patients published by Rohm *et al.*, in 2014. All patients injected crushed tablets and all had a TIS above 2, yet 13 of these patients had a good outcome with a regimen that included heparin 5,000 IU bolus maintaining PTT 2-2.5 times control, and intra-arterial prostaglandin PGE_1 5 ug infusions alternating every four hours with the thrombolytic rt-PA 5 mg.[62] This compares with only ten of 24 patients with similarly severe injuries who had a good outcome utilizing a regimen of heparin, dextran, and dexamethasone.[2] In another study, five additional cases of intra-arterial injection and high TIS were reported. These were treated with heparin 60 $IU{\cdot}kg^{-1}$ followed by an infusion to maintain PTT 1.5-2.3 times control plus intra-arterial rt-PA 8 mg bolus and 1 $mg{\cdot}hr^{-1}$. All patients showed significant clinical and angiographic improvement.[65] Further support for the use of thrombolytics was reported in three cases of intra-arterial injection of dissolved flunitrazepam into patients with occluded distal blood flow (angiographically proven). Initial treatment with intra-arterial prostaglandin E1 did not help, but an alternating regimen using rt-PA and prostaglandin E1 resulted in complete reperfusion.

Excellent clinical outcomes were achieved in two patients and the third (who had the longest delay before treatment was initiated) suffered minimal loss of distal digits.[66] Good outcomes were reported in two cases of dissolved flunitrazepam injection treated with anticoagulation, prostaglandins, and thrombolysis. This offers further support for a treatment regimen that incudes heparin, prostaglandins, and thrombolysis.[70] It is important to note that the above reported case reports were in patients with illicit drug injuries only.

There is a single case report describing the use of thrombolytics after an iatrogenic injury. A 28-yr-old patient was accidentally injected with cloxacillin into the ulnar artery. He returned six days later complaining of extreme pain in his medial three fingers. These were noted to be cold, blue, and mottled. Initial treatment with heparin, nifedipine, and acetylsalicylic acid offered no improvement. Angiography confirmed diminished flow to the fingers. Treatment with urokinase and heparin improved pain and restored flow (shown by repeat angiography). The result was normal extremities.[78]

Prostaglandins

Prostacyclin (PGI_2) is synthesized by endothelial cells and binds prostacyclin receptors located on platelets and vascular smooth muscle. It inhibits platelet aggregation and causes vasodilatation, which is the rationale for its use in intra-arterial injection injuries that may damage endothelial cells.[54,62] In some treatment regimens, prostaglandin E1 (PGE1) is used, which also inhibits platelet aggregation and causes vasodilation.[60] The efficacy of prostaglandins is difficult to evaluate because prostaglandins, heparin, and thrombolytics are usually used in combination.[62,70,71] Nevertheless, some case reports have indicated that prostaglandins may be of benefit. An intra-arterial injection of crushed diazepam, which resulted in a high TIS, was treated with heparin and a nerve block with little effect. The addition of intra-arterial prostaglandin E1 20 mg twice daily and intra-arterial nitroglycerine resulted in marked improvement and a good limb outcome.[72] An additional case report describing the iatrogenic injection of intra-arterial penicillin reported severe pain and a high TIS. The patient was successfully treated with heparin and streptokinase. A recurrence of symptoms 14 days later was initially treated with heparin with little effect and subsequently treated with Iloprost, (prostaglandin PGI_2, 0.25 $ng \cdot kg^{-1} \cdot min^{-1}$ via intra-arterial catheter) with good results.[13] The rationale for combination therapy with prostaglandins and thrombolytics is the increased efficacy of thrombolytics with the platelet inhibiting properties of prostaglandins.[60] This effect was possibly illustrated in a case report noted previously where three patients with intra-arterial flunitrazapam injuries and a high TIS were treated with heparin and 20 μg intra-arterial PGE_1 with little effect. Marked improvement was noted when the regimen was changed to infusions of 5 mg rt-PA over four hours alternating with 10 μg PGE_1. Two patients made a full recovery, and the third had residual finger-tip necrosis.[64] These results are consistent with those of Rohm *et al*., who used heparin in addition to four-hour cycles of intra-arterial 5 mg rt-PA alternating with PGE_1 5 μg.[60] Although difficult to prove with a limited number of case reports, it appears that prostaglandins may best be used in combination with thrombolytics.

Summary recommendations

Accidental intra-arterial injection of medications continues to occur in clinical settings. Iatrogenic injection can be reduced by vigilant placement of intravenous cannulae, and by avoiding injection sites that are close to an adjacent artery (in particular with the brachial artery and cephalic vein). Early recognition of inadvertent intra-arterial cannulation is particularly important to mitigate long-term injury.[20] Cognitive aids (i.e., coloured tubing) can help identify arterial tubing injection ports.[14] Should an intra-arterial injection occur, knowledge of the agents that are likely to cause permanent injury is important. Table 4 summarizes commonly used anesthetic drugs that were injected intra-arterially, signs and symptoms of the injury, treatment undertaken, and outcomes. Thiopental, diazepam, penicillin, and clindamycin are commonly implicated in severe injury. An experimental animal study involving sugammadex is included.[37]

The presentation, time sequence, and complications of injuries caused by illicit intra-arterial injections and iatrogenic injuries suggest a similar pathophysiology and it may be possible to extrapolate the evaluation of injury severity and treatment options derived from one group to the other.

Initiation of treatment of an iatrogenic injury can be guided by the TIS, but importantly should rely on repeated clinical evaluation. Ongoing monitoring for important signs of ischemia including cyanosis, delayed capillary refill, cool temperature, and sensory deficits are key to timely and appropriate treatment.[2] There is no strong evidence to suggest that mandatory treatment in the absence of clinical symptoms improves outcome. Keeping the offending arterial cannula in place is recommended to allow angiography to evaluate blood flow throughout the extremity and the direct administration of medications such as thrombolytics and prostaglandins by intra-arterial infusion.[5] Early consultation with experts in

Table 4 Summary of reported iatrogenic cases, treatments, and outcomes

Medication	Signs/symptoms	Treatment	Outcome	Reference (year)
Diazepam Case 1	Pain on injection Day 1 increased pain, normal pulses Day 2 pain, decreased sensation, discolouration, and poor cap refill	Streptokinase 2 days after injury for 3 days followed by heparin for 3 days	Amputation	Rees and Dormandy[9] (1980)
Diazepam Case 2	Pain on injection Day 1 increased pain Day 2 increased pain and discolouration, pulses present	Intra-arterial heparin Brachial plexus block Lidocaine	Persistent pain for 1 month Power and sensation gradually improved	Rees and Dormandy[9] (1980)
Diazepam	Increasing pain for 3 days Cyanosis Angiogram showed complete distal blockage	Presented 3 days after injury: Urokinase for 2 days Heparin Prostaglandin started 4 days after injury	Amputation	Iblher *et al.*[25] (2011)
Diazepam	Pain on injection Day 2 red swollen cold with paresthesia Day 5 discolouration and necrosis	Heparin 10 days after injury	Amputation	Joist *et al.*[17] (1999)
Diazepam	Pain on injection 3 hr later paresthesia and severe pain 7 hr later swelling, pallor, and loss of peripheral pulses	Heparin Lidocaine Surgical exploration	Amputation at elbow	Mirzatolooei and Afshar[21] (2008)
Propofol	Pain Hyperemia	None	Normal	Chong and Davis[10] (1987)
Propofol	Pain Hyperemia	None	Normal	Holley *et al.*[12] (1990)
Propofol	Sedated patient no change in vital signs noted	None	Normal	Shenoi *et al.*[30] (2014)
Propofol	Pain Hyperemia Swelling	None	Normal	Kjaergaarn and Rovsing[23] (2010)
Propofol	Pain Hyperemia, then blanching	None	Normal	Ohana *et al.*[18] (1999)
Propofol	Increased heart rate under anesthetic	None	Normal	Mitani *et al.*[22] (2009)
Ephedrine	Normal colour Warm Vasospasm angiographically	Heparin Nitroglycerine reversed vasospasm	Normal	Kozar and Kurnik[33] (2015)
Rocuronium + Fentanyl	Hyperemia Sluggish capillary refill	Intra-arterial heparinized saline and lidocaine	Normal	Shukla et al.[31] (2008)
Atracurium	Mottled lower extremity from femoral injection Cold	Caudal block resulted in vasodilatation	Normal	Kessel[16] (1996)

Table 4 continued

Medication	Signs/symptoms	Treatment	Outcome	Reference (year)
Clindamycin	No immediate changes Cold and discoloured extremity 5 hr later Discolouration	Axillary block Intra-arterial papavarine Heparin Dexamethasone	Chronic pain	Lehavi *et al.*[26] (2011)
Benzyl penicillin Case 1	Pain on injection with blanching 12 hr later discolouration Cold	Heparin immediately	Amputation distal phalanx	Singh *et al.*[34] (2015)
Benzyl Penicillin Case 2	Pain on injection blanching, paresis, numbness, and burning Cold, clammy with absent pulses 30 min later improved blanching and return of peripheral pulses	Patient already taking anticoagulants ASA and clopidogrel and started on LMWH and hydrocortisone	Gangrene distal phalanx	Singh *et al.*[34] (2015)
Penicillin	50 mg dose given	Heparin	Amputation	Ozel *et al.*[15] (1995)
Floxaciline	7-yr-old developed severe pain and cyanosis on injection	Stellate ganglion block Surgical exploration Heparin	Amputation	Aghoutane *et al.*[24] (2011)
Atropine + Neostigmine	None	None	Normal	Jain *et al.*[27] (2012)
Atropine + Glycopyrrolate	None	None	Normal	Jain *et al.*[27] (2012)
Paracetamol in benzyl alcohol	Pain on injection	Heparin	Amputation	Samanta *et al.*[32] (2014)
Paracetamol in aqueous solution	None	Heparin	Normal	Samanta *et al.*[32] (2014)
Dopamine	None 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min	None	Normal	Jones[14] (1995)
Midazolam + meperidine	Pain on injection Red with white spots	Intra-arterial heparin Lidocaine	Normal	Saad and Horn[20] (2010)
Midazolam	None	None	Normal	Marsch and Schafer[11] (1990)
Dexmedetomidine	None	None	Normal	Ghatak[36] (2013)
Sugammadex	Animal study only inject intra-arterial rabbit ear	None	Histologic arterial damage	Hanci[37] *et al.* (2016)

ASA = acetylsalicylic acid; LMWH = low molecular weight heparin

vascular surgery and interventional radiology should be strongly considered.

Reports of accidental intra-arterial injections of illicit drugs have facilitated the evaluation of possible treatments. While much remains uncertain, evidence suggests that certain therapies are worthwhile. For those at risk of limb ischemia or necrosis, the most supported treatment paradigms include immediate anticoagulation with heparin, urgent infusion of both thrombolytics and prostaglandins through an intra-arterial catheter, and supportive pain control.[62,65,66,70] There is little evidence from these case studies to support other vasodilators, steroids, or sympathetic blocks.

There are limitations to this review. It is based upon retrospective case reports and series rather than randomized trials. Multiple therapies were often initiated simultaneously after highly variable periods of time. Nevertheless, our recommendations may be of value in reducing the potentially significant morbidity from intra-arterial drug injection.

We suggest a protocol primarily based on knowledge gained from the treatment of injuries from intra-arterial injections of illicit drugs being adapted to iatrogenic

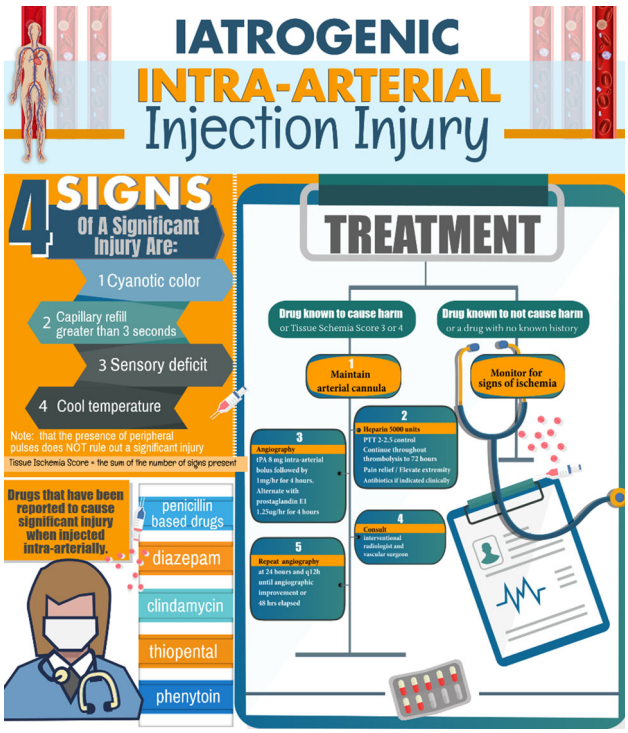

Fig. 2 Infographic outlining a clinical approach to dealing with iatrogenic intra-arterial injection injury

injuries (Fig. 2). The recommended protocol is based upon a review of available literature and not intended to be an evidence-based practice guideline. With iatrogenic injuries, treatment can begin immediately if the drug is suspected to cause significant injury. Symptoms of ischemia may not appear for hours (or days) and peripheral pulses do not preclude significant injury.

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