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Guidelines for management of actual or suspected inadvertent intra-arterial injection of sclerosants

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Abstract

Background: Inadvertent intra-arterial injection of sclerosants is an uncommon adverse event of both ultrasound-guided and direct vision sclerotherapy. This complication can result in significant tissue or limb loss and significant long-term morbidity.

Objectives: To provide recommendations for diagnosis and immediate management of an unintentional intra-arterial injection of sclerosing agents.

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Methods: An international and multidisciplinary expert panel representing the endorsing societies and relevant specialities reviewed the published biomedical, scientific and legal literature and developed the consensus-based recommendations.
Results: Actual and suspected cases of an intra-arterial sclerosant injection should be immediately transferred to a facility with a vascular/interventional unit. Digital Subtraction Angiography (DSA) is the key investigation to confirm the diagnosis and help select the appropriate intra-arterial therapy for tissue ischaemia. Emergency endovascular intervention will be required to manage the risk of major limb ischaemia. This includes intra-arterial administration of vasodilators to reduce vasospasm, and anticoagulants and thrombolytic agents to mitigate thrombosis. Mechanical thrombectomy, other endovascular interventions and even open surgery may be required. Lumbar sympathetic block may be considered but has a high risk of bleeding. Systemic anti-inflammatory agents, anticoagulants, and platelet inhibitors and modifiers would complement the intra-arterial endovascular procedures. For risk of minor ischaemia, systemic oral anti-inflammatory agents, anticoagulants, vasodilators and antiplatelet treatments are recommended.
Conclusion: Inadvertent intra-arterial injection is an adverse event of both ultrasound-guided and direct vision sclerotherapy. Medical practitioners performing sclerotherapy must ensure completion of a course of formal training (specialty or subspecialty training, or equivalent recognition) in the management of venous and lymphatic disorders (phlebology), and be personally proficient in the use of duplex ultrasound in vascular (both arterial and venous) applications, to diagnose and provide image guidance to venous procedure. Expertise in diagnosis and immediate management of an intra-arterial injection is essential for all practitioners performing sclerotherapy.

Keywords
Sclerosants, sclerotherapy, necrosis, intra-arterial injection, practice guidelines

Introduction

Tissue necrosis is a significant adverse event of sclerotherapy of lower limb superficial veins. Multiple pathogenic mechanisms have been implicated in the aetiology of skin necrosis following sclerotherapy (Table 1). Inadvertent intra-arterial injection of sclerosants is the most devastating cause of necrosis with potential for significant morbidity including severe and long-term debilitating pain, paraesthesia and dysesthesia, motor dysfunction including foot drop, tissue loss, compartment syndrome and critical ischaemia, gangrene of the toes or the foot complicated by infection and septicaemia requiring limb amputation.[1,2]

The true incidence of this adverse event is unknown and is presumably an under-reported event. In a review of adverse events reported to the Federal Adverse Event Reporting System (FAERS) of the United States Food and Drug Administration (FDA) between 1970 and 2021, 18 cases of "injection site necrosis" were reported. These were broadly attributed to perivascular extravasation, injection into arterioles, extension through arteriovenous (AV) anastomoses or excessive post-treatment compression.[3]

These consensus recommendations were developed based on a request by the Office of the Health and Disability Commissioner (HDC), New Zealand, following a catastrophic case of bilateral intra-arterial injection of sclerosants into the

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Table 1. Proposed pathogenic mechanisms implicated in the aetiology of skin necrosis following sclerotherapy.

Mode of Delivery	Intravenous	Intravenous	Intra-arterial	Extravasation
Pathogenic mechanism	Veno-arteriolar reflex vasospasm (VAR-VAS)[57]	Open arteriovenous (AV) anastomoses (shunts)[57] and incompetent boundary valves	Arterial/arteriolar occlusion	Soft tissue toxicity
End-target event	Skin infarction secondary to arteriolar occlusion		Skin and soft tissue infarction secondary to arterial vessel occlusion	Non-target cell toxicity causing tissue necrosis
Immediate symptoms	Tissue necrosis secondary to VAR-VAS and open AV shunts is not usually painful immediately - but is often painful as necrosis develops over days to weeks		Severe radiating and burning pain	Minimal or no pain (detergents); painful (irritants/osmotic agents)
Immediate physical signs	Blanching/mottling that evolves into stellate retiform purpura		Blanching mottling that evolves into stellate retiform purpura. Devitalised skin/ digits	Swelling Erythema
Outcome	Stellate necrosis Usually small areas (<5cm2)		Stellate necrosis Soft tissue necrosis Complicated by infection and gangrene May require amputation	Round necrosis
Increased risk	High pressure injections	Areas affected by lipodermatosclerosis	Medial ankle Popliteal fossa - small saphenous artery	Irritant and osmotic sclerosants
Error/Cause	High pressure High volume High concentration sclerosants	Normally no technical error in the delivery of the procedure	Lack of anatomical consideration Ultrasound technical error	Technical error, excessive volume
Prevention	Avoid high pressure/ high volume/high concentration	If possible avoid gaiter area/distal to calf muscle and if not, use extreme care	Take extreme caution when treating high risk areas. Utilise ultrasound guidance. Do not inject if in doubt	Direct visualisation of injection, utilise ultrasound guidance, utilise magnification

dorsalis pedis arteries resulting in bilateral limb amputations.[4] The aim of these recommendations is to provide medical practitioners standardised guidelines to prevent and manage this rare but significant complication of a commonly performed procedure. Comprehensive knowledge and expertise in managing this adverse event is crucial to mitigate potentially catastrophic outcomes.

Methods

The consensus process

The project was initiated by the Australasian College of Phlebology (ACP) based on a request by the office of New Zealand HDC. The document was written by the primary author (KP) and reviewed and edited by the co-editors (MDM, AvR, CR). An international and multidisciplinary expert panel representing the endorsing societies and relevant specialties of vascular and endovascular surgery, interventional radiology, dermatology, vascular medicine (angiology), anesthesiology, vascular sonography and nursing reviewed and further contributed to the manuscript. The medicolegal considerations were provided by two practising barristers specialising in medico-legal negligence (JD and WB) with contributions from two phlebologists with law degrees (CL, KP).

Given the lack of specific data on this adverse event, expert opinions of panel members were sought to generate the recommendations. Hence, these guidelines represent a multidisciplinary consensus-based approach to the management of these patients.

Review of literature

Published biomedical and scientific literature was reviewed including MEDLINE and EMBASE, journal articles and product information sheets. Keyword combinations used in search engines included: sclerosant, sclerotherapy, necrosis, intra-arterial, adverse event, complication.

Scope

These recommendations are applicable to sclerotherapy of lower limb superficial veins using liquid or foam sclerosants performed under direct vision, ultrasound guidance or catheter-directed; performed independently or in conjunction with other endovenous interventions. These guidelines are not applicable to sclerotherapy performed for other indications or body regions such as treatment of vascular malformations or oesophageal varices. These guidelines are also not applicable to other procedures that incorporate sclerosing agents, such as sclerotherapy or embolisation of vascular anomalies or tumours.

Target audience

The recommendations were developed for phlebologists, vascular specialists and interventionists who perform sclerotherapy of superficial lower limb veins. The recommendations will be also useful for emergency specialists, vascular and endovascular surgeons, interventional radiologists, dermatologists, plastic surgeons, other physicians, allied health professionals and in particular sonographers and nursing staff involved in the early and long-term management of this complication. Secondary target audiences include primary care physicians.

Part 1 clinical considerations

Background

Sclerotherapy. Sclerotherapy is a non-invasive venous intervention used to treat incompetent superficial veins of lower limbs in the management of chronic venous disease (CVD), esophageal varices and vascular malformations.[5] The aim of the procedure is to occlude and permanently eradicate the target vessels. The procedure is performed by percutaneous injection of the sclerosing agent into the target vessel or delivery of the sclerosant via a catheter. The procedure is commonly guided by ultrasound when treating lower limb varicose veins, and by direct vision when treating dermal and subdermal veins and telangiectasias.

Treatment indications and contraindications. Indications for sclerotherapy treatment of lower limb veins include (a) clinical, (b) preventive and (c) cosmetic indications. These have been detailed in a previous UIP guideline.[5] In brief, clinical indications include of symptoms and signs of chronic venous disease (CVD), and emergency treatment of bleeding varicose veins. Preventive indications include treatment of asymptomatic patients presenting with venous incompetence detected clinically or on duplex ultrasound (DUS). Cosmetic indications include provision of treatment for cosmetic improvement independent of any medical indications.

Sclerosing agents. Different classes of sclerosing agents including detergents, osmotic agents and irritant sclerosants are used in the sclerotherapy treatment of lower limb venous incompetence. The most commonly used are detergent sclerosants and in particular sodium tetradecyl sulphate (STS) and polidocanol (POL). These agents function by inducing endothelial lysis and exposure of the basal layer collagen of the target vessel, ultimately aiming to induce endofibrosis of the target vessel.[6] Both agents and in particular POL cause significant vasospasm that clinically assists with reduction of the target vessel diameter which facilitates its occlusion. These agents can be used in the original liquid state or mixed with a gas to create a foam. Both liquid and foam sclerosants are used in clinical practice but the foam format is shown to have numerous advantages over the liquid and is the most widely used.[7] This is due to the ability of foam sclerosants to displace intravascular blood, hence minimising deactivation and dilution,[8] as well as their visibility on ultrasound that facilitates monitoring of the treatment process.[9] Other classes of sclerosants include osmotic agents such as hypertonic saline and irritant agents such as ethanol and poly-iodinated iodine.

Direct vision sclerotherapy. Direct vision sclerotherapy is performed by direct percutaneous puncture and injection of the sclerosing agent into the target veins (varicose veins, reticular veins or telangiectasias) without ultrasound or other forms of image guidance. Direct vision sclerotherapy of telangiectasias is referred to as 'micro-sclerotherapy'. Visual magnification, polarised lights and other adjunct techniques such as transillumination and infrared imaging may be used with microsclerotherapy.

Ultrasound guided sclerotherapy. Sclerotherapy guided by DUS is referred to as ultrasound guided sclerotherapy (UGS), also referred to as 'Echosclerotherapy'. UGS was first described by French phlebologist Michel Schadeck in 1984.[10] Kanter and Thibault[11] described the application of this procedure in treating saphenofemoral incompetence in 1996, emphasising the importance of accurate ultrasound guidance in reducing the incidence of intra-arterial injection of sclerosant. Ultrasonic guidance of sclerotherapy and in fact image guidance of most surgical interventions is standard practice in modern medicine.[12,13] Ultrasound guidance provides the clinician with the ability to visualise the target vessels and monitor the flow of the sclerosing agent, limiting the exposure to non-target sites. UGS increases the safety of the procedure by identifying critical anatomical structures such as arteries and nerves, hence minimising the risk of an inadvertent injury to vital structures.

Catheter-directed sclerotherapy. Catheter-directed sclerotherapy (CDS) involves the introduction of the sclerosing agent via a catheter to the target vein under ultrasound

guidance.[14,15] CDS was described by Parsi in 1997 as "Extended Long Line Echosclerotherapy (ELLE)"[16] and a review of the technique was subsequently published by Parsi and Lim in May 2000.[14] The procedure involves introduction of a catheter under ultrasound guidance into a target vein such as a saphenous vein. The catheter is then advanced to the most proximal aspect of the target vein. The sclerosant is then injected as the catheter is withdrawn. This technique is typically used to treat saphenous trunks and when performed under ultrasound guidance reduces the risk of inadvertent injections into non-target vessels such as arteries.[17,18]

Mechanochemical ablation (MOCA). In this procedure, the sclerosing agent is delivered via a special catheter that induces mechanical damage to the vessel wall. The additional mechanical component intends to enhance the chemical action of the sclerosing agent.[19,20] Similar to CDS, the main indication for MOCA is treatment of saphenous trunks.[21] Discussion of MOCA is beyond the scope of these recommendations.

Complications of sclerotherapy. Sclerotherapy is associated with rare but significant adverse events including anaphylaxis and death, deep vein thrombosis (DVT), pulmonary embolism (PE) and stroke.[3,22] Unintentional intra-arterial injection of sclerosants is one of the most serious and potentially devastating complications of this procedure where, rather than a target vein, the sclerosant is injected in an arterial vessel (artery or arteriole) causing tissue ischaemia.

Inadvertent intra-arterial injection of drugs. Unintentional intra-arterial injection of drugs causing tissue ischaemia was first reported by van der Post in 1942.[23] Numerous reports of accidental or iatrogenic intra-arterial injection of illicit drugs and medications causing necrosis of hand and fingers have since appeared in the literature.[24–27] This adverse event when involving the upper extremities carries an amputation incidence of nearly 30%.[25] Inadvertent intra-arterial injection of corticosteroids during an epidural spinal injection can result in arteriolar obstruction and spinal infarction.[28] Inadvertent occlusion of the superficial femoral artery (SFA) has been caused by deployment of Angio-Seal at the puncture site following cardiac catheterisation procedure.[29]

Inadvertent arterial injury and varicose vein surgery. Accidental arterial injury has been reported with other vascular procedures. Inadvertent stripping or interruption of the SFA has been reported as an adverse event of varicose vein surgery.[30–32] Injury to SFA after venous stripping has been associated with a high amputation rate due to delay in diagnosis.[33]

In a systematic review of vascular injuries in varicose vein surgery, the incidence was found to be low at 0.0017%-0.3%.[34] The amputation rate was 34% for arterial injuries during varicose vein surgery but rose to 100% if combined with an intra-arterial injection of sclerosants.

Illustrated case. The report by the New Zealand Office of the HDC ("illustrated case") describes the case of a 70-year-old female who saw a general practitioner, self titled "procedural phlebologist" for treatment of varicose veins.[4] The practitioner performed radiofrequency ablation (RFA) simultaneous with foam UGS on both legs, all in one sitting. Injections were made into her right ankle where the right dorsalis pedis artery was mistakenly injected. Soon after, injections were made into "the left ankle" and the left dorsalis pedis artery was also erroneously injected. Details of the sclerosant type or concentration do not appear in the HDC report. The patient described her pain in the right ankle and foot as "building", when the left ankle was injected. She described her left ankle "exploded" in pain when the injection was stopped. The practitioner observed her feet to turn pale and on ultrasound saw what appeared to be foam bubbles in the right dorsalis pedis artery. He later told HDC that he was unsure whether these were "artefacts, blood cells or foam sclerosant". He then noted that "the pain settled quickly followed by numbness bilaterally that resolved on standing and arterial return started to improve." He anticoagulated the patient with oral rivaroxaban 10 mg daily. Despite the severity of symptoms, the patient was sent home. No compression stockings were applied after the procedure, according to the patient, but stockings were recommended and provided on the following day when she attended a review appointment. On the second day, she presented to the emergency department where she was given pain management and advised to return if the discoloration and pain worsened. On day 6, she was admitted to a public hospital under the vascular service and found to have developed gangrene of both feet complicated by infection and septicemia. She underwent bilateral below knee amputations (BKA) 15 days following the procedure.

Diagnosis and clinical manifestations

The most important warning signs of an immediate inadvertent intra-arterial injection are symptoms experienced by the patient and clinical signs observed by the clinician. Although variable, the initial clinical manifestations would significantly influence the critical decision making of the proceduralists. The most commonly reported symptom is an immediate and severe radiating or burning pain that propagates distally in the affected limb.[35] This is followed by the immediate development of a sharply demarcated area of skin colour change that corresponds with the distribution of the angiosomes supplied by the injected arterial vessel.

The symptoms and signs may be variable depending on the injected vessel and presumably the sclerosant type, concentration, volume and the format as liquid or foam.[1,2] The skin changes eventually evolve into a demarcated area of purpura that may progress to necrosis (Figure 1).

Symptoms. Pain is often the initial symptom of iatrogenic intra-arterial injections. A true intra-arterial injection of sclerosants would cause an immediate severe pain radiating along the length of the injected arterial vessel. The immediate radiating pain is most likely due to vasospasm, later compounded by an ischaemic and neuropathic pain.

In one report, an unintentional injection into the external pudendal artery caused immediate ipsilateral labial pain and significant skin discoloration.[35] Similarly, immediate pain was experienced in the posterior calf following an unintentional injection of sclerosant into the satellite artery of the SSV (medial superficial sural artery[36]; also named "small saphenous artery" [SSA][37]).[38] However, a presumably similar event involving the same artery was reported to be painless in another published report.[35]

Similar symptoms are well described in the intravenous drug use population where drugs are unintentionally injected intra-arterially. A Pubmed search of 'inadvertent intra-arterial injection AND ischemia' resulted in 36 publications, mainly related to the upper limb, following unintentional intra-arterial injection of illicit drugs by substance users. In the vast majority of cases arterial occlusion was diagnosed as the cause of ischaemia and pain. However, two publications reported arterial vasospasm only (without thrombosis) as the cause of ischaemia. One patient was successfully treated with sublingual nitroglycerin and one with papaverin.[39–41] Immediate pain secondary to vasospasm is a key feature of an inadvertent intra-arterial injection.

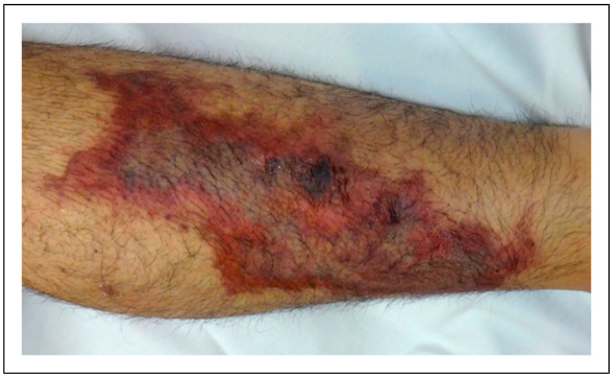

Figure 1. Intra-arterial Injection of polidocanol (POL). Area of well-demarcated stellate (star-shaped) purpura 15 days following ultrasound-guided sclerotherapy using polidocanol 2% liquid to treat the distal great saphenous vein (GSV). Repeat Duplex ultrasound 7 months post treatment revealed an artery alongside the distal GSV (photo courtesy of Dr Stefania Roberts, Australia).

It is conceivable that an intra-arterial injection of low volumes of a mild sclerosant into a larger vessel can presumably cause no significant vasospasm, or distal ischaemia, and hence remain painless. This is clinically observed with smaller aliquots of deliberate intra-arterial delivery of liquid embolic agents such as ethanol when treating AV malformations (AVMs). There needs to be sufficient volume and wall contact time to result in vasospasm, endothelial injury and permanent ischemia.

Clinical signs

Evolution of skin necrosis. Skin colour change and demarcation is an important feature of skin ischaemia that follows an acute arterial or arteriolar occlusion.[1,2] The demarcation takes on a stellate (star-like) configuration that corresponds with the angiosomal distribution of the affected arteries or arterioles. The affected skin undergoes the following distinct changes: (1) *pallor* (immediate), (2) *re-perfusion erythema* (within minutes), (3) *retiform purpura* appearing as a localised mottled violaceous patch (within hours lasting for days), (4) *stellate purpura* appearing as a dusky grey cyanotic plaque (within days) and (5) *stellate necrosis* (within weeks).[1]

The initial striking pallor appears to be confined to a well defined patch of skin. The pallor typically appears within minutes of the inadvertent event. Pallor is followed by a delayed re-perfusion which starts at the periphery of the affected area, gradually reaching the centre. The delay in re-perfusion may be as short as a few seconds, but may be as long as 1-2 min depending on the site, degree of injury and presence of collateral perfusion. The longer the delay, the higher the likelihood of significant ischaemia and subsequent necrosis.

The skin pallor and its subsequent reperfusion erythema may be missed by the practitioner performing UGS in a dark room, especially if the patient is asymptomatic. The immediate re-perfusion erythema will be replaced by a violaceous, irregular retiform (mottled) localised purpura that may last for days (Figures 2(A) and (B)). The mottled retiform morphology signifies compromised skin perfusion. When the ischaemic insult is significant, the mottled morphology is replaced over the following days, with a dusky cyanotic plaque which exhibits dendritic edges (Figure 2(C)). The plaque will eventually evolve into a demarcated area of stellate purpura (Figure 2(D)) that may ultimately progress to necrosis (Figure 2(E)).

Inadvertent injection into a named artery will correlate with the angiosomal distribution of the occluded vessels and result in necrosis of larger areas of skin (Figure 3). In 1984, Oesch reported 4 accidental arterial injections into the posterior tibial artery (PTA), all resulting in distal necrosis and severe sequelae including one amputation.[42] Larger areas of necrosis have required amputation of toes, the entire foot or the leg.[42–44]

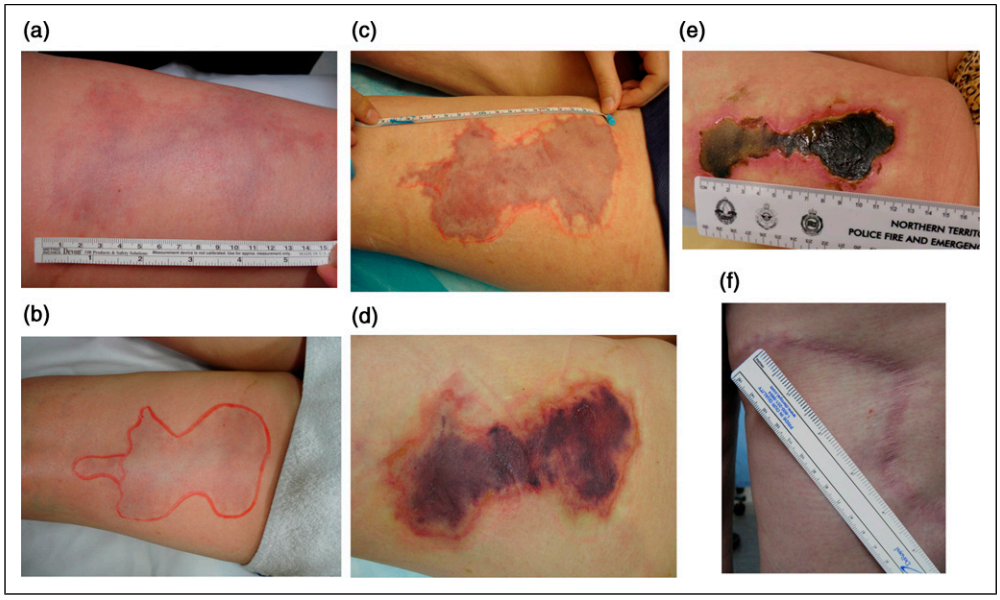

Figure 2. Intra-arteriolar Injection of polidocanol (POL). Clinical evolution of skin necrosis localised to the right posterior thigh following injection of polidocanol 1.5% liquid under ultrasound guidance to treat the thigh extension of the small saphenous vein (vein of Giacomini). No arterial signal was detected on duplex at the time of injection. An inadvertent sclerosant injection into the small intra-fascial arteriole accompanying the vein of Giacomini can be presumed. No pain was experienced by the patient at the time of injection. (A) Within 10 minutes- retiform purpura. A violaceous and localised patch of retiform (mottled) purpura was noted after the initial pallor. (B) Demarcation of retiform purpura marked at 10 min of the incident. The mottled retiform morphology signifies compromised skin perfusion. (C) Day 4- Stellate purpura (Day 4). Dusky grey cyanotic plaque exhibiting dendritic edges. These skin changes signify impending necrosis. (D) Stellate purpura (Day 9). Demarcated area of intense purpura. (E) Stellate necrosis (Week 6). Skin necrosis developed despite treatment with oral prednisone and subcutaneous enoxaparin. (F) Week 12. Excision of the ulcer and flap repair was performed 7 weeks post event. The surgical scar (shown here) was further revised with subcisions and vascular laser (photos courtesy of Dr Stefania Roberts, Australia).

Stellate retiform purpura. Skin changes that follow an intra-arterial injection take on characteristic skin changes that correlate with the angiosomal distribution of the affected vessels. The lesions are sharply demarcated livedoid, purpuric violaceous plaques with peripheral dendritic extensions. Dermatologically, the lesions are best described as *Stellate Retiform Purpura,* with *stellate* describing the peripheral dendritic extensions, *retiform* describing the mottled reticulate morphology and *purpura* describing the histological finding of red cell extravasation.

Stellate retiform purpura signifies compromised skin perfusion (Figure 4). The reticulate pattern signifies reduced perfusion of skin angiosomes by ascending arterioles that serve those angiosomes. In a report by Yébenes *et al* localised retiform purpura was observed following sclerotherapy using 0.5% POL.[45] A skin biopsy from the centre of the lesion demonstrated a thrombosed arteriole.

Several other conditions present with a similar pattern of stellate retiform purpura and necrosis due to arteriolar occlusion. The skin eruption is identical and goes through the same stages of cyanosis and purpura that can progress to stellate necrosis. Examples of such conditions include warfarin necrosis,[46] calciphylaxis,[47] cholesterol and septic emboli and cold related gelling.

Embolia cutis medicamentosa. Embolia Cutis Medicamentosa or Nicolau's syndrome refers to iatrogenic ischaemic necrosis of skin and deeper tissues that can follow an intramuscular injection, but may also occur following injections by other routes.[48] Drugs and substances implicated include local anaesthetics, vitamin B complexes, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs).

The European medical literature has used "Nicolau's Livedoid Dermatitis" to refer to the demarcated skin changes observed following arterial adverse events of sclerotherapy.[49–52] Nicolau's syndrome has also been reported with sclerotherapy of pyogenic granulomas appearing on fingers.[53] Intralesional injection of STS into the lesions of pyogenic granuloma of the fingers has caused gangrene requiring finger amputation.[54]

Ultrasound findings. Absence of normal arterial flow in the inadvertently targeted arterial vessel, distal from the injection site, may be seen on DUS. However, ultrasonic detection of the affected artery may not be readily possible due to immediate vasospasm and oedema that ensues the event. In larger arteries, *to and fro* movement of the sclerosant foam bubbles may be visualised in the arterial vessel on B-mode ultrasound ("ping pong" sign).[55] Given the echogenicity of foam, the ping pong sign is more likely to be detected with

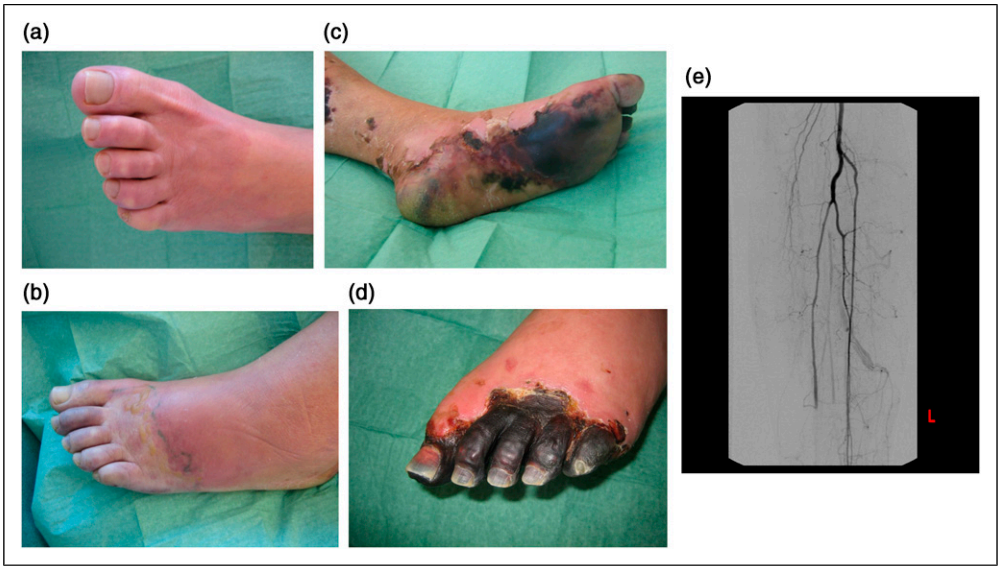

Figure 3. Inadvertent intra-arterial injection of polidocanol (POL). Significant tissue necrosis following an injection of polidocanol (POL) 2% foam into the left medial calf inadvertently targeting the posterior tibial artery (PTA).[1] Procedure was performed by a resident surgeon without considering the preoperative duplex mapping of the leg. 1.5 mL of POL was injected without any ultrasound guidance 7-10 cm above the medial malleolus. (A) Day 1- Left dorsum foot showing a demarcated area of mild cyanosis. (B) Day 14- area of pallor signifying de-vascularisation of the forefoot, oedema and hyperaemia proximal to the demarcation line. (C) Day 30- significant areas of necrosis affecting the sole of the foot. (D) Week 10- dry gangrene of all affected toes ultimately requiring a foot amputation (E) Angiogram of the left leg showing complete occlusion of the PTA and absence of collateral arteries (images courtesy of Dr Franz Hafner, Austria).

foam sclerosants than liquid agents. In the illustrated case from New Zealand, foam bubbles were visualised in the distal arteries.

Clinical sequelae

Skin ulceration and amputations. Skin ulceration following arterial events of sclerotherapy may take several weeks to develop and when secondary to reversible ischaemia may take months to years to heal (Figure 5). Significant tissue atrophy including skin, fat and muscle atrophy may follow.[38]

Ulceration can be complicated by severe infection, septicemia and gangrene. Irreversible ischaemia, especially when complicated by severe infection and septicemia would necessitate an amputation.[44] Amputation of the toes, feet, below-knee (BKA) and above-knee (AKA) amputations have all been reported.[42–44] In 1996, Natali and Farman reviewed 58 French insurance case files and reported 40 cases of intra-arterial injections leading to seven amputations (two AKA, five BKA), six amputations of one or more toes and 27 severe sequelae due to retraction of the triceps surae (gastrocnemius and soleus) muscle.[43] The vast majority of patients had a permanent disability and even following the healing of the ulcers, the debilitating neurological symptoms have persisted. One co-author (PRM) reports compartment syndrome and foot drop following an unintentional intra-arterial injection of 3% polyiodinated iodine (un-published).

Chronic pain and neurological symptoms. Long-term neuropathic pain can be debilitating and can last for months.[38] Pain may be accompanied by paraesthesia, dysesthesia, temperature hypersensitivity and motor dysfunction[38] and may not respond to conventional oral treatments such as gabapentin, pregabalin or amitriptyline.[38]

Mental health and psychosocial effects. Prolonged rehabilitation compounded by its effect on the patient's mental health, depression and loss of productivity may persist for years. The impact of prolonged hospitalisation compounded by potential for a limb loss is immense. Further discussion of the psychosocial impact is beyond the scope of these recommendations.

Differential diagnoses

Several adverse events may mimic an intra-arterial injection of sclerosants leading to similar immediate clinical signs that can ultimately lead to skin necrosis. An attempt should be made to distinguish these as they may influence treatment strategy.

Intravenous injections causing skin ischaemia. Significant skin changes and stellate necrosis may follow *intravenous* or *intra-telangiectatic* injection of sclerosants (Table 1). In such cases, the injection of the sclerosant into the lumen of the target vein or telangiectatic vessel has led to an

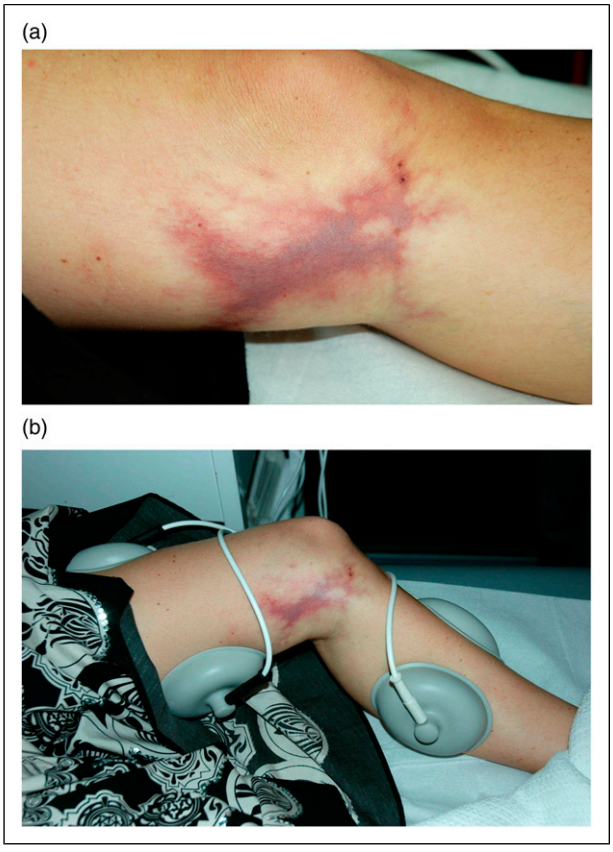

Figure 4. Retiform purpura following injection of polidocanol (POL). (A) Retiform purpura with distinct dendritic extension following microsclerotherapy using polidocanol liquid. Patient was referred by another practitioner for management of the adverse event. Severe pain was experienced by the patient at the time of the adverse event and became excruciating the next day. A nitroglycerine patch was applied and she was admitted to hospital for dextran infusion. None of the interventions helped with the pain. She was commenced on oral prednisone at 50 mg a day over the next 2.5 months which prevented ulceration. (B) Pain was not responsive to conventional oral medications and could only be temporarily relieved by application of BodyFlow™- a proprietary electrical neurostimulation system (photo courtesy of Prof. Kurosh Parsi, Australia).

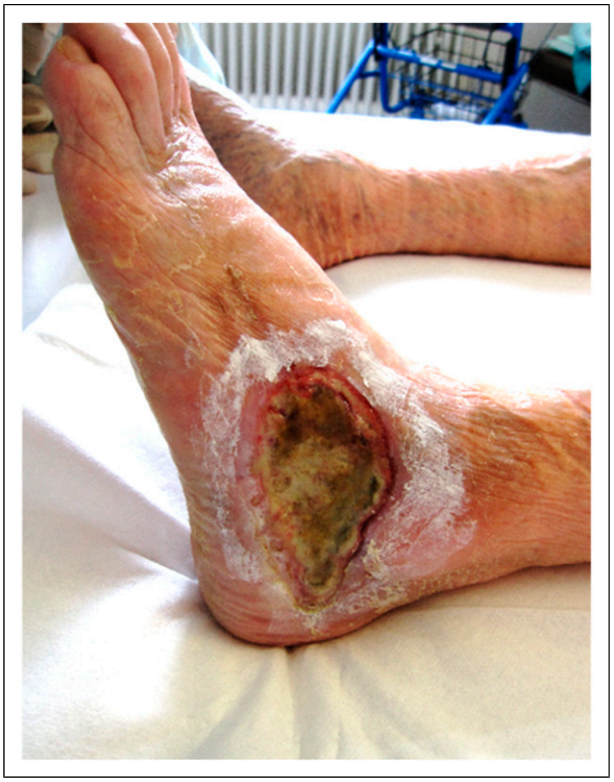

Figure 5. Retromalleolar ulcer following injection of polidocanol (POL). Large left retromalleolar ulcer several weeks after injection of POL 1% liquid (5 mL) to treat varicose veins. The patient reported immediate pain at the time of injection. Such ulcers may take months to years to heal (photo courtesy of Dr Albert-Adrien Ramelet, Switzerland).

unexpected ischaemic change in the overlying skin. The vessels are typically dermal (telangiectases) or subdermal (reticular) veins. Several mechanisms have been postulated to describe the pathogenesis of these observations but ultimately the clinical outcome is compromised skin perfusion at the level of microcirculation.[49,55–58] No cases of severe necrosis requiring an amputation have been reported with this complication.

Veno-arteriolar reflex vasospasm (VAR-VAS). Veno-arteriolar Reflex Vasospasm (VAR-VAS) was proposed by Tran and Parsi[56] as the pathogenic mechanism leading to ischaemic changes that follow an *intravenous* or *intra-telangiectatic* injection of sclerosants.[55–57] Here, the practitioner is certain of having delivered the sclerosant into the lumen of the target vein (or telangiectases) but despite the accuracy, typical ischaemic changes with a stellate pattern of necrosis follow (Figure 6).[55–57,59–61] The technical error is thought to be due to a high pressure/high speed delivery of the injection.[22,56,57] What constitutes a 'high pressure' injection has not been defined but has been anecdotally and universally reported by phlebologists as possibly the most relevant risk factor for this pattern of necrosis following sclerotherapy.[5] The rapid rise in the intravenous pressure is thought to induce a reflex vasospasm of the associated arterioles and subsequent opening of the AV anastomoses which allow the entry of sclerosant into the arterial side of the circulation.[55,57]

The immediate signs of VAR-VAS include skin pallor followed by a well-demarcated stellate purpura with dendritic extensions that may ultimately result in a stellate pattern of necrosis (Figure 6). The morphology and sequence of the observed skin changes resemble that of an unintentional intra-arterial injection but at a smaller and more limited scale.

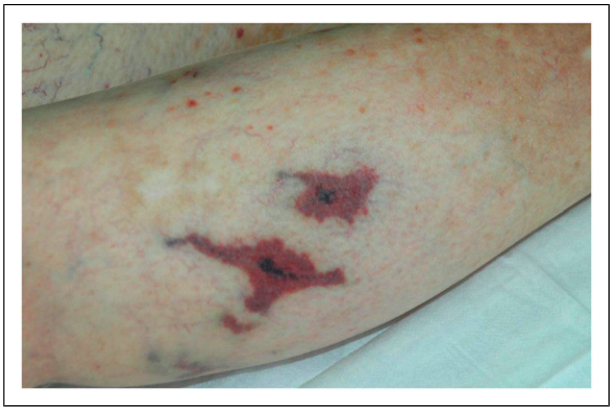

Figure 6. Veno-arteriolar Reflex Vasospasm (VAR-VAS). Stellate purpura and small areas of necrosis at the centre of each lesion following sclerotherapy of dermal telangiectasias of the left medial calf 1 week after the event. The adverse event most likely followed venoarteriolar reflex vasospasm (VAR-VAS) of cutaneous arterioles. In contrast to an intra-arterial injection, this complication follows a high-pressure *intravenous* or *intra-telangiectatic* injection but clinically presents with a similar pattern of demarcated stellate purpura that may progress to necrosis but at a smaller scale to an intra-arterial injection due to involvement of a smaller number of angiosomes (photo courtesy of Prof. Kurosh Parsi, Australia).

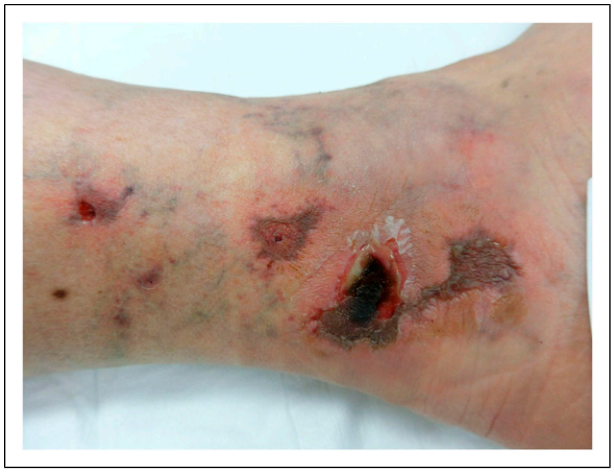

Figure 7. Intra-telangiectatic injection of polidocanol (POL). Stellate necrosis following direct vision sclerotherapy of telangiectasias in the medial ankle area using polidocanol (POL) 0.5% foam. Injections were not delivered with high pressure. The entry of sclerosant from telangiectasias into the arterioles in this region (medial ankle) is thought to be facilitated by open arteriovenous (AV) anastomoses or incompetent boundary valves (photo courtesy of Prof. Kurosh Parsi, Australia).

The diagnosis is clinical and based on the observed features described above. Investigations are of little value in confirming the diagnosis. DUS may detect the entry of foam sclerosants into dermal vessels. DSA may be helpful if an intra-arterial injection is suspected but is of no value in locating arteriolar occlusion. Skin biopsies may locate the occluded dermal arterioles.

Open arterio-venous anastomoses and incompetent boundary valves. Injection of sclerosants into tributary veins, reticular veins or telangiectases in the medial ankle regions (Figure 7) or regions affected by lipodermatosclerosis (Figure 8) has lead to a similar pattern of stellate necrosis. This is postulated to be related to permanently open AV anastomoses[58,62,63] or incompetent boundary valves which allow more extensive retrograde filling into the microcirculation.[57,64] Whilst VAR-VAS has been associated with a high pressure injection, this complication can follow a perfectly administered, slow and low pressure *intravenous* or *intra-telangiectatic* injection. The open AV anastomoses or the incompetent boundary valves are thought to facilitate the entry of sclerosing agent from the venous side to the arterial side of the microcirculation.

Intravenous versus intra-arterial causes of skin ischaemia. The distinction between *intravenous* injections resulting in a stellate pattern of necrosis and a true intra-arterial injection of sclerosants may be difficult. Historically, an intra-arterial sclerosant injection was the assumed cause of stellate necrosis following sclerotherapy. The older phlebology literature did not differentiate between *intravenous* injections resulting in stellate necrosis and a true intra-arterial injection. Biegeleisen *et al*[35] described such a case where the treatment was performed under ultrasound guidance and the needle was "equivocally intraluminal". There was no pain at the time of injection but stellate purpura ensued. The authors classified this event as an "intra-arterial injection".

In a case report by the group of Braithwaite, the very experienced clinician having performed 3000 sclerotherapy treatments describes having injected a total of 4 mL of liquid POL 0.5% into the telangiectasia on the anterior aspect of the patient's right shin.[65] The patient left the clinic with no pain. The next day the patient noticed a mottled "dark and light discolouration" surrounding an injection site. Photographs provided demonstrate a typical pattern of stellate necrosis. As evident from this case, this adverse event followed an *intra-telangiectatic* injection by an experienced practitioner who would have readily identified arterial vessels.

It is quite evident that most authors have attributed necrosis post-sclerotherapy to either extravasation or an intra-arterial injection. Key features that will help distinguish VAR-VAS from an intra-arterial injection include:

1. VAR-VAS follows an *intravenous* or *intra-telangiectatic* injection.
2. Similar to an intra-arterial injection, VAR-VAS presents with a stellate pattern of necrosis but tends to affect a limited number of dermal

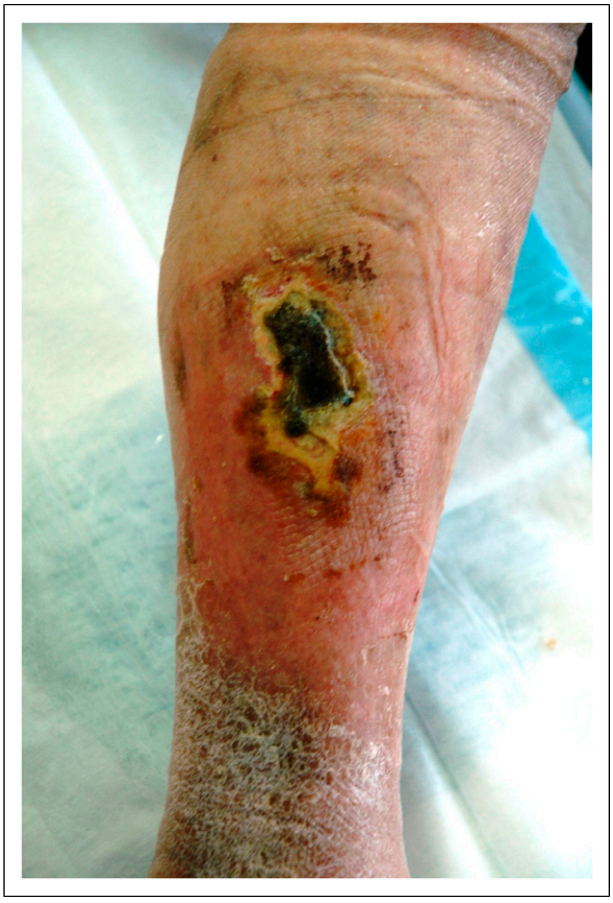

Figure 8. Intravenous Injection of sodium tetradecyl sulphate (STS). Stellate necrosis following sclerotherapy of great saphenous vein tributaries using sodium tetradecyl sulphate (STS) 1.5% foam in the left medial calf. The region was affected by lipodermatosclerosis. The entry of sclerosant foam from the venous side to the arteriolar side is thought to be facilitated by open arteriovenous (AV) anastomoses or defective boundary valves (photo courtesy of Prof. Kurosh Parsi, Australia).

angiosomes resulting in a small area of necrosis (typically <5 cm^2).

3. In contrast to most reported cases of an intra-arterial injection, VAR-VAS is typically painless at the time of injection.

Extravasation. Extravasation of sclerosants by delivery of sclerosant outside the venous lumen may at times lead to skin necrosis. Here, necrosis is caused by direct tissue toxicity of the extravasated sclerosant rather than arterial ischaemia. Extravasation necrosis is more likely to happen with the use of chemical irritants such as ethanol and sodium iodide rather than detergent sclerosants. Extravasation of chemical irritants is typically very painful. Extravasation of small volumes of detergent sclerosants, especially in the foam format, is unlikely to cause tissue necrosis (Table 1).[66] However, extravasation of larger volumes of higher concentrations of these agents, especially in liquid format may cause fat suppuration and tissue necrosis.[67,68] Extravasation presents with round, rather than a stellate pattern of skin necrosis and hence does not follow the same stages of tissue ischaemia observed with intra-arterial injections or VAR-VAS.

Risk factors

Patient-related risk factors

High risk normal anatomy. These are anatomical sites in patients with a normal vascular anatomy where superficial veins are in close proximity to arterial vessels. Examples of such high risk areas and the associated at-risk arterial vessels are summarised in Table 2. In addition, all perforating veins have accompanying arterioles that may be unintentionally targeted during an attempt to inject perforating veins.

Anatomical variations. The presence of anatomical variations has been identified as a potential risk for iatrogenic intra-arterial injection of drugs in the upper limbs.[69] In the lower limbs, anatomical variations involving the termination of the GSV have been detected at the saphenofemoral junction.[70–74] In a study of 2093 patients undergoing stripping of the GSV, 14 cases of rare anatomical variations were identified which included 12 cases of femoral artery and vein transposition and variations in termination of the GSV.[75] In this study, the pre-operative duplex detection of these variations was 71% (10/14). Anatomical variations in the femoral triangle and a superficial position of the SFA can pose a significant risk of an inadvertent injection (Figure 9). Similarly, superficially placed femoral-popliteal bypass grafts may pose a significant risk if not recognised on DUS (Figure 10).

Variations in the anatomical pathway of the external pudendal artery (EPA) may pose a risk of inadvertent injection when treating tributaries in the groin. In a study of 228 patients, the EPA crossed anterior to the SFJ in 39.5% and posterior in 60.5%.[76]

Lower leg anatomical variations can also pose a significant risk. Variations in the anatomical location of the small saphenous artery (SSA) was first described by Schadeck as a risk for intra-arterial injection during UGS of the SSV.[77]

Jones and Parsi[78] reported superficial collateral arteries masquerading as varicose veins of the posterior calf in a patient with popliteal artery occlusion. Fortunately this was detected on ultrasound prior to UGS and thus an inadvertent intra-arterial injection was avoided (Figure 11). Ultrasonic features of normal arterial and venous vessels are summarised in Table 3.

Vascular anomalies. Grommes *et al* [44] reported an intra-arterial injection into the SFA due to a vascular anomaly

Table 2. High risk anatomical sites and the associated at-risk arterial vessels that may be inadvertently targeted during sclerotherapy. Great Saphenous vein (GSV); Small Saphenous vein (GSV).

High risk site	Possible inadvertent target	Clinical tips
Medial ankle	Posterior tibial artery (PTA)[1,42]	The artery is situated *below* the fascia and accompanied by the pair of posterior tibial veins
Anterior ankle	Anterior tibial artery (ATA)/dorsalis pedis[4]	The artery is situated *below* the fascia and accompanied by the pair of anterior tibial veins
Posterior calf	Medial superficial sural artery (small saphenous artery, SSA)[38,77,108,109]	SSA is a satellite arteriole of the SSV and typically follows SSV in its mid-proximal segments
Popliteal fossa	Popliteal artery	Popliteal artery is located quite deep. Sclerotherapy of small saphenous vein should only be performed in its superficial path, above the deep fascia, and not at its entry into the popliteal vein where the risk of an intra-arterial injection is very high
Inner knee	Septo-cutaneous arterioles[57]	These arterioles leave the fascia to reach the skin but may be targeted during an attempt to inject the intra-aponeurotic GSV.[38,49]
Groin, medial	External pudendal artery (EPA)[35]	Artery is typically situated at the saphenofemoral junction where the great saphenous vein enters the common femoral vein
Groin, anterior	Superficial femoral artery (SFA)	SFA is located very superficially on the upper anterior thighs, non-compressible and pulsatile on ultrasound
Be aware of past vascular reconstructive surgery, i.e. femoral-popliteal or tibial bypass surgery		

requiring a BKA. This complication followed a catheter-directed procedure without ultrasound guidance. In this case, an inguinal crossectomy was first performed followed by a cut-down to insert a KAVS catheter into the GSV. No ultrasound guidance was performed. Following the injection of 2 mL of 3% POL foam, ischaemia of the lower leg was noticed some minutes later. The inguinal incision was extended and an aberrant communication, presumably an AV fistula, between the anterior accessory saphenous vein (AASV) and the SFA was located. The diagram provided in the publication demonstrates a KAVS catheter having deviated from the GSV into the AASV and then into the SFA via the fistula. Despite a SFA reconstruction, thromboembolectomy and anticoagulation, foot mummification, severe infection and septicemia followed requiring a below-knee amputation.

AVMs of lower limbs are rare but can be potentially targeted inadvertently if not detected pre-operatively. Acroangiodermatitis of lower limbs secondary to an underlying AVM (Stewart-Bluefarb syndrome) presents with atypical pigmentation which can be misdiagnosed as pigmentation secondary to chronic venous hypertension.[79] Careful pre-treatment ultrasound examination followed by contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) is required to diagnose vascular anomalies that may be misdiagnosed as superficial venous incompetence.

Conditions predisposing to poor wound healing and ulceration. Several dermatological conditions such as lipodermatosclerosis, panniculitis, livedo vasculopathy and pyoderma gangrenosum (PG) increase the risk of cutaneous necrosis and ulceration. PG can arise at sites of minor trauma such as the insertion site of a catheter. Immunosuppression, vasomotor instability syndromes, oedema and poor tissue perfusion due to systemic causes or peripheral arterial disease (PAD) increase the risk of poor wound healing.[57]

History of PAD including an assessment of symptoms and current treatments must be obtained prior to sclerotherapy. Critical limb ischaemia (CLI) as diagnosed by typical clinical manifestations and an ankle brachial index (ABI) < 0.5 or ankle pressures <50 mmHg is a contraindication to sclerotherapy.[5] Sclerotherapy treatment may be considered in patients with moderate PAD, as diagnosed by clinical manifestations, ABI 0.5–0.8 or ankle pressures 60–100mmHg provided that excessive post-treatment compression is not applied.[5] Such patients are at a higher risk of skin necrosis and poor wound healing and hence additional care must be taken.

Procedure-related risk factors

Practitioners training and competence. Human error has been identified as the most significant risk factor for medical errors.[80] Certain medical complications can occur despite practitioners' absolute exercise of due diligence in carrying out the procedure. Practitioners performing medical procedures are expected to be competent not only in carrying out the procedure but in detection and management of potential complications (see Medicolegal Considerations-Proceduralist Competencies).

Ultrasound guidance. Intra-arterial injections have been reported with both UGS and direct vision "blind" sclerotherapy. Ultrasound guidance delivered by competent

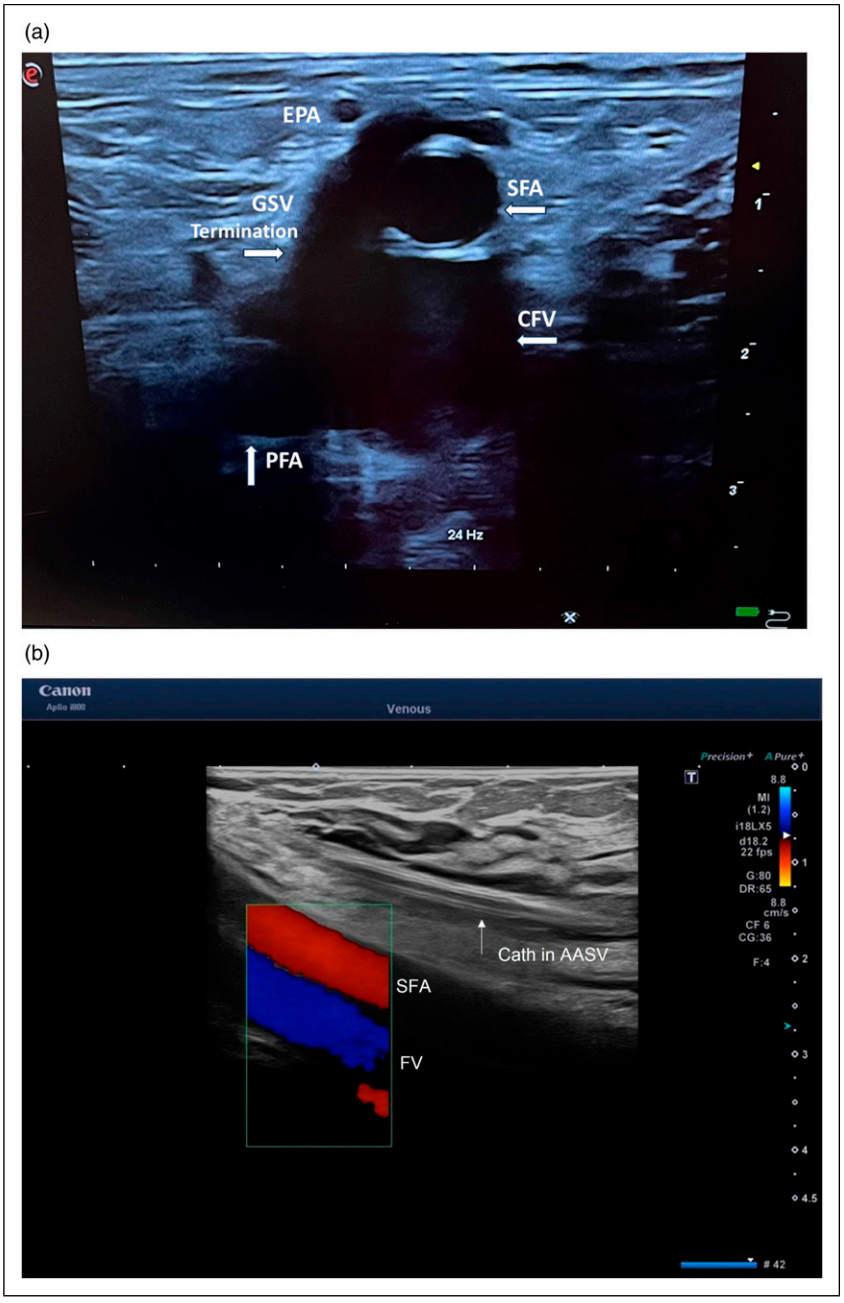

Figure 9. Superficial position of the superficial femoral artery (SFA) (A) Duplex ultrasound of the right groin (transverse view), showing a rare anatomical variation of the termination of the great saphenous vein (GSV) into the common femoral vein (CFV), laterally from the superficial femoral artery (SFA). Note the superficial position of the SFA and the external pudendal artery (EPA). PFA, profunda femoris artery (ultrasound image courtesy of Dr Pauline Raymond-Martimbau, Canada). (B) Duplex ultrasound of the right groin (longitudinal view) demonstrating the positioning of a catheter (CATH) in the anterior accessory saphenous vein (AASV) in close proximity to the SFA which is shown to overly the femoral vein (FV) (image courtesy of Prof. Kurosh Parsi).

practitioners enhances the safety of the procedure by visualisation of target vessels as well as the adjoining structures such as arteries and nerves. Although ultrasound guidance is highly recommended to increase the accuracy, safety and efficiency of the procedure, ultrasound guidance is only as reliable as the practitioner's interpretation of what is seen on ultrasound at the time of the procedure. Hence proficiency of the proceduralists in interpretation of live ultrasound images is critical in prevention of catastrophic outcomes.

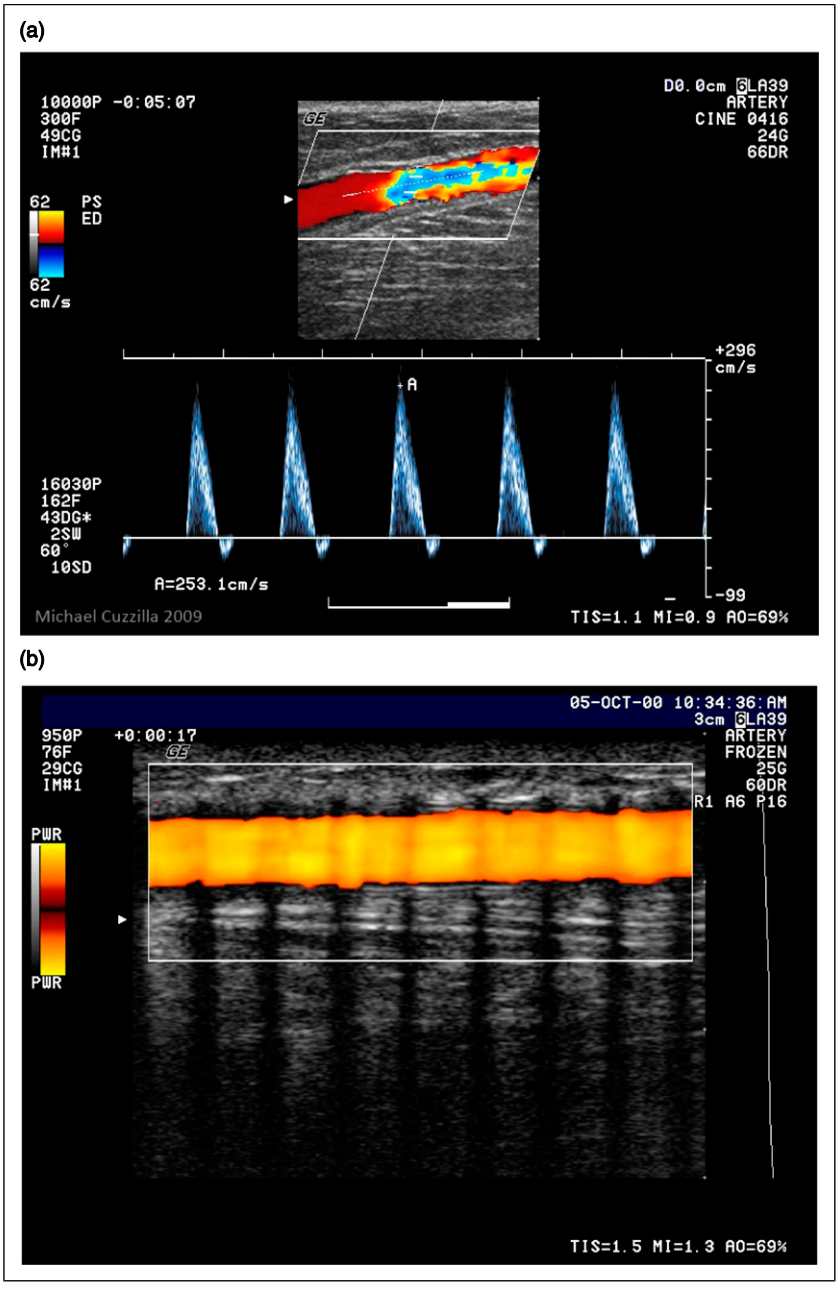

Figure 10. Superficial position of Femoral-popliteal Bypass Grafts (A) Spectral and colour Doppler of a stenotic femoral-popliteal vein graft demonstrating a superficial position in the right medial thigh. (B) Power Doppler of a femoral-popliteal synthetic bypass graft demonstrating a superficial position in the right medial thigh (ultrasound images courtesy of Michael Cuzzila, Australia).

Use of catheters. Delivery of sclerosants via a catheter, CDS, is thought to increase the safety of sclerotherapy and reduce the risk of intra-arterial injections. However, the application of CDS is limited to sclerotherapy of larger truncal veins and not to venous tributaries or visible varicose veins. CDS has been mostly replaced by thermal ablative methods such as laser and radiofrequency ablation that achieve better long-term results.[81]

For CDS to achieve safer results compared to other sclerotherapy techniques, it needs to be performed under ultrasound guidance.[15,17,82] The BKA reported by Grommes *et al*[44] followed a CDS performed without ultrasound guidance where the catheter inadvertently entered the femoral artery. Competent and accurate ultrasound guidance is crucial to ensure the safety of the procedure.

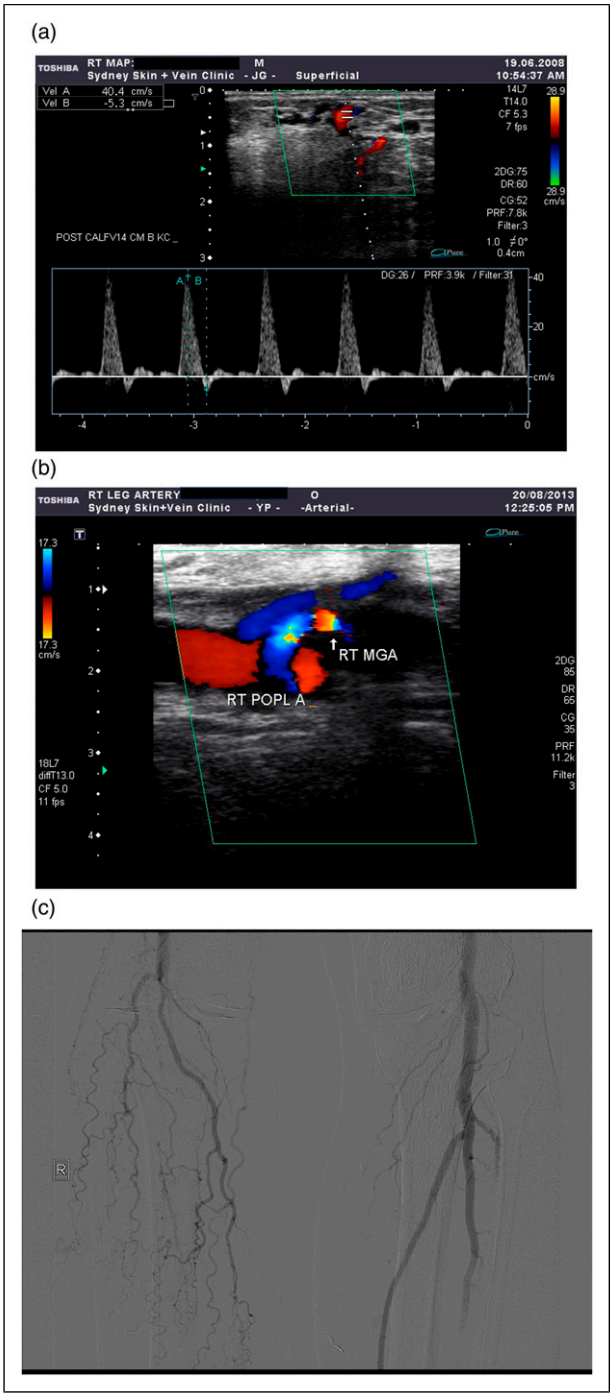

Figure 11. Arteries masquerading as varicose veins (A) Duplex ultrasound B-mode, colour and spectral Doppler of the right posterior calf (transverse view). Superficial arterial collaterals in a patient with popliteal artery occlusion. Spectral Doppler shows pulsatile flow pattern. Such vessels can be mistaken for superficial varicose veins and inadvertently injected. (B) Colour Doppler of the right (Rt) posterior calf demonstrating a sharp termination of the popliteal artery (POP a) and the origin of the medial gastrocnemius artery (MGA). (C) Digital subtraction angiography of lower limbs demonstrating absence of the right distal popliteal artery and formation of collateral circulation (ultrasound images courtesy of Prof. Kurosh Parsi, Australia).

Injection pressure and volume. The injection pressure plays an important part in the aetiology of both VAR-VAS and the clinical sequelae of an unintentional intra-arterial injection. VAR-VAS is thought to be induced by a high speed/high injection pressure. The rapid dilatation of the injected vein would induce a reflex vasospasm of the associated arterial vessel mediated via a sympathetic response.[55–57,59–61] Injection pressure may also play an important role in the clinical outcome of an intra-arterial injection. Unintentional injection into a small arterial vessel would likely cause ischemia in the antegrade distribution (angiosome) associated with that vessel (e.g. calcaneal branch). However, with greater injection pressure, the sclerosant may pass retrograde into the parent vessel causing ischemia throughout the parent vessel angiosome. A larger volume delivered could also cause distal vessel spasm and absence of antegrade flow which would then result in similar retrograde flow into the parent vessel even under lesser injection pressure/speed.

Selection of sclerosant. There are no controlled trials investigating the effect of sclerosant type on the incidence of skin necrosis. Most reports of an intra-arterial injection of sclerosants have involved the two most commonly used detergent agents, STS and POL. STS is a stronger detergent than POL but both agents have been implicated in reported cases of necrosis following an intra-arterial injection. In a recent review of serious adverse events reported to the FAERS database of the FDA in a 51-year period (1970–2021), DVT and PE were the most common complications reported with POL, whilst local injection site reactions and necrosis were the most common complications reported with the use of STS.[3]

Irritant sclerosants such as polyiodinated iodine and ethanol are well known to cause necrosis when extravasated.[55] One co-author (PRM) reports a case of an intra-arterial injection of polyiodinated iodine resulting in compartment syndrome, foot drop and stellate necrosis (un-published).

Sclerosant format: Foam versus liquid. Both foam and liquid sclerosants have been implicated in the published cases of intra-arterial injection of sclerosants. It cannot be conclusively stated that one format is safer than another. However, foam has a number of theoretical advantages, the most important being visibility on ultrasound which allows the agent to be traced and visualised in target and non-target vessels. If injected in an arterial vessel, foam would be readily visible on ultrasound, the so called *ping pong* sign,[38] and as described in the illustrated case from New Zealand.[4] Foam sclerosants are five orders of magnitude ($x10^5$) more viscous than liquid agents.[83] Hence, foam sclerosants displace the blood better but propagate less from the injection site compared to liquid agents. The higher viscosity of foam sclerosants prevents high-pressure injections (Poiseuille's law) and the lesser likelihood of VAR-VAS response or

Table 3. Ultrasonic features of lower limb arterial and venous vessels.

Ultrasound findings		Arterial	Venous
B-mode	B-mode profile on transverse view	- Circular (erect or supine)	- Circular (erect) - Circular to oval (supine)
	Vessel wall	- Echogenic ring - Usually thicker than veins - Walls are usually parallel unless aneurysmal	- Non-echogenic - Thinner than arteries
	Compressibility	- Non-compressible - Pulsatility on light probe pressure	- Compressible unless thrombosed or sclerosed
	Variation in size	- Do not vary in size with augmentation - Do not coapt with probe pressure	- Vary in size with augmentation - Vessel walls coapt with light probe pressure (unless thrombosed or sclerosed)
Doppler	Flow	- Spontaneous pulsatile flow - Reversed flow in calf arteries acting as collaterals in severe ischaemic patients	- Flow induced by augmentation
	Pulsatility[a]	- Pulsatile	- Non-pulsatile
	Velocity	- Pulsed systolic flow	- Non-phasic[b]
	Max velocities	- High	- Low

[a]Pulsatility detected on transverse view after applying probe pressure.
[b]Feature of lower limb venous flow with the exception of flow detected in the common femoral vein which is normally in phase with respiration. Continuous low resistance flow (monophasic) would indicate a proximal obstruction.

retrograde flow of sclerosants if injected intra-arterially.[66,84] Although foam sclerosants are safer and more effective than liquid agents in general, both formats if inadvertently injected intra-arterially can result in tissue necrosis and hence care must be taken with either format.

Patient position and stability during the procedure. Sclerotherapy similar to most other medical procedures is universally taught to be performed with the patient lying down on a procedure table in a stable position. The patient is required to stay still during the delivery of injections to avoid extravasation or inadvertent injections into non-target structures, such as adjoining arteries, veins or nerves.

Patients suffering from anxiety, needle phobias or restless leg syndrome may have great difficulty staying still during the procedure. Such patients should either be offered other treatment options, or have sclerotherapy performed under mild sedation.[85]

Before the advent of ultrasound, injection sclerotherapy was performed by some practitioners with the patient standing to engorge the target veins making them easier to puncture. This trend continued until the 1950's but became redundant with the advent of UGS in the 1990s[86] This practice is now obsolete. In addition to an increased risk of extravasation and inadvertent injection of non-target structures, patients injected while standing are at increased risk of falls, head injuries and other traumas.

Bilateral procedures. The illustrated case highlights the added risk of an adverse event affecting the contralateral limb when both limbs are treated simultaneously. The practitioner's error in not identifying the dorsalis pedis on one side, was repeated on the contralateral side resulting in bilateral limb loss. The medicolegal implications are discussed in the next section.

Part 2 medicolegal considerations

Proceduralist competencies

Sclerotherapy of lower limb superficial veins is a commonly performed procedure.[2] A wide range of medical practitioners of varying levels of training and experience including general practitioners, cosmetic physicians, general surgeons, cosmetic surgeons, dermatologists, angiologists (in countries such as France), interventional radiologists, plastic surgeons, vascular surgeons and specialist phlebologists perform this procedure. In the United States, sclerotherapy is also performed by "physician-assistants" and nurses. Training in phlebology is not standardised in most countries and standards of practice vary widely. There is a widespread misperception that sclerotherapy is a simple procedure, hence practitioners from various backgrounds and with no phlebology training attempt to perform this procedure. Another misperception is that sclerotherapy is an "aesthetic" procedure requiring minimal training. Not infrequently, sclerotherapy is advertised together with other "injectables" such as cosmetic fillers and botulinum toxin, and promoted as a "simple office-based" procedure.

Various phlebology and vascular craft groups have recognised this problem and provide training to practitioners interested in practising phlebology. The UIP curriculum provides a recommended syllabus for topics to be considered for training in phlebology and requires competency in

medical, surgical and interventional aspects of the management of venous and lymphatic disorders, including competency in DUS.[87]

The phlebology community recognises that sclerotherapy and other endovenous interventions are far from simple procedures, and appropriate and adequate training by training and educational bodies is essential in ensuring safe and effective outcomes. The title "phlebologist" is not protected by law, and self-certification by untrained practitioners is not uncommon.

Despite its apparent simplicity, sclerotherapy is a complex procedure requiring a comprehensive knowledge of venous anatomy, technical procedural training, duplex ultrasound and sclerosing agents. Hundreds of published cases detailing significant adverse events such as DVT and PE,[3,88,89] Stroke,[90,91] tissue necrosis,[55,57] intra-arterial injections [1,35,38,44] and the illustrated case highlight the catastrophic adverse events that can complicate this deceptively "simple" procedure.

Practitioner training as provided, or recognised by an appropriately validated training or educational body is essential in ensuring patient safety and provision of effective treatments.

Ultrasound guidance

In the illustrated case, the medical practitioner employed ultrasound in guiding sclerotherapy. An error was made and the sclerosant was injected into the dorsalis pedis artery, a deep inter-muscular artery, rather than a superficial vein. A suggestion may be raised that the assistance of a qualified vascular sonographer during the procedure could have prevented this error. In practice, some phlebologists perform these procedures without any assistance, whilst others perform the same procedures assisted by sonographers/technicians.

The panel acknowledges that phlebologists may work closely with trained vascular sonographers, and that the preoperative venous mapping and ultrasound guidance during sclerotherapy may be provided by a vascular sonographer/technician, *or* by the practitioner. However, the medical practitioner performing the procedure is ultimately responsible for the patient care provided by that practitioner. Other members of the treating team owe a personal duty of care to the patient, reflecting the scope of their own professional role in the provision of that care. In case of an adverse event, such as an intra-arterial injection, the practitioner may still be held liable even if a technician was present during the procedure. This is especially applicable to certain US states, where a *Captain of the Ship* doctrine[3] is recognised, by virtue of which a surgeon, as the captain, is liable for all the actions of their surgical team in the provision of that particular treatment.[92] This doctrine however does not apply in many other jurisdictions and in particular not applicable in Australia, the UK or New Zealand where the liability of each individual team member would be assigned in law according to the rules governing multiple causation and joint and several liability.

The inter-relationship between an operating surgeon and an anaesthetist should be distinguished from that of a proceduralist and a sonographer. In *Sparks v Hobson, Gray v Hobson*[4] the Court of Appeal found that a surgeon was entitled to rely on the anaesthetist to inform him/her of any matters of concern within the scope of duties of the anaesthetist. The anaesthetist was found to have breached his duty of care and liable to the plaintiff.

To our knowledge, the reliance of a surgeon or proceduralist on a sonographer/technician in a tort case has not been tested. Nonetheless, it is the panel's opinion that a skilled vascular specialist deemed competent to perform a vascular procedure would not rely solely on the technical expertise of an assisting sonographer or technician. Ultimately the medical practitioner offering and performing the procedure must be proficient in the use of DUS in both venous and arterial applications, and able to correctly interpret the diagnostic findings observed live on imaging while performing the procedure.

Disclosure of risks

Duty of care and actions in negligence. Medical practitioners owe a duty of care to their patients. This duty requires competency in assessment and delivery of care to the standards expected of a skilled medical practitioner. Breach of the standards of care resulting in harm to a patient gives rise to an action in negligence.[5]

In common law jurisdictions, the courts are required to take into account what a *reasonable* person would have done under the same circumstances, and the standard of care is that of the *ordinary skilled person* exercising and professing the skills. In the UK, practitioners must act in accordance with a practice that is accepted by a responsible body of medical opinion (*Bolam principle*).[6] This implies that Doctors could resort to their craft group standards and guidelines to defend their practice. In Australian jurisdictions, in accordance with the Civil Liability Acts, the practitioner has a defence if he or she can prove they acted in accordance with a *manner* of practice which is accepted by peer professional opinion as competent medical practice.[7]

Although evidence of acceptable medical practice in accordance with professional standards set by the profession is used as a guide, the court is the ultimate arbiter and will refer to expert opinions and case laws to determine a judgement. In Australia, the courts may even disregard any peer professional opinion should the court consider the opinion irrational.[8] The irrationality exception applies differently in different Australian jurisdictions and also applies in the UK.[9]

In the illustrated case, though a no fault liability regime applies, expert opinions from vascular and endovascular surgeons and non-surgeon phlebologists were sought and it was determined that the practitioner had departed from the expected standards of care, and had breached the Code of Health and Disability Services Consumers' Rights.[10]

Duty to warn

Informed consent and patient autonomy. Medical practitioners have a duty to warn patients of material risks including inherent material risks in the proposed procedure or treatment. A risk is deemed *material*, if a reasonable person in the patient's position, if warned of the risk, would likely attach significance to it; or if the doctor knows, or ought to know, that this patient would attach significance to it.

In *Rogers v Whitaker*[11] a landmark Australian High Court case, the court found that a doctor had breached his duty of care by failing to inform a patient of the remote risk (1 in 14,000) of sympathetic ophthalmia causing blindness in a contralateral healthy eye associated with a procedure on a poorer visioned eye.

The principle of patient autonomy, and importance of providing other treatment options was illustrated in *Montgomery v Lanarkshire Health Board.*[12] Here, the court held that, had the patient been warned of the risk of shoulder dystocia, she would have opted for a caesarean section rather than a vaginal delivery. In the illustrated case from New Zealand, although an "informed consent" is said to have been obtained, it is not evident whether the additional risk inherent to bilateral sclerotherapy was discussed with the patient, and whether the patient was offered to consider other treatment options including the option of having no treatment.

Bilateral procedures. Patients with CVD typically require multiple ablative, surgical or sclerotherapy procedures to complete the treatment of a single leg. CVD is a chronic condition and in general there are no strong medical indications for both legs to be treated simultaneously. One exception is bleeding varicose veins which may require a bilateral intervention. Otherwise, non-emergency treatment of CVD is typically staged. Reasons cited for performing bilateral simultaneous procedures are predominantly non-medical, and include patient preference, social and travel engagements, financial considerations and insurance reimbursement.

The illustrated case has highlighted the increased risk imposed by a bilateral simultaneous procedure.[13] The patient underwent both a thermal ablative procedure (RFA) and UGS simultaneously on both legs. The error committed on the first leg was repeated within minutes on the contralateral side, resulting in a catastrophic adverse outcome resulting in the loss of both legs.

Data with regards to the additional risks imposed by performing bilateral sclerotherapy procedures is lacking for several reasons. Sclerotherapy is mostly performed in private practices and complications arising in private practices are not mandated to be reported to regulatory agencies, adverse event committees, Colleges or the manufacturers of the sclerosing agents. In addition, practitioners who have experienced these complications are not mandated to publish their adverse events in the medical literature, and hence such data is not captured by systematic reviews or meta-analyses. Therefore the true incidence of intra-arterial sclerosant injections and bilateral complications is unknown.

From a clinical standpoint, there is no evidence to support any benefits for performing a bilateral or simultaneous sclerotherapy procedure when treating CVD. The published case provides no details whether the practitioner had compelling reasons to treat both legs simultaneously. It is unstated whether the patient was warned of the risk of the bilateral procedure resulting in bilateral amputations and whether the patient was willing to undergo a bilateral procedure. Amputation and in particular bilateral amputation would be a material risk to any reasonable person, and any reasonable person would decline the option of a bilateral procedure for the sake of convenience or similar reasons, if warned of the risk. Whilst the risk is deemed to be low, it is a significant risk, *material* to any reasonable patient. Hence, practitioners performing bilateral venous procedures must have compelling reasons to do so and must inform their patients of the added probability of bilateral complications when performing bilateral simultaneous procedures.

Risk mitigation. Patients rely on medical practitioners' good decision making. The focus of the treatment and the proposed treatment strategies should be in the best interest of patients and relevant medical indications. Non-clinical indications such as social and financial considerations should not compromise the clinical decision making process of medical practitioners.

If a procedure is considered to carry a high risk of complications, a higher standard of care will be applicable to ensure all necessary precautions are taken to mitigate the additional risks. There are additional risks associated with simultaneously operating on multiple body regions or limbs. Combining multiple procedures necessitates a longer operative time, anaesthetic time (if relevant) and in case of sclerotherapy the possibility of drug overdose. In high risk patients or when treating high risk sites, a reasonable treatment approach would be to limit the procedure to a single site to gauge the patient's clinical response to the procedure, especially when initiating a course of treatments. Sclerotherapy procedures are typically staged over multiple sessions. Staging of the procedure ensures the practitioner has a better understanding of the patient's clinical response to the procedure, can adopt a systematic approach to treating the presenting pathology, and helps to limit any potential complications to a single region.

Another failure to mitigate risk, is failure to cease the procedure when faced with an adverse event.[14] In *Sparks v*

Hobson, Gray v Hobson, the anaesthetist failed to stop the procedure for approximately 30 min after the onset of respiratory acidosis. Rather, he contacted two colleagues for advice and tried various measures to correct the abnormality. In the illustrated case, the practitioner injected the contralateral leg almost immediately after the first leg. This allowed insufficient time to detect the complication in that first leg, or respond to the patient's experience of severe pain. The clinical awareness that the treatment has not gone to plan and has departed from routine management should have been sufficient notice *not* to initiate the injection on the contralateral side. Failure to stop the procedure that caused an adverse outcome and initiating the same procedure on the contralateral side would be a serious departure from good clinical judgement and a breach of standard of care.

Part 3 guidelines

Section 1. Immediate management of actual or suspected intra-arterial injection of sclerosants

The following consensus-based recommendations are to be applied in the management of actual or suspected inadvertent intra-arterial injection of sclerosants (Figure 12). Given the severity of potential outcomes and lack of published data in this setting, the treatment strategies suggested here are consensus recommendations based on first principles. In applying these guidelines the practitioner needs to consider the severity of the presentation, the evolving changes, the associated comorbidities, and the relative risk of the treatment options as well as their own level of confidence in managing the situation. Consideration should be given to the local availability and possible off-label use of drugs. The order and timing of providing the interventions should be planned and executed based on the evolving clinical presentation and response to treatment. Practitioners should use their clinical judgement to select the most appropriate treatment strategy that would suit the individual circumstances.

Immediate bedside management. Prompt recognition of the adverse event is essential and the following actions must be commenced without delay (Table 4).

Immediate bedside actions

(1) Stop injecting immediately at the onset of severe pain, skin blanching or the subsequent stellate purpura, or if there is ultrasonic evidence of an intra-arterial injection. Stop the procedure and do not continue further.
(2) Do not apply compression stockings or bandages.
(3) Place the affected leg in a dependent position.
(4) If an intra-arterial injection is suspected based on ultrasonic and/or clinical findings, or if the treating physician is unsure about the patient's clinical evolution, the staff should be asked to immediately call an ambulance. Rapid transfer to an appropriate facility with a vascular/interventional unit to commence urgent intervention is critical.
(5) Contact a more experienced or senior colleague for advice on immediate management, support and advice.
(6) Explain to the patient what complication is suspected to have occurred, and what additional measures are required to manage the complication. The disclosure must be done promptly, clearly and honestly following open disclosure principles.

Immediate documentation and monitoring

(1) Ascertain and document clinical features and initiate monitoring.
    (a) Use DUS to ascertain the extent of vascular injury.
    (b) Ultrasound images and/or video clips of the inadvertently targeted vessel should be saved for future reference.
(2) Patient's severity of pain must be assessed and an initial pain score recorded. Pain score must be repeated periodically eg every 5 min.
(3) Neurovascular assessment must be performed, recorded and repeated periodically eg every 5 min. This includes an assessment of skin colour, pulse, capillary refill, temperature, sensation and motor function.
(4) Obtain photos of skin discoloration in the affected region. Outline the area of the affected skin with a marker and document the size using rulers.

Immediate bedside treatment

(1) The following interventions should be implemented at the bedside for an actual or suspected intra-arterial sclerosant injection:
    (a) Sublingual nitroglycerin[39]
    (b) Low molecular weight heparin (LMWH): enoxaparin 1.5 mg/kg subcutaneous injection (SCI) *stat* (single immediate dose); (150 IU anti-Xa activity/kg bodyweight), or equivalent
    (c) Systemic corticosteroids:
        (i) Dexamethasone 0.25-0.5 mg/kg IV, or
        (ii) Hydrocortisone 0.75-1 mg/kg intramuscular (IM) or intravenous (IV) stat
    (d) Systemic NSAIDs:
        (i) Parecoxib 20-40 mg IM or IV stat; or if not available
        (ii) Ketorolac 30 mg IM or IV stat.
(2) Intervention and treatments of unknown or of doubtful value should be avoided.[15]

Transfer to hospital

(1) All actual and suspected cases of an intra-arterial sclerosant injection should —
    (a) be immediately transferred with an ambulance to an emergency facility at a hospital with a vascular/interventional unit, and

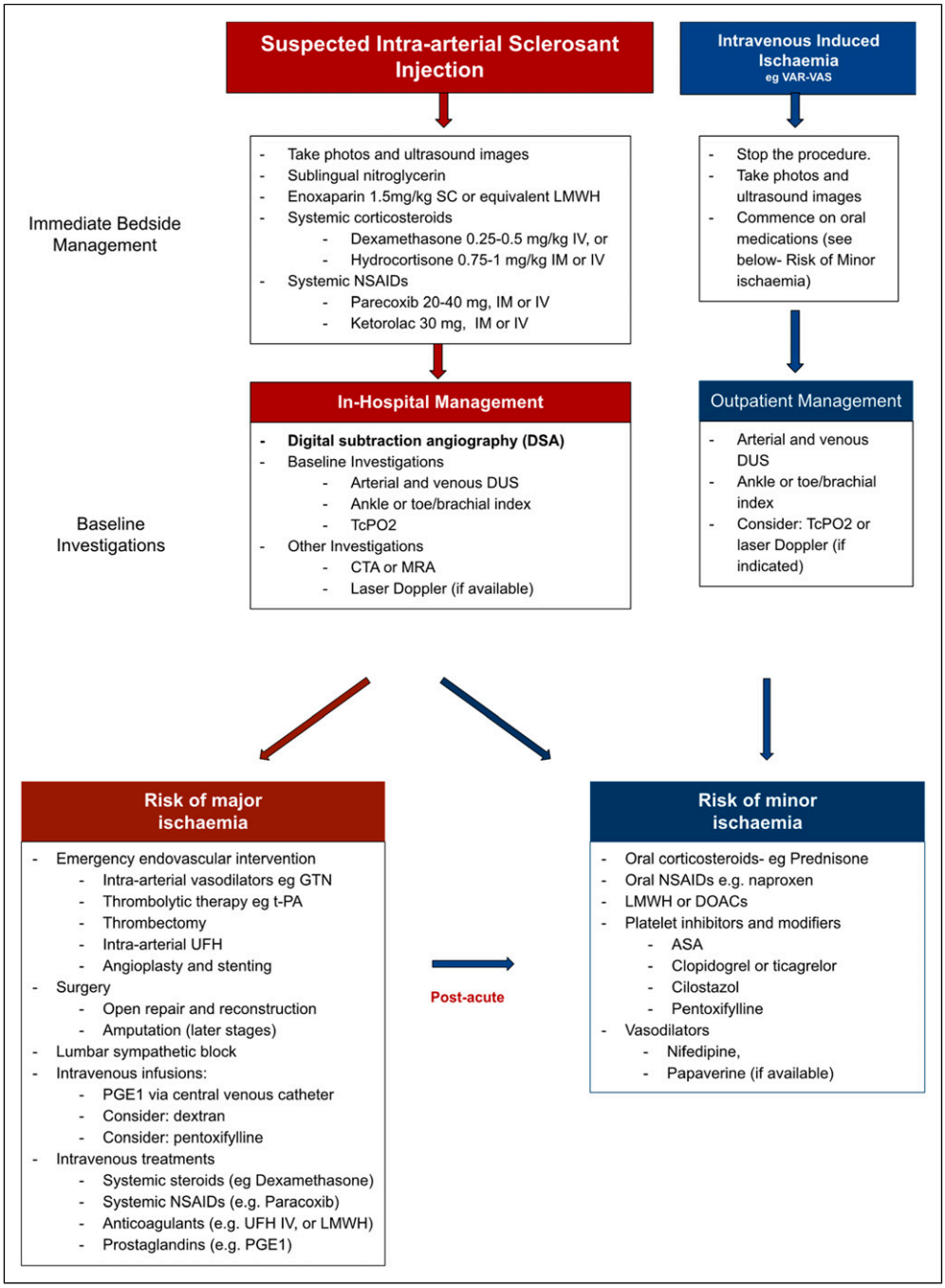

Figure 12. Management Flowchart. Flowchart for acute management of actual or suspected intra-arterial injection of sclerosants. ABI, ankle brachial pressure index; CTA, Computed Tomography and Angiography; DOACs, Direct Oral Anticoagulants; DUS, duplex ultrasound; GTN, glyceryl trinitrate; IM, intramuscular; IV, intravenous; LMWH, low molecular weight heparin; MRA, Magnetic Resonance Angiography; NSAIDs, Non-steroidal anti-inflammatory drugs; PGE1, prostaglandin E1; SC, Subcutaneous; TcPO2, transcutaneous oxygen measurements; t-PA: tissue plasminogen activator; UFH, unfractionated heparin; VAR-VAS: venoarteriolar reflex vasospasm.

(b) receive neurovascular assessment on arrival and be assessed for appropriate pain management.

(2) Speak to the admitting officer at the emergency department and with the admitting specialist to brief them on the details of the incident.[16] Provide your contact details for any further follow-up queries.

(3) Copies of the current Guidelines should be made available to the admitting doctors and interventionists in charge of patient management.

Table 4. Immediate Bedside actions and treatment following a suspected intra-arterial sclerosant injection. IM, intramuscular, IU, international unit; IV, intravenous, LMWH, low molecular weight heparin; NSAIDs: Non-steroidal anti-inflammatory Drugs; SC, subcutaneous injection, stat, single immediate dose.

Immediate bedside management
A. Immediate bedside actions
(1) Stop injecting immediately at the onset of severe pain, skin blanching or the subsequent stellate purpura, or if there is ultrasonic evidence of an intra-arterial injection. Stop the procedure and do not continue further
(2) Do not apply compression stockings or bandages
(3) Place the affected leg in a dependent position
(4) If an intra-arterial injection is suspected based on ultrasonic and/or clinical findings, or if the treating physician is unsure about the patient's clinical evolution, the staff should be asked to immediately call an ambulance. Rapid transfer to an appropriate facility with a vascular/interventional unit to commence urgent intervention is critical
(5) Contact a more experienced or senior colleague for advice on immediate management, support and advice
(6) Explain to the patient promptly, clearly and honestly using open disclosure principles what complication is suspected to have occurred, and what additional measures are required to manage the complication
B. Immediate documentation and monitoring
(1) Ascertain and document clinical features and initiate monitoring
(a) Use DUS to ascertain the extent of vascular injury
(b) Ultrasound images and/or video clips of the inadvertently targeted vessel should be saved for future reference
(2) Patient's severity of pain must be assessed and an initial pain score recorded. Pain score must be repeated periodically eg every 5 min
(3) Neurovascular assessment must be performed, recorded and repeated periodically eg every 5 min. This includes an assessment of skin colour, pulse, capillary refill, temperature, sensation and motor function
(4) Obtain photos of skin discoloration in the affected region. Outline the area of the affected skin with a marker and document the size using rulers
C. Immediate bedside treatment
(1) The following interventions should be implemented at the bedside for an actual or suspected intra-arterial sclerosant injection
(a) Sublingual nitroglycerin[39]
(b) LMWH- enoxaparin 1.5 mg/kg SC *stat*; (150 IU anti-Xa activity/kg), or equivalent
(c) Systemic corticosteroids
(i) Dexamethasone 0.25-0.5 mg/kg IV, or
(ii) Hydrocortisone 0.75-1 mg/kg IM or IV *stat*
(d) Systemic NSAIDs
(i) Parecoxib 20-40 mg IM or IV stat; or if not available
(ii) Ketorolac 30 mg IM or IV stat
(2) Interventions and treatments of unknown or of doubtful value should be avoided
D. Transfer to hospital
(1) All actual and suspected cases of an intra-arterial sclerosant injection should —
(a) be immediately transferred with an ambulance to an emergency facility at a hospital with a vascular/interventional unit, and
(b) Receive neurovascular assessment on arrival and be assessed for appropriate pain management
(2) Speak to the admitting officer at the emergency department, and with the admitting specialist to brief them on the details of the incident. Provide your contact details for any further follow-up queries
(3) Copies of the current guidelines should be made available to the admitting doctors and interventionists in charge of the patient management

Immediate management of major ischaemia

Admission is urgent and action to save a limb would require immediate intervention (Table 5). Management will depend on the clinical state of the patient and the diagnostic findings, either pointing at (a risk of) 'major ischaemia' or 'minor ischaemia'.

For the purpose of this consensus,—

(a) *Major ischaemia* is defined as ischaemia threatening to cause limb or major tissue loss as evident by acute onset of progressive pain in the affected limb, loss of pulse, loss of sensation or paresthesia, abnormal limb temperature or pallor, onset of paralysis, requiring intervention.

(b) *Minor ischaemia* is defined as ischaemia limited to skin and subcutaneous tissue not meeting the definition of major ischemia.

Investigations. Investigations should be arranged based on the individual presentations, comorbidities and treatment

Table 5. Immediate In-Hospital Management of Major Ischaemia. (5A) Investigations, endovascular interventions and surgery and lumbar sympathectomy. (5B) Medical management. ABI, ankle-brachial index; TBI, toe-brachial index; TcPO2 (Transcutaneous oxygen measurement); MRA, magnetic resonance angiography; CTA, computed tomography angiography; NSAIDs, non-steroidal anti-inflammatory drugs.

Immediate In-Hospital Management of Major Ischaemia
A. Investigations
(1) Immediate investigation
(a) Digital subtraction angiography (DSA)
(2) Baseline investigations
(a) Baseline bloods
(b) Duplex ultrasound; ABI/TBI.
(c) TcPO2
(3) Other investigations if indicated: MRA, CTA, laser Doppler
B. Emergency endovascular interventions and surgery
(1) Emergency endovascular intervention
(a) Intra-arterial administration of vasodilators[96] where spasm is thought to be a significant component using agents such as papaverine,[41,97] glyceryl trinitrate (GTN), tolazoline,[98] verapamil and prostaglandin E1 (PGE1)[99,100]
(b) Thrombolysis with direct infusion of thrombolytic agents such as intra-arterial tissue plasminogen activator (t-PA) or urokinase
(c) Thrombectomy with endovascular mechanical thrombectomy[17]
(d) Intra-arterial unfractionated heparin (UFH)
(e) Angioplasty and/or stenting of the affected artery and the inflow vessel where inflow-limiting concomitant atherosclerotic stenosis or occlusion is present
(2) Surgical interventions
(a) Open surgery may be required where endovascular options are not available or appropriate to achieve reperfusion and if a reconstructive procedure is required
(b) Amputation of the affected limb or digits as well as wound debridement may be required early on but more typically the need for these interventions occurs during subsequent days
C. Lumbar sympathetic block
(1) Chemical lumbar sympathetic block of the affected limb to reduce vasospasm and enhance collateral reperfusion with vasodilatation
(2) Relevant guidelines for the perioperative management of anticoagulants and antiplatelet therapy should be consulted.[101,102]
D. Medical management
(1) General measures
(a) Explain the diagnosis and discuss the management plan
(b) Cease triggers that worsen ischaemia
(c) Do not apply compression
(d) Supportive measures: Fluids, pain and sleep management, infection risk
(e) Consult other relevant specialists as appropriate
(f) Provide psychosocial support, arrange counselling if required
(2) Intravenous infusions
(a) Prostaglandins: PGE1 (alprostadil) via central venous catheter
(b) Anti-sludging agent: Dextran-40 (Buerger's disease protocol) 500 mL over 24 h[103]
(c) Consider: Pentoxifylline 2g diluted in 450 mL of dextrose in parallel at 21 or 35 drops per minute
(3) Intravenous treatments
(a) Systemic steroids
(i) Dexamethasone 0.25-0.5 mg/kg IV, or
(ii) Hydrocortisone 2-3 mg/kg IV bd
(b) Systemic NSAIDs
(i) Paracoxib 40 mg IV bd, or
(ii) Ketorolac 30 mg IV bd
(c) Anticoagulants at therapeutic dose
(i) UFH IV, or
(ii) LMWH SC[18]
(iii) Consider: Sulodexide IV (or IM) if available
(4) Oral agents- to substitute or as an adjunct to intravenous measures and continued for up to 12 weeks
(a) Corticosteroids
(i) Prednisolone 0.5-1 mg/kg, and tapered slowly over 12 weeks. Prednisone should not be ceased abruptly as it may trigger worsening[38]
(b) NSAIDs

(continued)

Table 5. (continued)

Immediate In-Hospital Management of Major Ischaemia
(i) Naproxen 1000 mg slow release (SR) PO daily
(c) Anticoagulants
(i) Direct oral anticoagulants (DOACs)
(d) Platelet inhibitors and modifiers
(i) Acetylsalicylic acid (ASA)
(ii) Clopidogrel or ticagrelor
(iii) Cilostazol (antiplatelet and vasodilator): 50-100 mg PO bd
(iv) Pentoxifylline: 400 mg PO tds[19]
(e) Vasodilators
(i) Nifedipine
(ii) Papaverine

options available at the treating hospital. The objective is to identify the affected vessel(s) and carry out suitable interventions based on the findings.

(1) Immediate investigation: Digital subtraction angiography (DSA)
In case of suspected major ischaemia, intra-arterial digital subtraction angiography (DSA) should be considered as the first priority to confirm the diagnosis and implement treatment strategies for limb salvage if feasible. Detergent sclerosants and in particular POL cause immediate vasospasm of targeted vessels,[94] and can cause vessel occlusion at distal non-target sites. DSA will help assess the state of arterial inflow, and identify sites of vessel occlusion or compromised flow that require endovascular interventions to re-establish perfusion.[95]

(2) Baseline investigations
DSA is the most important investigation to be conducted immediately and should be followed by active intervention if feasible. Other investigations listed below should be carried out at an appropriate time during the admission but should not delay immediate endovascular interventions.
   (a) Baseline bloods including coagulation parameters.
   (b) Arterial and venous DUS.
   (c) ABI or toe/brachial index (TBI) measurements (e.g. if dorsalis pedis has been inadvertently injected, ABI may be normal).
   (d) Transcutaneous oxygen measurements (TcPO2).

(3) Other investigations if indicated
   (a) CT or MR angiography may help confirm larger occluded vessel(s) but will be of limited value to identify even significant angiosomal damage.
   (b) Laser Doppler (if available) to evaluate skin perfusion.

Emergency endovascular interventions and surgery. Interventions proposed here provide a guide, and may be implemented individually or in combination with other measures as determined by the clinical presentation and comorbidities.

(1) Emergency endovascular intervention
The selection of appropriate intervention will be based on arteriographic findings and feasibility of strategies required to re-perfuse the affected territory:
   (a) Intra-arterial administration of vasodilators[96] where spasm is thought to be a significant component using agents such as papaverine,[41,97] glyceryl trinitrate (GTN), tolazoline,[98] verapamil and prostaglandin E1 (PGE1)[99,100]
   (b) Thrombolysis with direct infusion of thrombolytic agents such as intra-arterial tissue plasminogen activator (t-PA) or urokinase;
   (c) Thrombectomy with endovascular mechanical thrombectomy;[20]
   (d) Intra-arterial unfractionated heparin (UFH) if patient not therapeutically anticoagulated;
   (e) Angioplasty and/or stenting of the affected artery and the inflow vessel where inflow-limiting concomitant atherosclerotic stenosis or occlusion is present.

(2) Surgical interventions
   (a) Open surgery may be required where endovascular options are not available or appropriate to achieve reperfusion and if a reconstructive procedure is required.
   (b) Amputation of the affected limb or digits as well as wound debridement may be required early on but more typically the need for these interventions occurs during subsequent days.

Lumbar sympathetic block

(1) Chemical lumbar sympathetic block of the affected limb to reduce vasospasm and enhance collateral reperfusion with vasodilatation.
(2) This procedure is associated with a risk of bleeding and anticoagulation must be managed in the perioperative period. Relevant guidelines for the perioperative management of anticoagulants and antiplatelet therapy should be consulted.[101,102]

Medical management. Medical measures are adjunctive to the procedures described above especially if the interventions have had limited success or failed in achieving re-perfusion. These interventions can also be used as a primary treatment when the endovascular approach is not suitable or contraindicated or for ongoing treatment post-intervention to optimise reperfusion and revascularisation.

(1) General measures
  (a) Explain the suspected diagnosis to the patient and discuss the management plan.
  (b) Cease triggers that worsen ischaemia
    (i) Stop drugs with vasoconstrictive activity (e.g. certain migraine medications and psychoactive drugs).
    (ii) Advise the patient to stop smoking (if relevant).
  (c) Do not apply antiembolic compression and remove any stockings or bandages if already applied.
  (d) Consider supportive measures
    (i) Fluids
    (ii) Pain and sleep management
    (iii) Assess risk of infection and treat accordingly
  (e) Consult other relevant specialists as appropriate.
  (f) Provide psychosocial support, arrange counselling if required.
(2) Intravenous infusions
  These measures may be considered to enhance re-perfusion and can be used as an adjunct to endovascular interventions.
  (a) Prostaglandins: PGE1 (alprostadil) via central venous catheter
  (b) Consider anti-sludging agent: Dextran-40 (Buerger's disease protocol) 500 mL over 24 h[103]
  (c) Consider: Pentoxifylline 2g diluted in 450 mL of dextrose in parallel at 21 or 35 drops per minute.
(3) Intravenous treatments
  These measures may be considered to reduce the inflammatory response in the acute phase and assist with restoration of normal flow.
  (a) Systemic steroids
    (i) Dexamethasone 0.25-0.5 mg/kg IV, or
    (ii) Hydrocortisone 2-3 mg/kg IV bd.
  (b) Systemic NSAIDs
    (i) Paracoxib 40 mg IV bd, or
    (ii) Ketorolac 30 mg IV bd
  (c) Anticoagulants at therapeutic dose
    (i) UFH IV, or
    (ii) LMWH SC,[21]
    (iii) Consider: sulodexide IV (or IM) if available.
(4) Oral agents
  Appropriate selection of the following oral measures should be made based on the clinical presentation, contraindications, co-morbidities and local availability of the suggested agents. Some of these agents may be started in the post-acute phase or upon discharge and maintained for up to 12 weeks, unless contraindicated.
  (a) Corticosteroids
  To substitute intravenous steroids in the post-acute phase.
  (i) Prednisolone 0.5-1 mg/kg, and tapered slowly over 12 weeks. Prednisone should not be ceased abruptly as it may trigger worsening.[38]
  (b) NSAIDs
  To substitute intravenous NSAIDs in the post-acute phase and to be continued post-discharge.
  (i) Naproxen 1000 mg slow release (SR) PO daily.
  (c) Anticoagulants
  To substitute intravenous heparin if clinically indicated.
  (i) LMWH- is preferred over Direct Oral anticoagulants (DOACs) in this setting due to its anti-inflammatory effects.[104]
  (ii) DOACs- dose to be determined based on individual clinical findings.
  (d) Platelet Inhibitors and Modifiers
    (i) Acetylsalicylic acid (ASA),
    (ii) Clopidogrel or Ticagrelor,
    (iii) Cilostazol (antiplatelet and vasodilator): 50-100 mg PO bd,
    (iv) Pentoxifylline: 400 mg PO tds,[22]

(e) Vasodilators
(v) Nifedipine,
(vi) Papaverine.

Management of minor ischaemia. The following consensus-based recommendations are to be applied in the management of sclerosant-induced minor ischaemia (Figure 12).

Triage

Minor Ischaemia following an Intra-arterial Injection: In-hospital Assessment. All actual and suspected cases of intra-arterial injection of sclerosants should be assessed at a hospital facility with a vascular/interventional unit (see 1.1 above). Following the vascular assessment, some patients may be found to be at risk of minor ischaemia due to the limited involvement of skin and subcutaneous tissue (see definitions, 1.2 above). The areas of ischaemia are usually smaller but may take some time to evolve and may not progress to develop frank necrosis. Following the assessment, patients with minor ischaemia can be discharged to be treated on an outpatient basis following the protocol described below. Otherwise, patients with a more severe presentation, those with comorbidities and those where the clinical evolution seems uncertain are best to stay in hospital for a few days for monitoring and to optimise care before discharge for outpatient management (Table 6).

Minor Ischaemia following an Intravenous Injection: Outpatient Management. VAR-VAS and other *Intravenous* causes of skin ischaemia post-sclerotherapy can be treated following the outpatient protocol for minor ischaemia (see below) but these patients may not need to be assessed at a hospital facility.

Minor Ischaemia where the cause is uncertain: In-hospital Assessment. Cases where the ischaemia appears to be minor but the practitioner is uncertain whether an intra-arterial injection has occurred are best referred for an in-hospital vascular assessment. Advice from a senior or more experienced colleague should be obtained where there is uncertainty.

Treatment protocol

(1) Manage as in-patient if unsure about the clinical evolution, otherwise manage as outpatient.
(2) General Measures
  (a) Explain the suspected diagnosis to the patient and discuss the management options; provide the patient the option of assessment at a hospital facility if preferred by the patient.
  (b) Cease triggers that worsen ischaemia
    (i) Avoid compression in the acute phase. Compression may be required post-acute phase to prevent and manage oedema.
    (ii) Stop drugs with vasoconstrictive activity.
    (iii) Advise the patient to stop smoking (if relevant).
  (c) Supportive measures
    (i) Pain and sleep management
    (ii) Assess risk of infection
  (d) Consult other relevant specialists as appropriate.
  (e) Provide psychosocial support, arrange counselling if required
(3) Oral Treatments
Occasionally small areas of tissue ischaemia fail to ulcerate and may heal without active treatment. For larger affected areas, the following measures, individually or in combination, may be considered. Appropriate selection of the oral measures should be made based on the clinical presentation, contraindications, co-morbidities and local availability of the suggested agents. Oral treatments may need to be continued for up to 12 weeks or longer, unless contraindicated.
  (a) Corticosteroids
    (i) Prednisolone 0.5-1 mg/kg, and tapered slowly over 12 weeks.
  (b) NSAIDs
    (i) Naproxen 1000 mg slow release (SR) PO daily.
  (c) Anticoagulants
    (i) Direct Oral anticoagulants (DOACs)- dose to be determined based on individual clinical findings.
  (d) Platelet Inhibitors and Modifiers
    (i) Acetylsalicylic acid (ASA),
    (ii) Clopidogrel or Ticagrelor,
    (iii) Cilostazol (antiplatelet and vasodilator): 50-100 mg PO bd,
    (iv) Pentoxifylline: 400 mg PO tds,[23]
  (e) Vasodilators
    (i) Nifedipine
    (ii) Papaverine.

Section 2. Long term management of tissue ischaemia

Discharge and follow-up. On discharge, change the treatment to oral medications as clinically indicated and give the

Table 6. Immediate Treatment of Minor Ischaemia. For suspected intra-arterial sclerosant injection, these treatments should be initiated on an in-patient basis to observe the clinical evolution of ischaemia. For an intravenous induced skin ischaemia, e.g. veno-arteriolar reflex vasospasm (VAR-VAS) these measures can be instituted on an outpatient basis. ASA, acetyl salicylic acid; bd, twice a day; tds, three times a day; DOACS, direct oral anticoagulants; LMWH, low molecular weight heparin; PO, oral route; SC, subcutaneous.

Immediate Treatment of Minor Ischaemia
(1) Manage as in-patient if unsure about the clinical evolution, otherwise manage as outpatient
(2) General measures
(a) Explain the suspected diagnosis to the patient and discuss the management plan
(b) Cease triggers that worsen ischaemia
(i) Avoid compression in the acute phase. Compression may be required post-acute phase to prevent and manage oedema
(ii) Stop drugs with vasoconstrictive activity
(iii) Advise the patient to stop smoking if relevant
(c) Supportive measures
(i) Pain and sleep management
(ii) Assess risk of infection
(d) Consult other relevant specialists as appropriate
(e) Provide psychosocial support, arrange counselling if required
(3) Oral agents
Oral treatments may need to be continued for up to 12 weeks or longer, unless contraindicated
(a) Corticosteroids
(i) Prednisolone 0.5-1 mg/kg, and tapered slowly over 12 weeks
(b) NSAIDs
(i) Naproxen 1000 mg slow release (SR) PO daily
(c) Anticoagulants
(i) Direct oral anticoagulants (DOACs)- dose to be determined based on individual clinical findings
(d) Platelet inhibitors and modifiers
(i) Acetylsalicylic acid (ASA)
(ii) Clopidogrel or ticagrelor
(iii) Cilostazol (antiplatelet and vasodilator): 50-100 mg PO bd
(iv) Pentoxifylline: 400 mg PO tds
(e) Vasodilators
(i) Nifedipine
(ii) Papaverine

patient clear instructions/contact information and the advice to contact the practitioner if the patient has any concerns. Provide a follow-up appointment within 1 week to assess the clinical evolution.

The follow up will depend on the severity of the injury and success or otherwise of the in-hospital care. The aim of the continued management will be to optimise reperfusion and revascularisation, management of symptoms, wound care and rehabilitation. While devastating tissue losses may have occurred, not all areas of ischemia lead to irreversible tissue loss and substantial recovery is possible but this may take long periods of time.

Monitoring. The neuro-vascular state of the affected limb(s) must be monitored closely following discharge. Serial photographs should be obtained and the wound size measured on each visit. DUS and ABI measurements should be compared to baseline studies to monitor change. Medical treatment will need to be adjusted depending on the clinical state, laboratory findings and progress imaging studies.

Pain management. Pain management can be the most challenging aspect in the long-term management of this adverse event and consultation with pain specialists is likely to be required.[55] The neuropathic pain may be debilitating and responds poorly to conventional treatment with oral medications such as pregabalin, gabapentin or amitriptyline. Transcutaneous electrical neurostimulation (TENS) or similar devices may provide some relief. Neurology assessment may be required and nerve conduction studies and electromyogram (EMG) may need to be organised. For relentless pain, sympathectomy may be considered although the utility of this surgical intervention in this patient population is unknown.

Wound management. It should be explained that healing may be slow and careful follow-up is needed. The area of skin affected should be protected when vulnerable to further

injury. Where the skin is irreversibly ischemic, necrosis may lead to ulcer formation and be prone to infection. Healing with revascularisation and wound contraction may occur.

For open wounds, appropriate wound dressing should be applied in accordance with the stage of wound healing. Sequential photography should be obtained and the size of the wound recorded in the photographs. Compression may need to be re-introduced to reduce oedema. Resultant ulcers may be persistent and may take many months to heal. Skin grafting and flap repair reconstructive surgery in certain anatomical regions such as the thighs may provide an excellent outcome (Figure 2(F)). In areas with poor vascular perfusion skin grafts may fail. Tissue atrophy may persist despite reconstructive plastic surgery.

Hyperbaric oxygen has been used to expedite wound healing and in particular for treatment of local vascular occlusion secondary to tissue fillers.[105,106] Whilst there is no consensus amongst authors with regards to its effectiveness in this setting, it can be used as an adjunctive treatment for wound management.

Rehabilitation. Patients who have suffered limb loss requiring prosthesis and those with compromised limb function as a result of soft tissue necrosis and muscle loss or nerve damage will require long term physiotherapy and occupational therapy.

Mental health and psychosocial recovery. Major vascular trauma and limb loss will have an immense effect on the patient's mental health, day to day activities and ability to resume function in the society. The diagnosis should be openly disclosed to the patient from the outset and psychosocial support provided through the course of recovery. The impact of trauma on the patient's mental health is hugely influenced by good support and communication, and this should start from the moment the injury occurs.

Section 3. Recommendations for prevention

The following recommendations provide a guide for prevention of inadvertent intra-arterial sclerosant injection and increase the safety of the procedure (Table 7).

Proceduralist competencies

(1) Medical practitioners performing sclerotherapy of lower limb veins—
   (a) must have completed a course of formal training (specialty or subspecialty training, or equivalent recognition) in the management of venous and lymphatic disorders (phlebology), and
   (b) be personally proficient in the use of DUS in vascular applications to diagnose and provide image guidance to venous procedures,[5] and
   (c) should not underestimate the risk of an intra-arterial sclerosant injection and its devastating outcomes, by
      (i) maintaining their knowledge and competencies over time, and
      (ii) reviewing and optimising their practical skills and treatment techniques on a regular basis.

(2) Trainees and medical practitioners with limited experience in sclerotherapy must perform this procedure under supervision till deemed competent by appropriate training colleges or educational bodies.

Setting

(1) Facilities conducting sclerotherapy should maintain an adequate stock of therapeutic agents for the emergency management of an intra-arterial injection (Table 8).

(2) Medical, allied health and administration staff should undergo regular training in emergency management of acute adverse events associated with sclerotherapy and achieve relevant competencies as required by local regulatory health organisations.

Imaging

(1) Preoperative Imaging
   (a) Venous Mapping
      (i) Careful, comprehensive and detailed ultrasound imaging (venous incompetence study) supplemented by accurate graphic venous mapping should be performed at the initial assessment, and prior to the procedure.
      (ii) Pre-operative ultrasound studies should be used to assist with treatment planning, identify anatomical variations and anomalies, and localise high risk sites susceptible to an inadvertent intra-arterial event.
      (iii) Proceduralists planning a venous procedure should rely on their own venous mapping, or that obtained at a facility where the quality and standards of the examination is known to the proceduralist.
   (b) Other imaging studies—
      (i) such as CTA, MRA or DSA may be required if anatomical variations or vascular anomalies are suspected.
      (ii) should be performed well in advance of any planned procedure to detect potential anatomical variations or anomalies that could jeopardise the safe delivery of the treatment.

Table 7. Recommendations for prevention of intra-arterial injection of sclerosants.

Recommendations for Prevention of Intra-Arterial Injections
A. Proceduralist competencies
(1) Medical practitioners performing sclerotherapy of lower limb veins—
(a) Must have completed a course of formal training (specialty or subspecialty training, or equivalent recognition) in the management of venous and lymphatic disorders (phlebology), and
(b) be personally proficient in the use of DUS in vascular applications to diagnose and provide image guidance to venous procedures, and
(c) Should not underestimate the risk of an intra-arterial sclerosant injection and its devastating outcomes, by
(i) Maintaining their knowledge and competencies over time, and
(ii) Reviewing and optimising their practical skills and treatment techniques on a regular basis
(2) Trainees and medical practitioners with limited experience in sclerotherapy must perform this procedure under supervision till deemed competent by appropriate training colleges or educational bodies
B. Setting
(1) Facilities conducting sclerotherapy should maintain an adequate stock of therapeutic agents for the emergency management of an intra-arterial injection (Table 8)
(2) Medical, allied health and administration staff should undergo regular training in emergency management of acute adverse events associated with sclerotherapy and achieve relevant competencies as required by local regulatory health organisations
C. Imaging
(1) Preoperative imaging
(a) Venous mapping
(i) Careful, comprehensive and detailed ultrasound imaging (venous incompetence study) supplemented by accurate graphic venous mapping should be performed at the initial assessment, and prior to the procedure
(ii) Pre-operative ultrasound studies should be used to assist with treatment planning, identify anatomical variations and anomalies, and localise high risk sites susceptible to an inadvertent intra-arterial event
(iii) Proceduralists planning a venous procedure should rely on their own venous mapping, or that obtained at a facility where the quality and standards of the examination is known to the proceduralist
(b) Other imaging studies—
(i) Such as CTA, MRA or DSA may be required if anatomical variations or vascular anomalies are suspected
(ii) Should be performed well in advance of any planned procedure to detect potential anatomical variations or anomalies that could jeopardise the safe delivery of the treatment
(2) Ultrasound systems
To ensure optimal visualisation of target structures—
(a) High quality ultrasound systems utilising transducers with appropriate frequencies, and
(b) Operator-initiated optimisation of B-mode and Doppler settings must be employed at all times before and during ultrasound-guided procedures
(3) Ultrasound guidance
(a) Ultrasound guidance must be available at all times to guide sclerotherapy of lower limb superficial veins
(b) Ultrasound guidance may be provided by a qualified vascular sonographer/technician or by the proceduralist
(c) Even if assisted by a qualified vascular sonographer/technician, the proceduralist must be personally proficient in the use of duplex ultrasound in vascular applications
D. Disclosure of risks and other treatment options
(1) Inherent and known risks of sclerotherapy must be disclosed to patients who are considering to undergo this procedure
(2) If there are compelling reasons to provide a bilateral procedure, any additional risks should be disclosed to patients
(3) Appropriate treatment options other than sclerotherapy should be discussed and include: (i) Having no treatment at all, (ii) compression and other general measures, (iii) other venous interventions performed under ultrasound-guidance including catheter-directed sclerotherapy and endovenous thermal or non-thermal ablation, (iv) ambulatory phlebectomy, and (v) surgery
E. Treatment strategy and technique optimisation
(1) Baseline neurovascular status and pain score[24] as related to the limb to be treated should be obtained and recorded ahead of the procedure
(2) Technique optimisation strategies should be adopted to minimise the risk of necrosis post-sclerotherapy.[5] When performing sclerotherapy, —
(a) Pressure and volume of injection at each puncture site should be minimised, and

(continued)

Table 7. (continued)

Recommendations for Prevention of Intra-Arterial Injections
(b) Inappropriately too high or too low concentrations should be avoided[55]
(3) Patient position
(a) Sclerotherapy must only be performed with the patient lying down (supine, prone or recumbent) on a procedure table in a stable position
(b) Sclerotherapy must not be performed with the patient standing
(4) Bilateral procedures
(a) There is no scientific evidence to support any benefits for performing a bilateral simultaneous sclerotherapy procedure
(b) Unless there are compelling reasons, bilateral sclerotherapy especially when initiating the treatment of varicose veins should be avoided to gauge the patient's clinical response to the sclerosing agents, detect any adverse reactions, identify any anatomical variations and help limit any adverse reactions to one limb only
F. Risk mitigation
(1) High risk anatomical sites
(a) Additional care must be taken when performing sclerotherapy in high risk areas such as the medial malleolus, anterior ankle, popliteal fossa and groin
(b) Ultrasound guidance must be used at all times
(c) Bilateral sclerotherapy procedures must be avoided
(2) High risk patients
(a) Additional care must be taken and sclerotherapy treatment provided in controlled settings capable of dealing with potential serious adverse events
(b) Bilateral sclerotherapy procedures must be avoided
(3) Proceduralists faced with an unfamiliar or unusual anatomy, an unusual tissue response to the treatment including skin demarcation and discoloration, severe pain or other unexpected symptoms or signs experienced by the patient should—
(a) Stop the procedure, reassess and follow the recommended guidelines for treatment of acute events
(b) Not treat the contralateral limb on the same occasion

(2) Ultrasound Systems

To ensure optimal visualisation of target structures—

(a) high quality ultrasound systems utilising transducers with appropriate frequencies, and

(b) operator-initiated optimisation of B-mode and Doppler settings must be employed at all times before and during ultrasound-guided procedures.

(3) Ultrasound Guidance

(a) Ultrasound guidance must be available at all times to guide sclerotherapy of lower limb superficial veins.[5,107]

(b) Ultrasound guidance may be provided by a qualified vascular sonographer/technician or by the proceduralist.

(c) Even if assisted by a qualified vascular sonographer/technician, the proceduralist must be personally proficient in the use of duplex ultrasound in vascular applications (see 1b above).[5]

Disclosure of risks and treatment options

(1) Inherent and known risks of sclerotherapy must be disclosed to patients.[25]

(2) If there are compelling reasons to provide a bilateral procedure, the potential for bilateral complications should be discussed with patients.

(3) Appropriate treatment options other than sclerotherapy should be discussed and include: (i) having no treatment at all, (ii) compression and other general measures, (iii) other venous interventions performed under ultrasound-guidance including catheter-directed sclerotherapy and endovenous thermal or non-thermal ablation, (iv) ambulatory phlebectomy, and (v) surgery.

Treatment strategy and technique optimisation

(1) Baseline neurovascular status and pain score[26] as related to the limb to be treated should be obtained and recorded ahead of the procedure.

(2) Technique optimisation strategies should be adopted to minimise the risk of necrosis post-sclerotherapy.[5] When performing sclerotherapy, —

(a) pressure and volume of injection at each puncture site should be minimised, and

(b) inappropriately too high or too low concentrations should be avoided.[55]

(3) Patient position

Table 8. Recommended therapeutic agents to be maintained at facilities providing sclerotherapy for immediate management of inadvertent intra-arterial injections. LMWH, low molecular weight heparin; NSAIDs, non-steroidal anti-inflammatory drugs.

Therapeutic agents for Immediate Bedside Management of an Intra-arterial Injection
(1) Sublingual nitroglycerin
(2) LMWH: Enoxaparin 1.5 mg/kg
(3) Intravenous corticosteroids
(i) Dexamethasone 0.25-0.5 mg/kg IV, or
(ii) Hydrocortisone 0.75-1 mg/kg IM or IV stat
(4) Systemic NSAIDs
(i) Parecoxib 20-40 mg IM or IV stat; or
(ii) Ketorolac 30 mg IM or IV stat

(a) Sclerotherapy must only be performed with the patient lying down (supine, prone or recumbent) on a procedure table in a stable position.
(b) Sclerotherapy must not be performed with the patient standing.

(4) Bilateral procedures
(a) There is no scientific evidence to support any benefits for performing a bilateral simultaneous sclerotherapy procedure.
(b) Unless there are compelling reasons, bilateral sclerotherapy especially when initiating the treatment of varicose veins should be avoided to gauge the patient's clinical response to the sclerosing agents, detect any adverse reactions, identify any anatomical variations and help limit any adverse reactions to one limb only.

Risk mitigation

(1) High Risk Anatomical Sites
(a) Additional care must be taken when performing sclerotherapy in high risk areas such as the medial malleolus, anterior ankle, popliteal fossa and groin.[55]
(b) Ultrasound guidance must be used at all times.[27]
(c) Bilateral sclerotherapy procedures involving high risk anatomical sites should be avoided.

(2) High Risk Patients
(a) When treating high risk patients, sclerotherapy treatments should be provided in controlled settings capable of dealing with potential serious adverse events.
(b) Bilateral sclerotherapy procedures in high risk patients should be avoided.

(3) Proceduralists faced with an unfamiliar or unusual anatomy, an unusual tissue response to the treatment including skin demarcation and discoloration, severe pain or other unexpected symptoms or signs experienced by the patient should—
(a) stop the procedure, reassess and follow the recommended guidelines for treatment of acute events.
(b) not treat the contralateral limb on the same occasion.

Conclusion

Intra-arterial injection of sclerosants is a potentially devastating adverse event of sclerotherapy of lower limb superficial veins that can result in significant tissue or limb loss and long-term significant morbidity. Careful ultrasound guidance and practitioners adequate training in phlebology and use of ultrasound is critical in prevention of this complication. Expertise in diagnosis and immediate management of this complication is essential for all practitioners performing endovenous procedures. The risk should not be underestimated and medical practitioners and in particular new graduates must perform these procedures under supervision till deemed competent.

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Author Contributions

KP, MdM and AvR were the primary authors for the manuscript. KP, MdM, AvR, and CR co-edited the manuscript. WB, JD, CL and KP provided medicolegal analysis. All remaining authors contributed to the manuscript and approved the content.

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Disclaimer

The medicolegal analysis in this publication provides general policy guidance only. These recommendations are not intended to, nor should be used or relied upon as actual legal advice. Legal advice is fact dependent and requires a review of facts before legal advice is sought and provided. Any references to individuals involved in the *illustrated case* are made with the intention of illustrating the clinical aspect of the case for educational purposes. The factual statements were derived from the published case by the New Zealand Health and Disability Commission and based on factual findings of the commission.[4] Comments on the clinical and medicolegal aspects of the case reflect the opinion of the panel and not intended to harm the reputation of any individuals involved in the case.

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Notes

1. *Stellate* describes the peripheral dendritic extensions, *retiform* describes the mottled reticulate morphology and *purpura* describes the histological finding of red cell extravasation.
2. These medicolegal considerations provide general policy guidance only. These recommendations are not intended to, nor should be used or relied upon as actual legal advice. Legal advice is fact dependent and requires a review of facts before legal advice is sought and provided.
3. *McConnel v. Williams*, 361 Pa. 355, 65 A.2d 243, 246 (1949).
4. *Sparks v Hobson, Gray v Hobson* [2018] NSWCA 29. In this case, the plaintiff, Mr Hobson, suffered from Noonan Syndrome. Surgery was planned by his orthopaedic surgeon, Dr Gray, in two stages to correct his spine to help with breathing difficulties. The first operation was uncomplicated. In the second operation, the patient was in a prone position and the anaesthetist had difficulty ventilating him as evident from deteriorating blood gases. The operation started at 7p.m. but by 8:50p.m., the CO2 levels remained elevated despite various measures. The anaesthetist, Dr Sparks sought phone advice from two colleagues who could not recommend any further measures to treat the respiratory acidosis. At 9:25p.m., the anaesthetist informed the surgeon that the procedure should be terminated and the surgeon stopped promptly. When the patient was returned to a supine position his condition improved but by this time, he had suffered severe ischaemia of the spinal column resulting in paraplegia. The Court of Appeal found that the surgeon had not breached his duty of care as he was entitled to rely on the anaesthetist to be informed of any matters of concern, within the scope of practice of the anaesthetist. He stopped the procedure promptly when informed by the anaesthetist. In addition, he had informed the patient of the specific risk of "neurological injury including paralysis". But the anaesthetist was found to have breached his duty of care for allowing the procedure to continue and ignoring a serious and imminent intraoperative threat to the patient's health. Dr Sparks was found liable in negligence to the plaintiff in the amount of AUD$3,828,075.
5. *Wighton v Arnot* [2005] NSWSC 637.
6. *Bolam v Friern Barnet Hospital Management Committee* [1957] 1 WLR 582. McNair J stated that a doctor would not be negligent if:"...he acted in accordance with a practice accepted as proper by a reasonable body of medical men skilled in that particular art.
7. *Civil Liability Act 2002* (NSW) s5O.
8. *Civil Liability Act 2002* (NSW) s5O(2).
9. *Bolitho v City and Jackney Health Authority* [1997] UKHL 46.
10. *Health and Disability Commissioner (Code of Health and Disability Services Consumers' Rights) Regulations 1996* (NZ) 4(1).
11. *Rogers v Whitaker* [1992] HCA 58; 175 CLR 479; 23 NSWLR 600; 109 ALR 625.
12. *Montgomery v Lanarkshire Health Board* [2015] UKSC 11. The patient who was of a small stature consulted her obstetrician concerned about vaginal delivery. The risk of shoulder dystocia with a vaginal delivery was not disclosed to her, hence she did not request a caesarean section. The delivery was complicated by shoulder dystocia and her son was born with hypoxic brain damage resulting in cerebral palsy.
13. From a statistical point of view, whilst the absolute risk of an adverse event associated with a procedure remains the same on every occasion the procedure is repeated, the probability of an event eventually occurring increases with the number of occasions the procedure is repeated. For instance, if the risk of death from skydiving is estimated at 0.1%, if the dive is repeated 10 times, the probability of death will be 0.65% as calculated by the formula: $1-(0.9)^{10}$. In the current case, if the

risk of an intra-arterial injection in a single leg sclerotherapy is taken to be one in 1000 (0.1%), the probability of the event occurring in a bilateral procedure will be 1-$(0.9)^2$ = 0.19%. This means the higher the number of attempts, the higher the probability of the adverse event occurring.

14. *Sparks v Hobson, Gray v Hobson* (n3).
15. Treatments of unknown or doubtful value. Many treatments and manoeuvres have been proposed as helpful and published in the older literature including textbooks. Some are of limited or unknown value and some are unsafe. Examples include: (1) Maintaining the needle in the injected arterial vessel and attempting to aspirate and inject intra-arterial heparin. This is impractical and unsafe advice as the intra-arterial position of the needle cannot be guaranteed and injection of any drug via such a needle can result in extravasation. In addition, the patient is usually in considerable pain and together the practitioner's stress may lead to even more unsafe outcomes. (2) Local application of a nitrate patch or application of a nitrate based ointment such as those used in the treatment of haemorrhoids to induce local skin vasodilation has never been shown to be effective. (3) Local peri-lesional injection of corticosteroids at the puncture site has been recommended but its safety and effectiveness is of doubtful value. (4) Peri-lesional injection of procaine 1%. Procaine being a cationic agent was thought to inactivate sodium tetradecyl sulphate (STS), an anionic detergent. It was subsequently demonstrated that procaine had no neutralising effect on STS.[93] (5) Cooling, heating, massage and other manual measures are of doubtful benefit.
16. Relevant documents to accompany patients include a letter to the admitting doctor detailing the incident, the suspected adverse events, the sclerosant used, any immediate treatments given, copies of the observation records, medical history ensuring and infectious status, and advanced care directives if applicable.
17. Main injury caused by detergent sclerosants is vessel spasm and occlusion via sludge and coagulum formation. Thrombus is not a common feature of sclerosant-induced arterial occlusion.
18. Not concurrent with an intra-arterial infusion.
19. Not if delivered intravenously.
20. Main injury caused by detergent sclerosants is vessel spasm and occlusion via sludge and coagulum formation. Thrombus is not a common feature of sclerosant-induced arterial occlusion.
21. Not concurrent with an intra-arterial infusion.
22. Not if delivered intravenously.
23. Not if delivered intravenously.
24. The patient's self-assessment of their preoperative pain in the limb to be treated.
25. Patients in New Zealand must additionally be provided with the information required to be provided to them by the Code of Health and Disability Services Consumers' Rights 1996.
26. The patient's self-assessment of their preoperative pain in the limb to be treated.
27. Recommendation 3F(1) mandates the use of ultrasound in high risk anatomical sites. This is in distinction to Recommendation 3C(3) above where ultrasound guidance is recommended to be available at all times during sclerotherapy procedures.
28. Food and Drug Administration. Guidance for Industry, Warnings and Precautions, Contraindications, and BoxedWarning Sections of Labelling for Human Prescription Drug and Biological Products—Content and Format. [2011]. Available at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> accessed 25 May 2020.

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Appendix

Glossary

AASV	Anterior accessory saphenous vein	INR	International normalised ratio
ABI	Ankle brachial pressure index	IV	Intravenous
AKA	Above-knee amputation	LMWH	Low molecular weight heparin
ASA	Acetyl-salicylic acid (aspirin)	MGA	Medial gastrocnemius artery
ATA	Anterior tibial artery	MOCA	Mechanochemical ablation
AV	Arteriovenous	MRA	Magnetic resonance imaging angiography
AVM	Arteriovenous malformation	MRI	Magnetic resonance imaging
BKA	Below-knee amputation	NSAIDs	Non-steroidal anti-inflammatory drugs
CFV	Common femoral vein	PAD	Peripheral arterial disease
CLI	Critical limb ischaemia	PE	Pulmonary embolism
CDS	Catheter-directed sclerotherapy	PGE1	Prostaglandin E1
CDT	Catheter-directed thrombolysis	POL	Polidocanol
CT	Computed tomography	POP	Popliteal
CTA	Computed tomography and angiography	PTA	Posterior tibial artery
CVD	Chronic venous disease	RFA	Radiofrequency ablation
DOACs	Direct oral anticoagulants	SCI	Subcutaneous injection
DSA	Digital subtraction angiography	SFA	Superficial femoral artery
DUS	Duplex ultrasound	SSA	Small saphenous artery
DVT	Deep vein thrombosis	SSV	Small saphenous vein
EMG	Electromyogram	STS	Sodium tetradecyl sulphate
EPA	External pudendal artery	TBI	Toe brachial pressure index
FAERS	Federal adverse event reporting system	TcPO2	Transcutaneous oxygen measurements
FDA	(United States) food and drug administration	TENS	Transcutaneous electrical neurostimulation
GSV	Great saphenous vein	t-PA	Tissue plasminogen activator
GTN	Glyceryl trinitrate	UFH	Unfractionated heparin
HDC	(New Zealand) health and disability commission	UGS	Ultrasound-guided sclerotherapy
IM	Intramuscular	VAR-VAS	Veno-arteriolar reflex vasospasm

Definitions

Adverse reaction[28]	An undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event
Adverse event	Any untoward medical occurrence associated with the use of a drug or delivery of a procedure, whether or not previously reported or considered to be drug or procedure related
Ischaemia	
Critical limb ischaemia	Ischaemia diagnosed by typical clinical manifestations (see below- *major ischaemia*) and an ankle brachial index (ABI) < 0.5 or ankle pressures <50 mmHg
Major ischaemia	Acute onset of progressive pain in the affected limb, loss of pulse, loss of sensation or paresthesia, abnormal limb temperature or pallor, onset of paralysis, requiring intervention
Minor ischaemia	Ischaemia which is limited to skin and subcutaneous tissue not meeting the definition of major ischemia

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Invasiveness	
Non-invasive	Procedures not requiring an incision and in this context would include direct vision and ultrasound-guided sclerotherapy
Minimally invasive	Procedures requiring small incisions and in this context would include ambulatory phlebectomy and interventional procedures such as catheter-directed sclerotherapy (CDS), mechanochemical ablation (MOCA), endovenous laser ablation (EVLA), radiofrequency ablation (RFA) and cyanoacrylate closure (CAC)
Invasive	General surgery and in this context varicose vein surgery
Material risk	A material risk is one that a reasonably prudent patient would think significant A doctor is under a duty to take reasonable care to ensure that a patient is aware of any material risks involved in any recommended treatment, and of reasonable alternative or variant treatments. The test of materiality is whether in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to it'
Sclerotherapy	
Sclerotherapy techniques	A non-invasive venous intervention commonly used to treat superficial venous disease, vascular malformations and other ectatic vascular lesions. It involves introducing a chemical agent into the target vessel to induce endovascular fibrosis. In the current manuscript, *sclerotherapy* refers to all technical variations including direct vision, ultrasound-guided (UGS) and catheter-directed (CDS) sclerotherapy but does not include sclerotherapy performed assisted with other technologies such as mechanochemical ablation (MOCA)
Direct vision sclerotherapy	Sclerotherapy performed by direct percutaneous puncture and injection of the target veins (varicose veins, reticular veins or telangiectasias) without ultrasound or other forms of image guidance. Direct vision sclerotherapy of telangiectasias is also referred to as"micro-sclerotherapy"
Ultrasound-guided sclerotherapy (UGS)	Also referred to as "Echosclerotherapy" is sclerotherapy performed under ultrasound guidance
Catheter-directed sclerotherapy (CDS)	Sclerotherapy of truncal or accessory saphenous veins performed by peripheral catheterisation of the target vein under ultrasound guidance and delivery of the sclerosing agent via the catheter
Sclerotherapy applications	Sclerotherapy may be performed under normal circumstances for routine medical indications, for cosmetic purposes or as an emergency treatment
Cosmetic sclerotherapy	Sclerotherapy performed for cosmetic indications. Important to note, some patients may have both cosmetic and medical indications for treatment
Routine sclerotherapy	Sclerotherapy performed under normal circumstances and not as an emergency procedure. This may be for both medical and cosmetic indications
Medically indicated sclerotherapy	Sclerotherapy performed for medical (non-cosmetic) indications
Emergency sclerotherapy	Sclerotherapy performed to achieve haemostasis to sclerose bleeding varices, venous malformations or other vascular anomalies. Emergency sclerotherapy may also be indicated in patients otherwise not suitable for routine sclerotherapy to treat highly symptomatic and localised varicose veins such as vulvar veins during pregnancy