CONSENSUS DOCUMENT

THE BENEFITS OF INTERMITTENT PNEUMATIC COMPRESSION AND HOW TO USE WOUNDEXPRESS™ IN PRACTICE

Wounds UK

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Foreword

In humans, the adoption of an upright posture presents challenges to the successful return of blood from the lower limb to the heart. With advancing age, and the development of venous disease, venous return can be further compromised by defects in venous valves. Postural venous hypertension develops which increases the risk of skin damage and venous ulceration. For over 2000 years, the local treatment of venous disease has been the application of compression using bandages and hosiery. Majno (1975) reported the treatment of a woman with varicose veins and an ankle wound in 220 BCE involved application of a bandage applying high compression to the wound, along with advice to avoid standing, walking or sitting down.

Sustained compression using bandages or hosiery may present challenges in both gaining and sustaining patient concordance with their use. Alternative approaches to limb compression have developed since the mid 1850s where pressure is applied for only short time periods, with rapid inflation and deflation of cuffs positioned around the limb. This approach, called intermittent pneumatic compression (IPC), is generally considered to be well tolerated by patients and provides benefits that may not be achieved using sustained compression – for example, prevention of venous stasis and formation of blood clots during surgery. Design of the inflation and deflation times of IPC devices allows 'waves' of compression to be applied from distal to proximal along the leg, supporting the return of venous blood to the trunk (sequential IPC).

This document presents consensus among a cohort of experienced UK clinicians around the use of IPC as a means of improving lower leg wound management, with specific emphasis upon the use of IPC applied solely to the thigh with no direct contact with lower leg wounds or their surrounding skin. The following discussion is not intended to reflect a systematic review of the effects of sustained compression, IPC and thigh-administered IPC but highlights recent and key publications to support or refute arguments offered within the text of this consensus report.

Summary of key findings

The single most important intervention to help improve the removal of fluids from the lower limb has been the application of external mechanical compression either to sections of, or across, the entire lower limb. Compression can be applied using a wide variety of bandages and hosiery, which exert relatively low levels of compression (around 40mmHg). These are sustained until the limb volume begins to reduce as fluids are removed. There are several biological benefits to sustained compression (Box 1).

Box 1. Sustained compression confers several biological benefits

- Improved venous haemodynamics
- Control of oedema
- Reduced production of inflammatory mediators
- Improved microcirculation
- Improved arterial flow to the limb
- Improved lymphatic drainage
- Improved wound healing.

However, these benefits are not enjoyed by all patients, with up to 80% of patients in some studies failing to be concordant with wearing sustained compression bandages and hosiery, given challenges of donning and removing hosiery, pain, wound exudate leakage, skin irritation and discomfort.

External compression can also be applied using devices that rapidly inflate and deflate air chambers placed around the lower limb. The chambers can be inflated to higher pressures than would be achieved using bandages and hosiery (60mmHg and above), with these higher pressures applied for seconds then rapidly deflated. This is repeated in a cycle of rapid inflation-deflation of the chambers, followed by periods of no inflation. This IPC has traditionally been viewed as being most suitable for people who are immobile; however, the expanding use of IPC within sports science suggests the therapy has value for people with active calf muscle pumps. The benefits of IPC closely mirror the effects of sustained compression, with additional benefits through the prevention of deep vein thrombosis during and post-surgery, and the management of lymphoedema. Patient concordance with IPC is reported to be high compared with the wearing of sustained compression.

The circulatory system is essentially a closed system, where the impact of mechanical compression at one location may be anticipated to have biological effects at sites far from the point of compression. Compression of the lower limb affects flow in the thigh, while IPC applied to the legs and abdomen influences blood flow in the arms. A new IPC device (WoundExpress™, Huntleigh Healthcare, UK) has been developed after testing of the effect of inflation-deflation cycle times upon blood flow in volunteers and patients. Early clinical data indicates positive results around wound healing and, importantly, pain reduction. This consensus document sets out guidance upon where, when and how to use this new intervention to obtain the greatest likelihood of positive clinical outcomes.

Lower leg wounds

SIZE OF THE PROBLEM

In 2015, Guest and colleagues published a summary of the estimated number of wounds treated across the UK in 2012/13, along with the financial cost of wound management. Over 2012/13, an estimated 2.2 million wounds required management, with the cost of this care falling between £4.5 and £5.1 billion pounds (Guest et al, 2015). Forty per cent (*n*=900,000) of these wounds were located on the lower limb or foot; this estimate excluded pressure ulcers (PUs) that develop at the heel or foot. Clark et al (2017) noted that 161/589 (27.3%) of patients with a PU across all hospitals in Wales had their most severe wound located at the heel. Leg and foot wounds are frequently encountered in clinical practice; Gray et al (2018) reported the community prevalence of venous leg ulcers (VLUs), diabetic foot ulcers (DFUs) and PUs per 10,000 patients to be 612, 488 and 348 respectively; equating to 6 patients with a VLU within every 100 patients managed in UK community care.

Recent exploration of large linked databanks has provided strong insights into the financial costs of treating leg wounds. Databanks typically bring together GP practice data along with other health records, including outpatient and inpatient data and A&E records, to create links between individual datasets, which allow tracking of anonymised journeys of individual patients through the health care system. Both Guest et al (2018a; 2018b) and Phillips et al (2020) have estimated the cost of VLU treatment within the UK and Wales respectively as costing either £7,600 or £7,706 per patient with a VLU per year. In both studies, the primary driver of the cost of leg ulcer management was the number of visits community nurses made to patients with a VLU. Guest et al (2018b) performed a similar analysis focused upon the annual cost of treatment per patient of a DFU. The mean cost of treating a patient with a DFU over 12 months was £7,800. These initial analyses of large datasets suggest the average cost of lower leg wound treatment per patient, per year falls around £7,600 to £7,800. However, the costs of lower leg management are substantially influenced by the clinical outcome of treatment; where wounds are successfully healed, the cost of treatment is substantially reduced from the mean costs reported above. For example, the average cost of treating a DFU that healed reduced from £7,800 to £2,140, while the mean cost of managing an unhealed DFU increased from £7,800 to £8,800. Similar trends were observed when tracking VLU management (Guest et al, 2018a), with the average cost of an unhealed VLU being £13,454, while a healed VLU consumed only £2,980. There is no data available upon the annual per patient cost of heel PU management. The increasing use of sophisticated databanks holding comprehensive data from multiple providers of healthcare across the UK will help enable rapid evaluation of the estimated number of patients with lower leg wounds, the treatments provided, and the costs associated with their management.

MANAGEMENT OF LOWER LEG WOUNDS

The primary approach to both prevention and management of VLUs, DFUs and PUs considers modification of the mechanical loads applied to each wound type. For PUs and DFUs, the goal is to reduce mechanical loading upon vulnerable soft tissues (NICE, 2015; EPUAP, NPIAP, PPPIA, 2019). However, prevention and management of VLUs takes a different approach and focuses upon applying external mechanical loading to the leg to counteract gravitational effects that impair venous and lymphatic return from the leg to the trunk (Partsch, 2012). In many cases, lower leg compression is applied using a wide variety of bandages, hosiery and patient-adjustable devices (compression wraps); each of these interventions seeks to apply constant, sustained compression of the leg. Partsch et al (2008) reported a classification system for describing sustained compression devices based on four properties:

- The amount of compression applied to the leg
- The number of layers of compression material applied to the leg
- The number of separate components of the compression system; for example, a 4-layer bandage would have four components
- The elasticity of the compression material.

Franks et al (2016) highlighted six perceived benefits of applying external sustained compression:

1. Improve venous haemodynamics

Lattimer and Mendoza (2019) described non-invasive tests to identify impaired venous return using air displacement plethysmography. This device calculates changes in calf volume during specific challenges to veins (for example, moving the leg from elevated to dependent) to record the venous filling index (VFI), a measure of the speed of filling veins. Another indicator of venous function is the venous drainage index (VDI), which measures how quickly the calf volume decreases as the leg is elevated, an index of venous obstruction. In non-impaired venous circulation, the VFI should be <2mL/s, with a VDI of <8mL/s indicative of venous occlusion. Lattimer et al (2016) used VFI and VDI indices to compare the effect of Class I (18–21mmHg) and Class II (23–32mmHg) knee-length hosiery among healthy volunteers, patients with varicose veins, post-thrombotic syndrome or lymphoedema. Patients with varicose veins showed VFI rates approaching normality with compression; however, changes in VDI were not associated with increasing compression, potentially due to the rapid fall in venous flow upon leg elevation, which occurred too quickly to be influenced by the low levels of compression applied by the hosiery.

2. Control oedema

Lee et al (2016) noted that oedema reduction by compression 'is clinically so evident that only relatively few studies have been interested in investigating a dose-response relationship' measuring levels of compression and leg volume reduction, while Rabe et al (2018) commented that all levels of compression improved lower leg oedema in venous disease. Partsch and Mortimer (2015) noted that 'the fact that compression reduces oedema is so well accepted means that up to now proof by randomised controlled trial (RCT) has not been considered necessary'.

3. Reduce inflammatory mediators

Early stages of VLU, DFU and PU development highlight the importance of local tissue inflammation (Rosyid, 2017; Gefen, 2018; Pan et al, 2019). Beidler et al (2009) reported that pro-inflammatory cytokine levels in peri-VLU tissue fell and anti-inflammatory cytokine IL-1 Ra was elevated following leg compression. In a separate study, Beidler et al (2008) reported that matrix metalloproteinase (MMP) levels were diminished following leg compression; MMPs play a key role in wound healing through the control of extracellular matrix degradation and disposition (Caley et al, 2015).

Regulation of cytokine production by compression is mediated through direct transmission of the compression forces to cells. This occurs through proteins called integrins that help cells adhere to the extracellular matrix; part of the integrin lies within the cell itself and so forms a 'bridge' between the extracellular matrix and the cytoskeleton of skin cells, allowing transmission of mechanical loads to modify cell activity (Ingber, 2003).

4. Improve microcirculation

While compression was shown above to improve venous haemodynamics, flow in arterioles, capillaries and venules (the microcirculation) is also enhanced by external compression of the leg. Neuschwander et al (2012) reported that 40mmHg external compression during simulated venous hypertension in healthy volunteers (65mmHg applied to the mid-thigh using an inflatable tourniquet) doubled skin microvascular flow with this increase, most likely due to local autoregulation increasing microvascular vessel diameter during external compression.

5. Improve arterial in-flow

Mosti et al (2012) reported the effect of three different compression levels (20–30mmHg, 31–40mmHg and 41–50mmHg) on arterial perfusion and venous return among 25 patients with mixed-aetiology leg ulcers. Applying compression increased arterial perfusion until the compression exerted exceeded 40mmHg, with no significant decrease in toe pressure or tissue oxygenation. In this study, venous return was increased, returning within a normal range when 31–40mmHg compression was applied. Blood flow was elevated during sustained compression, which appears surprising but probably reflects arteriolar vasodilation as one biological response to the mechanical load applied to the leg.

6. Improve lymphatic drainage

Keast et al (2019) reported Canadian data within the Lymphedema Impact and Prevalence International Study (LIMPRINT). 68 people with lymphoedema participated in the study. 76.5% had used compression garments, while 85.3% had used multilayer bandaging to manage their lymphoedema. Compression was also seen as an important element of lymphoedema management within clinical guidelines (Lee et al, 2013). The wide acceptance of compression within the maintenance of lymphoedema may account for the limited clinical data available. Lamprou et al (2011) reported a small RCT where 15 patients with moderate to severe unilateral leg lymphoedema were randomised to receive a two-component compression system or inelastic multicomponent compression bandages. Both compression systems achieved similar median leg volume reductions after 24 hours of treatment, with the compression applied by both systems falling after 2 hours wear time.

WOUND HEALING UNDER SUSTAINED COMPRESSION

O'Meara et al (2012) and Mauck et al (2014) have reported systematic reviews of the effect of sustained compression upon the healing of leg wounds of venous origin. Mauck et al (2014) reported three main comparisons:

1. Wound healing using hosiery or bandages
2. Wound healing with 4 component bandage systems or bandages with fewer components
3. Wound healing with elastic or inelastic bandages systems.

There were no differences between the number of wounds that healed, the time to healing or rate of wound recurrence where bandages or hosiery were used to compress venous leg wounds. The number of components in bandage systems did not appear to improve wound healing, while the selection of elastic or inelastic compression showed similar outcomes with regard to wound healing, time to healing or rate of recurrence. O'Meara et al (2012) included additional clinical outcomes of the use of sustained compression, which were summarised by Partsch and Mortimer (2015); see Box 2.

The findings of the two systematic reviews were inconsistent at times - for example, the number of components within bandage systems did not appear to enhance wound outcomes (Mauck et al, 2014), while multicomponent systems were considered to be more effective than single components (O'Meara et al, 2012). This highlights challenges in the interpretation of

Box 2. Additional clinical outcomes of the use of sustained compression (Partsch and Mortimer, 2015)

1. Applying compression results in increased wound healing
2. Multicomponent compression is more effective than single-component bandages
3. Multicomponent systems that contain an elastic component are more effective than wholly inelastic systems
4. Two component systems are as effective as four component bandages
5. Wound healing is increased where four component bandages are used compared with inelastic bandages
6. Wound healing is higher where high compression stockings are used rather than inelastic bandages
7. There is insufficient data to identify the relative effectiveness of high compression

the available studies of the effect of sustained compression on venous leg wound healing. The focus upon leg wounds of venous origin often excludes patients with mixed venous and arterial disease, reducing the generalisability of the study results to real-world patient populations. The choice of the products compared within studies may hamper interpretation of data if a 'good' stocking is compared with 'poor' bandage systems (Amsler et al, 2009; Ashby et al, 2014). Most importantly, studies have not controlled the experience and expertise of clinicians to apply bandages consistently, nor has the dose of compression been quantified and standardised across patients within studies (Partsch and Mortimer, 2015). These final points (lack of standard application of compression and uncertainty over the compression applied to legs) restrict the ability to make strong recommendations regarding the effect of sustained compression on venous leg wound healing. Perhaps the most certain finding is that applying compression is more effective than not applying leg compression.

CONCORDANCE WITH SUSTAINED COMPRESSION

Guest et al (2018) reviewed the care delivered to a cohort of 505 UK patients with venous leg wounds. Prescription of compression systems was relatively common across the cohort, with only 25% not documented to have received a compression device falling over a course of 12 months of treatment, and only 14% not documented to have been allocated compression. However, prescription of compression does not necessarily mean concordance to wearing the compression device.

Moffatt et al (2009) reviewed studies that reported non-concordance with wearing compression devices either in RCTs or other studies. Within the RCTs, between 2% and 42% of patients did not wear compression devices as indicated, while 9.7% to 80% of patients in other studies of concordance failed to wear compression devices as indicated by clinicians. Moffatt et al (2009) identified several reasons why patients were non-concordant with leg compression: lack of education over the importance of wearing compression and physical factors such as pain, exudate leakage, skin irritation, discomfort and the physical challenges of donning and removing hosiery.

Heinen et al (2007) reported that 36% of 141 patients reported problems with their leg compression, including the challenge of finding footwear to fit over compression. Leg compression can be bulky, cosmetically unattractive and make the leg hot (Heinen et al, 2007; Moffatt et al, 2009). The common non-concordance with sustained compression can lead to negative clinical outcomes. For example, wound healing may reduce by 50%, with the median time to healing doubled where patients were non-concordant with sustained compression (Moffatt et al, 2009). The same review reported a 2 to 20 times greater probability of wound recurrence following healing where sustained compression was not worn.

CONTRAINDICATIONS FOR SUSTAINED LEG COMPRESSION

The contraindications for sustained leg compression have been evolving over the past few years. Dissemond et al (2016) reported a small number of absolute and relative contraindications for the use of sustained leg compression (Table 1).

However, an international consensus group recently reviewed and amended these contraindications (Rabe et al, 2020) with the most recent limitations on sustained compression being:

- In patients with severe peripheral arterial disease (PAD) with any of the following: ankle-brachial pressure index (ABPI) <0.6; ankle pressure <60mmHg; toe pressure <30mmHg; transcutaneous oxygen pressure <20mmHg
- Suspected compression of an existing epifascial arterial bypass
- Severe cardiac insufficiency (New York Heart Association [NYHA] functional classification level IV)
- Routine application of compression in patients with NYHA level III limitations (marked limitation of physical activity) without strict indication, and clinical and haemodynamic monitoring
- Confirmed allergy to compression material
- Severe diabetic neuropathy with sensory loss or microangiopathy with the risk of skin necrosis (this last contraindication may not apply to inelastic compression that exerts low sustained pressure).

The evolution of contraindications to sustained compression with some removals of restrictions on the use of compression, along with new limitations on the use of leg compression, highlight on-going rapid advances in the understanding of the effect of compression on both the legs and the general circulatory system.

ALTERNATIVES TO SUSTAINED COMPRESSION: IPC

The discussion above focused upon the effect of sustained, and ideally constant, compression of the leg over time. Compression of the leg can also be undertaken using systems intended

Table 1. Contraindications for the use of sustained leg compression

Absolute contraindications	■ Advanced PAD (critical ischaemia) ■ Decompensated heart failure: where the heart's structure or function prevents ejection or accumulation of blood within normal pressure levels ■ Septic phlebitis: blood clot within the vessel associated with bacterial or fungal infection ■ Phlegmasia cerulea dolens: uncommon severe form of deep vein thrombosis arising from extensive blood clots in the major and collateral veins of the leg.
Relative contraindications	■ Mild to moderate PAD ■ Advanced peripheral polyneuropathy ■ Chronic compensated heart failure ■ Intolerance or allergy to the compression material ■ Treatment-related pain ■ Florid infectious diseases (e.g. initial phase or erysipelas/cellulitis).

to apply mechanical force to the leg for short, controlled and repeatable time intervals. Originally, short periods of compression were alternated with the application of suction upon the leg; for example, Herrmann and Reid (1934) applied 20–40mmHg of compression to the entire leg for 5 seconds, then 80mmHg suction for 10 seconds, with this cycle repeated, initially for 30 minutes but subsequently increased to 1 to 2 hours. 75 patients with severe arteriosclerosis were treated using the combined suction/compression device, with 33 (44%) completely relieved of their major symptoms, while only 8 required amputation. Contemporary with Herrmann and Reid, Landis and Gibbon (1933) applied higher levels of compression and suction (80–100mmHg compression for 5 seconds, followed by 120mmHg suction for 25 seconds) to improve blood flow to the foot, measured using changes in skin temperature. Only 5 patients received Landis and Gibbon's suction and compression regimen, with all showing increased blood flow to the foot. The use of combined suction and compression, although successful, did not become commonplace due to cost, their physical size and the requirement to bring patients to hospital for treatment (Morris, 2008). Combined suction/compression was replaced by applying compression alone following growing knowledge and awareness of reactive hyperaemia, the increased arterial flow that follows ischaemia.

The application of short cycles of leg compression and relaxation has become known as IPC and is achieved using a wide range of inflatable cuffs or sleeves placed around specific sections of the leg, ranging from foot, calf or thigh compression alone or combinations of anatomical sites, eventually leading to compression of the entire leg. The inflatable cuffs can be sequenced to inflate and deflate to create a 'wave' or peristaltic effect, encouraging flow from the lower leg to the trunk, which is described as sequential intermittent compression. This document excludes discussion of the use of upper limb IPC to manage localised oedema. Partsch (2008) recommended IPC use primarily for immobile patients without active venous calf muscle pumps. While immobility may indicate use of IPC, sports science has added IPC to active individuals with functional calf muscle pumps, with enhanced vascular conductance during exercise and elevated arterial blood flow and tissue oxygenation during recovery (Zuj et al, 2019). This suggests that IPC may confer benefits even among individuals with functional calf muscle pumps.

WHERE AND WHY IS IPC USED?

A key indication for the use of IPC lies in the prevention of deep vein thrombosis (DVT) leading to venous thromboembolism (VTE) and/or pulmonary embolism (Chen et al, 2001). Multiple systematic reviews have reported the use of IPC to prevent VTE and DVT in a wide range of patient groups (Box 3).

Box 3. Patient groups where IPC has been used to prevent VTE and DVT

- Medical or surgical intensive care units (Haykal et al, 2020)
- Prolonged lithotomy position surgery (Gelder et al, 2018)
- Total knee and total hip arthroplasty (Zhao et al, 2014; Pierce et al, 2015)
- Hospital patients receiving pharmacologic prophylaxis for VTE (Fan et al, 2020)
- Neurosurgical patients (Pranata et al, 2020)
- General surgical patients (Urbankova et al, 2005; Morris and Woodcock, 2010)
- Stroke patients (Zhang et al, 2018)
- Orthopaedic and neurosurgical patients post-surgery (O'Connell et al, 2016)
- High-risk surgical patients (Pavon et al, 2016).

Overall, the conclusions of the systematic review trended towards support for IPC use, usually combined with chemoprophylaxis, as a means of reducing the risk of DVT and VTE. An early systematic review (Urbankova et al, 2005) reported significant benefits in terms of a 60% reduction in the incidence of DVT where IPC was used, compared with no intervention. Fan et al (2020) reported IPC reduced the risk of DVT and pulmonary embolism by 54% and 43% respectively among surgical patients who also received chemoprophylaxis, with strangely no apparent benefit of IPC over chemoprophylaxis in medical patients. A recent RCT of IPC and low molecular weight (LMW) heparin, compared with LMW heparin alone, appeared to show no incremental value of IPC in preventing new DVT, VTE or death (Arabi et al, 2019). The conclusion that IPC did not provide incremental benefits to chemoprophylaxis using LMW heparin prompted several editorials that questioned the use of IPC in thromboprophylaxis (Laupland et al, 2019). The recent systematic review by Fan et al (2020) that showed no clear benefit of IPC over chemoprophylaxis in medical patients may help resolve the apparent failure of IPC to have an incremental effect over LMW heparin, given that 77.9% of the patients who received pneumatic compression in Arabi et al (2019) were medical, rather than surgical admissions to ICU. Why IPC in medical patients may not reduce DVT or VTE over chemoprophylaxis remains unclear.

HOW DOES IPC PREVENT DVT AND VTE?

Chen et al (2001) described potential mechanisms through which the application of short duration, high-magnitude compression upon the limb may increase fibrinolysis, promote platelet aggregation and dilate blood vessels, thus reducing thrombus formation and blockage of vessels. The IPC rapidly compresses veins, resulting in a pulsatile flow of blood along the vessel, with both the increased blood volume and flow velocity applying forces upon the vascular endothelial cells. The increased blood volume will compress the endothelial cells, thereby changing their shape (deformation), while the increased flow velocity will apply forces parallel to the vascular endothelial cells (lateral shear stress). Both the tissue deformation and the shear stress applied by the increase in blood flow velocity may stimulate biochemical mechanisms, potentially involving the generation of tissue plasminogen activators from vascular endothelial cells, which activate plasminogen to become plasmin; the plasmin is a protease that degrades fibrin, so reducing thrombus formation (Chen et al, 2001). Morris et al (2006) reported elevated plasminogen activator activity following IPC therapy, along with elevated global fibrinolysis, but this rise was only observed using an IPC device that inflated cuffs to 40mmHg in 2 seconds (gentle IPC), compared with rapid higher cuff inflation (0.3 seconds, rapid IPC). While this model has attraction linking mechanical forces to biochemical changes, Swanson (2020) followed 50 consecutive plastic surgery outpatients, with 25 randomised to wear calf-length IPC during surgery and showed no significant changes in tissue plasminogen activator levels, both from pre-operative level or between patients who did or did not wear IPC during surgery.

Alternatively, Credeur et al (2019) reported increased shear within the posterior-tibial artery of people with spinal cord injury, which was associated with elevated flow-mediated dilation, a gold-standard measure of endothelial function. Martin et al (2015a) also noted IPC applied for 1 hour improved flow-mediated dilation systemically. Further evidence is required to ascertain whether there are any effects of IPC upon fibrinolysis. The interaction between mechanical forces and biochemical changes in cells and tissues is termed mechanobiology and brings together the disciplines of physics, biomechanics and biology (Lim et al, 2010), with the interactions between skin mechanobiology and wound healing explored by Kwon et al (2018). However, elucidating *in vivo* effects of IPC on blood vessel mechanobiology remains uncertain.

Morris (2020) extended the debate around the quality of studies that have investigated IPC within DVT prophylaxis. Several restrictions hamper the interpretation (and even conduct) of clinical studies that explore whether IPC affects DVT prevention:

- What is the control intervention? Should this be non-active (sham) IPC or another form of compression system?

- When comparing two forms of compression, how to interpret low DVT incidence within intervention groups? Are both treatments effective, or was the risk of DVT so low in the study population that neither had an effect?
- Interpretation of IPC used alongside concomitant therapies? If both are effective, then large sample sizes may be required to show incremental differences
- Diagnosis of DVT has varied over time
- Variability in the application of devices between study centres
- Different measurement protocols for haemodynamic parameters.

One further fundamental challenge regarding the evaluation of IPC devices lies in their ability to transfer the inflated pressure of the cuff to the skin. Lurie et al (2008) reported substantial variation from the cuff inflation pressure and the interface pressure actually applied to the calf. Two IPC devices with maximum inflation pressures of 52mmHg and 80mmHg applied 47mmHg and 29mmHg mean peak interface pressure with marked spatial heterogeneity in the distribution of pressure around the calf. It would appear that future studies should consider measuring the dose of IPC actually transmitted to the lower limb.

Interpretation of the effects of IPC have been severely hampered by the level of technical description around the myriad forms of IPC devices reported in studies. The remainder of this document attempts to illustrate the poor description of IPC systems by highlighting the level of technical description provided in selected studies, with the most commonly described parameter being the maximum inflation pressure within cuffs. Without a minimum data set that describes the inflation and deflation of IPC devices, interpretation of the contribution of IPC to tissue biology and wound healing will remain compromised.
A minimum data set (MDS) reporting IPC performance might include the following;

- Number of inflatable cells
- Location of garment upon the leg (e.g. whole leg, thigh only, calf only)
- Rate of pressure increase and rate of cuff deflation
- Maximum cuff inflation pressure
- Visual representation of the inflation times and sequence of cuff inflation from distal to proximal cuff
- Cycle time (number of cycles of cell inflation and deflation per minute)
- IPC duration – time (in minutes) when IPC is active and time subsequent when all cuffs inactive
- Dose, measure of the interface pressure applied to the skin by the inflated cuffs.

Without an MDS, comparison of the mechanical effects of different IPC systems will be problematic.

IPC AND LYMPHOEDEMA IN THE LOWER LIMB

Management of lymphoedema in the lower leg using IPC has been rarely studied (Franks and Moffatt, 2015). Zaleska et al (2015) applied sequential IPC to the whole leg of 18 patients with stage II to IV lymphoedema (stage II oedema limited to foot and lower calf; stage IV whole limb is oedematous) with a cuff inflation pressure of 120mmHg, while the total inflation time of the garment was 400 seconds. IPC was applied daily for 45 minutes for 24 to 36 months. The fluid that accumulated in the interstitial spaces due to obstructed lymph flow formed new tissue channels in subcutaneous tissue, and along the fascia of muscles. These channels increased in number during long-term IPC use, while changes in limb circumference correlated with the density of tissue channels in the thigh. Taradaj et al (2015) also reported limb oedema reductions of 38% with IPC that applied 120mmHg to the leg for a total inflation time of 36 seconds, while lower inflation pressures (60mmHg) only reduced limb oedema by 13% – similar to the reduction achieved using manual lymphatic drainage and sustained compression (12%). These studies point to high inflation pressures and prolonged inflation times perhaps being required for IPC to successfully manage lymphoedema. Reviewing literature published between 2010 and April 2017, Tran and Argáez (2017) identified six publications that described the impact of IPC on the management of primary and secondary lymphoedema. The available data did not suggest that adding IPC to routine management of lymphoedema conferred incremental benefits to patients with lymphoedema, although Tran and Argáez did concur that higher pressure IPC may be effective if supported in well-designed studies, with standard treatment protocols focused upon the latest iterations of IPC devices.

Contrary to these findings, Desai and Shao (2020) reported successful use of IPC among 128 patients with secondary lymphoedema followed prospectively over 3 years. In this study, two sequential IPC devices were used applying 40–50mmHg, with individual cuff inflation times of either 6.5 or 18 seconds. In this uncontrolled study, there was a 28.1% reduction in limb volume after 1 year of treatment and a 31.8% improvement in patient self-reported quality of life, with improved mobility and ability to perform activities of daily living. The two IPC devices performed differently; the IPC with shorter cell inflation times reduced limb volume after 1 year by 31.2%, while the longer cell inflation time IPC reduced limb volume by a smaller amount, 21.8% after 1 year of treatment.

The discrepancy between the findings of studies in 2015 and 2020 may result from advances in either IPC design, limb volume measurement or the severity of the lymphoedema, echoing Morris (2020) comments upon the challenges inherent in contrasting studies of the effects of mechanical compression of the leg.

IPC AND ARTERIAL AND VENOUS BLOOD FLOW

Multiple authors have reported increases in venous blood flow volume and velocity upon the application of IPC to the foot, calf or thigh individually or collectively, with summaries of the available evidence reported by Chen et al (2001), Morris and Woodcock (2004) and Helmi et al (2014), among others. During compression, the IPC device will compress veins, prompting a surge of blood with increased volume and velocity proximal to the compressed vein. Increasing levels of external compression tends to increase the velocity of flow within veins (Labropoulos et al, 2000; Morris and Woodcock, 2004), although the increases in blood velocity from external IPC will be heterogenous, both within and between patients, due to body position, breathing and natural variations within the blood flow to the leg. It is unlikely that IPC devices will completely compress arteries within the lower leg, although reduced arterial flow has been associated with inflation of IPC devices, with a consequent reactive hyperaemia upon deflation (Morris et al, 2020). The initial deficit in arterial blood supply and the consequent hyperaemic response may produce an overall percentage increase in arterial blood flow velocity (Morris and Woodcock, 2002).

Chen et al (2001) noted one potential mechanism for vein compression to increase arterial flow as IPC improved vein emptying and so lowered venous pressure. There was an increased pressure gradient between the arteries and veins, which increased lower limb arterial blood. Further study is required to fully elucidate the mechanisms through which compression of veins results in enhanced arterial flow.

USING IPC IN ARTERIAL DISEASE?

Given that the use of IPC may enhance arterial supply to the lower leg, can IPC provide measurable benefits to patients with lower limb arterial disease? Moran et al (2015) reviewed evidence for IPC use among patients with critical limb ischaemia (CLI) who were unsuitable for revascularisation. Although the available studies had a high risk of bias, IPC was probably associated with improved limb salvage, better wound healing and reduced pain, although higher-quality studies were required to support these findings. Broadly similar findings were reported by Zaki et al (2016) within a retrospective review of 153 patients with CLI who used IPC, and 34 who had no access to the IPC device for economic reasons. Within the IPC group, toe pressures increased from 61.4mmHg pre-IPC to 65.0mmHg post-IPC use. Rest pain diminished in 82% of the IPC-treated group but only in 8% of those not receiving IPC treatment. 35 patients required major (*n*=20) or minor amputations (*n*=15), with no clear differences between amputations among those who used or did not use IPC.

Further support for use of IPC among patients with CLI was provided by Alvarez et al (2015), who randomly allocated inoperable patients with CLI or peripheral vascular disease (PVD) to receive IPC (120mmHg, 3 cycles per minute, 4 seconds inflation, 16 seconds deflation) twice daily, or exercise consisting of 2 periods of 20 minutes walking each day, with both regimens followed for 16 weeks. The primary outcome of the study was increased peak walking time (PWT), defined as the maximum time that claudication pain could be tolerated. IPC increased PWT significantly over exercise at 16 weeks of treatment, with concurrent reductions in leg wound area, reduced leg pain and improved self-reported quality of life.

Zaleska et al (2019) also reported increased PWT and higher toe pressures among a cohort of 18 inoperable patients with PAD treated using IPC (120mmHg inflation; slow inflation for 5–6 seconds then 16 seconds deflation; daily treatment 45–60 minutes for 2 years). In this study, the main mode of action was proposed to be permanent capillary dilation, following repeated venous obstruction generated by the IPC device.

IPC AND REDUCTION OF OEDEMA

IPC has been shown to reduce lower limb oedema in multiple studies. For example, Tessari et al (2018) reported changes in subcutaneous skin thickness, leg circumference and volume among a small RCT, where 29 low-mobility patients with leg oedema were treated with IPC (50mmHg cuff inflation treatment twice daily for 50 minutes per session), while 21 did not receive IPC. All outcomes were assessed after 30 days of treatment and the IPC-treated group had significantly reduced leg oedema, better self-reported quality of life and improved ankle mobility. The study also measured a range of cytokines and chemokines postulated to affect either or both inflammation and angiogenesis. Small differences in cytokine and chemokine levels were seen between the IPC and control patients; however, these did not achieve statistical significance. IPC has also been shown to reduce lower limb oedema among patients following arterial revascularisation (Pawlaczyk et al, 2015).

OTHER REPORTED BENEFITS OF IPC

Several reports have claimed additional benefits from the use of IPC including:

- Improved achilles tendon rupture healing (Alim et al, 2018)
- Reduction of infection after ankle surgery (Winge et al, 2018). In this study, IPC was used along with sustained compression from bandages or stockings, while compression appeared to reduce necrosis at the site of surgery. The small number of subjects who developed surgical site infections (SSIs) (4/153; 2.6%) precluded any conclusion regarding the use of compression preventing SSIs
- Enhanced blood flow through lower leg bone (Morris et al, 2005)
- Reduced time to surgery following bone fracture (Dodds et al, 2014) with earlier discharge from hospital and reduced complications post-surgery. Other authors have found no benefit in using IPC to improve time to surgery (Arndt et al, 2017) or functional performance post-surgery for distal radial fractures (Alkner et al, 2018)
- Improved exercise performance through

increased limb blood flow (Zuj et al, 2018). Recovery after strenuous exercise has also been reported to be altered using IPC but with conflicting results. Hoffman et al (2016) reported immediate muscle fatigue scores post a 161 km ultramarathon, with no sustained benefits evident on the first day post the ultramarathon. Blood lactate clearance was elevated using IPC compared with sham IPC (Martin et al, 2015b) and this was proposed as one approach to improving recovery time after exercise. No improvement in recovery of muscle function or athlete perception of muscle soreness was reported by Northey et al (2016) following 45 minutes IPC (80mmHg inflation; deflation time 15 seconds). Draper et al (2020) reported no effect of 1-hour IPC in reducing delayed onset muscle soreness among athletes who completed two 20-mile runs (inflation pressure 90 or 100mmHg, duration of compression 30 seconds)

- Gene regulation in skeletal muscle (Martin et al, 2016) was altered by IPC (1-hour treatment for seven days with three modalities); sham IPC, 30–40mmHg, 70–80mmHg; 3-minute cycle time with 30 seconds cuff inflation for each of five cuffs arranged foot to hip, followed by 30 seconds deflation of all cuffs. Increasing cuff pressure altered skeletal muscle gene expression among 18 male subjects (six subjects per IPC mode). 1 hour after low compression IPC genes affecting cell morphology and cellular movement were altered, and at 24 hours after the last IPC treatment, genes affecting cellular development, cell growth and proliferation, free radical scavenging, molecular transport and cell death and survival were altered by low-pressure IPC. High-pressure IPC affected genes involved in cell movement, cell to cell signaling, cell assembly and organisation, cell function and maintenance and molecular transport. No gene expression was altered at 24 hours post the last treatment with high-pressure IPC. The data indicates that different levels of IPC alter different functional sets of genes in humans; the biological significance of these findings requires further study
- IPC may reduce intradialytic hypotension among patients with end-stage renal disease while improving the comfort of haemodialysis (Torres et al, 2019a). Despite this, the studies included in this systematic review were consistently rated at a high risk of bias. IPC has also been shown to reduce hypotension following spinal anaesthesia during cesarean sections (Zadeh et al, 2017), while Tyagi et al (2019) reported that sustained compression and IPC resulted in statistically similar incidences of hypotension in a RCT with 90 participants (hypotension incidence sustained compression 60%; IPC 83%, no intervention incidence 90%), with reduced use of vasopressors in the sustained compression group.

CONCORDANCE WITH IPC THERAPIES

Two systematic reviews have explored patient concordance with IPC. Craigie et al (2015) reviewed concordance to IPC post-surgery; seven studies reported concordance with IPC, with 75% concordant with IPC use during the first three days post-surgery (range 40% to 89%). Greenall and Davis (2020) identified eight factors that influenced concordance with IPC among inpatients post-surgery (Box 4).

No reviews were found that explored concordance with IPC in patients receiving IPC at home. Lurie and Schwartz (2017) compared concordance with an IPC device and high-compression hosiery among inpatients – patients previously known to have low concordance with compression. Among 66 limbs treated with IPC and 70 managed with sustained compression, the IPC device was easier to apply, easier to remove and comfortable to wear. However, concordance with both IPC and sustained compression was equivalent after 15 days wear (87% concordant with IPC, 85% concordant with sustained compression).

Box 4. Factors that influenced concordance with IPC among inpatients post-surgery (Greenall and Davis, 2020)

- Patient discomfort
- Knowledge and behaviour of healthcare professionals
- Mobilisation preventing IPC garment use
- Equipment supply and demand with no IPC device readily available
- The use of guidelines driving IPC use
- Intensive care patients having higher concordance with IPC
- Computer-assisted prescribing promoting use of IPC devices
- Patient knowledge of IPC.

Interestingly, Lurie and Schwartz compared patient self-reports of IPC use and the device's internal register of hours used, with self-reported use on average 2.5 hours higher than the internal record of use by the device.

Manfredini et al (2014) reported higher inpatient concordance with thigh-applied IPC compared with IPC applied at the foot and calf. The authors developed a simple questionnaire to record aspects of concordance with IPC (Table 2). A higher score marked greater concordance to the IPC device, while many of the questions posed by Manfredini et al (2014) cover pain and discomfort during treatment and may not reflect aspects of long-term concordance. The development and validation of an instrument that seeks to quantify concordance offers the potential for comparison between patient groups and between different IPC devices.

IS IPC COST-EFFECTIVE?

The cost-effectiveness of IPC has been reported in VTE prevention and in the management of lymphoedema. Secondary analysis of the Clots in Legs Or sTockings after Stroke (CLOTS) RCT that reported the benefits of IPC in reducing the risk of DVT among stroke patients, identified that IPC could be used if a decision-maker was willing to spend more than £610.88 for an additional day of quality-adjusted survival, concluding that IPC is an inexpensive but effective treatment that improves patient survival after stroke but may not reduce disability (CLOTS, 2014). A cost-effectiveness model related to outcomes after hip and knee

Table 2. A simple questionnaire to record aspects of concordance with IPC (Manfredini et al, 2014)

	Yes	No
Did the treatment get pain in your leg/foot?	0	1
Did you feel worsening of pain in your leg/foot during treatment?	0	1
Did you need to interrupt the treatment because of pain?	0	1
Did you feel relief from pain in your leg/foot during the treatment?	1	0
Did you experience pain in your leg/foot or worsening of pain after the treatment?	0	1
Did you feel discomfort/pain at the site of the sleeve?	0	1
Is the device easy to use?	1	0
Was the duration of treatment acceptable?	1	0
Would you be willing to continue the treatment at home for 7 days?	1	0
Would you recommend the use of the device to somebody with your problem?	1	0

arthroplasty compared the use of LMW heparin, other direct oral anticoagulents (DOAC) and IPC in preventing VTE (Torres et al, 2019b). The output from the models indicated that the lowest costs were associated with the use of IPC, while administration of a DOAC generated the highest quality-adjusted life years (QALYs). Combination of IPC and a DOAC was cost-effective over IPC alone in almost 90% of the model simulations, with IPC best used immediately post-surgery, and a DOAC provided when the risk of bleeding decreases and the patient becomes more mobile. The model developed by Torres et al (2019b) was based on data generated within Australian healthcare and was widened to include US patients by Saunders et al (2018), again showing that IPC alone or IPC with LMW heparin were cost-effective over LMW heparin alone, with the selection of intervention again determined by the risk of bleeding post-surgery.

IPC was also found to be a cost-effective treatment in the management of lymphoedema. The use of IPC upon reducing cellulitis, use of manual lymphatic drainage, outpatient costs and hospital admissions were explored within a retrospective administrative database by Karaca-Mandic et al (2015) following two patient cohorts (cancer-related lymphoedema and non-cancer-related lymphoedema). In both cohorts, use of IPC reduced the incidence of cellulitis, with less manual lymphatic drainage and lowered outpatient costs – the use of IPC was associated with a 36% to 37% reduction in overall cost. A second retrospective analysis of an administrative database also found use of IPC reduced the costs associated with lymphoedema management, following introduction of IPC (Brayton et al, 2014). Overall, 12 month costs of lymphoedema management were $62,190 but reduced by 18% in the year following introduction of IPC, with the key drivers of cost reduction being fewer visits to medical practices and reduced outpatient hospital costs. Cohen et al (2018) modelled the impact to a US payer organisation, with 10 million commercial members, if IPC was introduced to manage lymphoedema patients with either CVI or frequent infections. The model created three policy positions for the payer: exclusive access to IPC, expanded access to IPC or removal of a criterion where advanced IPC devices could only be used where simpler IPC devices had failed to improve a patient. Each scenario reduced 2-year costs for lymphoedema management. The greatest benefit was seen with expanded access to IPC, with a budget reduction of $613,179 among lymphoedema patients with frequent infections; the time for the payer to break even after payment of the IPC devices was 0.67 years in this scenario.

IPC AND WOUND HEALING

Nelson et al (2014) reported a Cochrane review of the impact of IPC upon VLU healing. Nine RCTs involving 489 patients were identified, with only one study assessed to be at low risk of bias. Five studies compared IPC and sustained compression with sustained compression alone, with contradictory results; two showed increased VLU healing where IPC was used, while three studies found no incremental benefit where IPC was used along with sustained compression. Two studies reported no difference in healing where IPC was used without additional compression, compared with sustained compression alone. One study showed IPC healed more VLU than not applying compression, while the final study included in Nelson et al (2014) noted that rapid application of IPC pressure healed more VLU than did IPC with a slower application of pressure.

Few reports of IPC and wound healing have been published since the 2014 updated systematic review. Arvesen et al (2017) reported a case series of 11 patients (seven VLU, three mixed aetiology wounds and one PU located at the ankle in an oedematous leg) treated as inpatients for 2 weeks with combined negative pressure wound therapy (NPWT) and IPC; then treated as outpatients for a further 2 weeks (IPC twice daily for 1 to 2 hours, inflation pressure 40–60mmHg). Many of the wounds were relatively young, with eight existing for less than six months. Over the combined treatments, all patients showed reduced wound size and depth.

Three showed moderate reduction in oedema, with one developing a wound infection. It is unclear whether the changes in the wounds treated were due to the actions of the NPWT or IPC alone or in combination.

Young et al (2017) reported a case report of an obese patient with bilateral lower leg wounds treated at home using IPC. 12 weeks after starting IPC use, the wounds had healed, pain reduced, body mass index fell from 62.83 to 47.65, with improved personal hygiene and greater social interactions. This case report noted multiple interventions for the patient, including nutritional support, provision of a bariatric bed allowing leg elevation, access to shower aids to help improve personal hygiene, manual lymphatic drainage and skin care. Based on the range of interventions implemented the rapid wound healing cannot be associated solely with the use of IPC.

Alvarez et al (2020) reported a RCT that compared the use of IPC and sustained compression against sustained compression alone in the treatment of chronic VLUs (over 1-year duration, >20cm^2 surface area and pain self-rated to be at least 6 on a scale from 0 to 10 and an ABPI >0.75). Subjects received a nonadherent wound dressing and four-component compression bandage. IPC was delivered for 1 hour, twice a day at a pressure of 40–50mmHg. All subjects were followed weekly for 96 weeks. IPC and compression were received by 25 patients and compression alone allocated to 27 patients. The rate of wound closure (mm/day) was greater in the IPC-treated patients (1.7 versus 0.8 in the control group). Both IPC and compression alone reduced ankle and calf circumference by week 20. Wound pain fell in the IPC-treated group during the first 3 weeks of treatment; after this time wound pain was similar in the two treatment groups. The median time to wound healing was 141 and 211 days for the IPC and compression and compression alone groups. This small RCT may be at risk of moderate to high bias; there is no information upon any loss-to-follow-up of patients during the study (with either 52 or 96 weeks reported as the length of follow-up), while there is no information upon allocation concealment or blinding of patients, personnel or outcome assessment. IPC may also assist VLU healing through improved lymph transport (Rasmussen et al, 2016), particularly during the early stages of venous ulcer formation given that long-duration VLUs were associated with few viable lymphatic vessels, and in these wounds, proximal movement of lymph and interstitial fluid was not seen during IPC therapy.

NEW INSIGHTS INTO IPC

The preceding discussion around the use of IPC has focused upon the benefits of IPC applied on the lower limb to the cells and tissues of that limb. Several authors have reported positive benefits of IPC being conferred to tissues far from the site of limb compression. Knight and Dawson (1976) reported that the use of IPC on the arms reduced DVT formation in the legs, while Amah et al (2016) noted how an IPC compression garment applied to the legs and abdomen of 24 healthy volunteers increased forearm blood flow.

The impact of lower limb IPC on upper limb arterial function was also reported by Rifkind et al (2014), where lower limb IPC reduced plasma nitrite and red blood cell nitric oxide, with the reduced circulatory levels of these vasculoprotective molecules perhaps related to their storage in hypoxic arm tissue to be later released to prevent occlusion-mediated constriction of the brachial artery. Within the lower limb, use of IPC at the calf increased microcirculatory blood flow in the thigh (Bahadori et al, 2017) by 117.3% over baseline; the generalisability of this study of 10 healthy volunteers to older patients with leg oedema may be challenging and the specific characteristics of the IPC device were not described. If thigh microcirculation is improved with IPC at the calf, is it feasible for IPC applied at the thigh to affect blood flow in the calf?

THE EFFECT OF THIGH COMPRESSION ON VENOUS HAEMODYNAMICS IN THE LOWER LEG?

Partsch et al (2002) investigated the effect of thigh compression on the diameter of the greater saphenous and femoral veins along with the VFI (see page 6 for a description of this test), among 12 hospital patients with a VLU. The two veins only began to narrow in diameter when the pressure applied to the thigh exceeded 40mmHg, while the VFI reduced (interpreted as reduced venous reflux) to around rates anticipated in individuals with no venous disease with a thigh pressure of 60mmHg. Partsch et al (2002) also measured the pressures applied to the thigh while the patients wore thigh-length compression hosiery or bandages, with the measured pressures being too low to alter vein narrowing and reduce VFI. IPC, which can safely apply short duration high pressure to the thigh, may be able to improve venous haemodynamics in the lower limb.

The potential benefits of thigh-only compression were explored by Manfredini et al (2014) where 20 ischaemic limbs of 12 supine patients with severe PAD (ABPI 0.5 +/- 0.2) were subjected to calf-level IPC or IPC applied through an exploratory thigh compression garment. The two IPC devices had differing operating parameters; both thigh and calf IPC applied a maximum of 120mmHg cuff inflation, with the thigh device set to apply the patient's systolic blood pressure minus 20mmHg. The cycle times of the two IPC differed; thigh compression for 20 seconds followed by no compression for 40 seconds, 1 cycle per minute; calf IPC applied 3 seconds calf compression followed by 17 seconds of no compression (3 cycles per minute), while the duration of treatment was 5 minutes active treatment and 5 minutes of no IPC at the thigh. This was repeated until the device had been active for 20 minutes and inactive for 15 minutes; however, the calf compression was applied for 2 consecutive hours. The three outcomes of this exploratory study were changes in oxygenated haemoglobin at the foot, blood velocity and flow in the popliteal artery and femoral vein, and patient concordance with IPC. Oxygenated haemoglobin, blood flow and velocity all increased with thigh IPC, whereas calf compression reduced levels of oxygenated haemoglobin and made no significant changes to blood velocity or flow. Nine of the 12 subjects completed the calf compression tests, whereas all tolerated thigh compression. Subject concordance and acceptance were higher for thigh IPC, which was rated to be significantly more acceptable with respect to symptom relief, lack of side effects, patient satisfaction, ease of device use and overall tolerance to the therapy.

The potential for thigh IPC to be successful in increasing venous return was explored by Lattimer et al (2015) who subjected the right leg of 19 healthy volunteers to thigh compression applied in 10mmHg increments, until the thigh was compressed by 80mmHg, at which point the compression was rapidly deflated. At each increment of 10mmHg, the venous volume of the lower leg increased, with the median change in volume at an 80mmHg inflation being 87mL. On release of compression, venous volume fell to -16mL below the original baseline, indicating enhanced venous emptying on release of thigh compression.

The effects of a prototype thigh IPC device upon arterial and venous blood flow in healthy volunteers and patients with a range of lower limb wounds was reported by Morris et al (2020). Twenty healthy volunteers (mean age 31 years; with 10 men and 10 women) received thigh compression from a three-chamber IPC device inflating the chambers to 60mmHg from the distal cuff to the proximal cuff, with venous reflux inhibited by the distal chamber inflating before the proximal deflated. The inflation pressure, cell inflation timing and rates of inflation and deflation were determined by O'Doherty (2008) within a PhD thesis, where various combinations of IPC parameters were compared within a single human volunteer.

Cuff inflation and deflation

One objective of Morris et al (2020) was to compare the performance of two variations of cuff inflation and deflation.

Sequence 1. The cuffs were inflated from distal to proximal for 10 seconds each, with a 5-second interval between inflation of adjacent cuffs.

Sequence 2. The distal cuff inflated for 15 seconds while the other two cuffs inflated for 10 seconds each, with a 5-second interval between inflation of the distal cuff and adjacent cuffs, with an 8-second interval between inflation of the central cuff and proximal cuffs, with the distal and proximal cuffs being both inflated for 3 seconds (Figure 1). The time to inflate and deflate the three cuffs was either 20 or 23 seconds.

Unfortunately, it was not possible to elucidate the effect of these subtle differences in inflation and deflation patterns and timing from the distal arterial blood flow recorded from the volunteers, who tended to respond to the overall effect of the device by reducing distal arterial flow during active compression, with a large reactive hyperaemia when the device was inactive. Venous return was enhanced with the slightly longer cycle time and different configuration of cuff inflation, where the proximal and distal cuffs were both closed for 3 seconds. Further volunteer and patient investigations were performed using the 23-second cycle time repeated for 2 minutes followed by a 2-minute inactivation of the device, with the 4-minute cycle of active/inactive IPC applied for 20 minutes (5 full cycles). Across the twenty volunteers, 20-minute thigh IPC slightly reduced arterial inflow by –1.2%, while venous velocity increased in all volunteers (mean increase 8.3cm/s). The prototype device was applied to the legs of 13 people with a variety

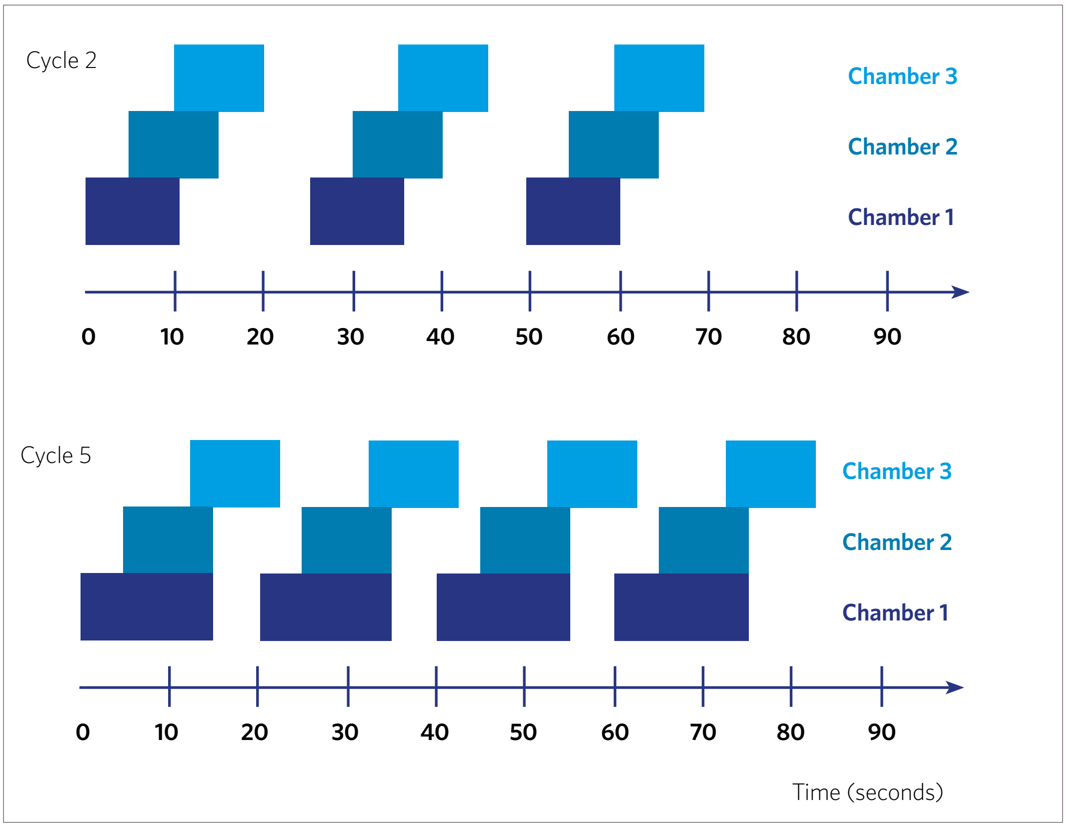

Figure 1.Cuff compression cycles (from Morris et al, 2020; reproduced with permission from International Wound Journal)

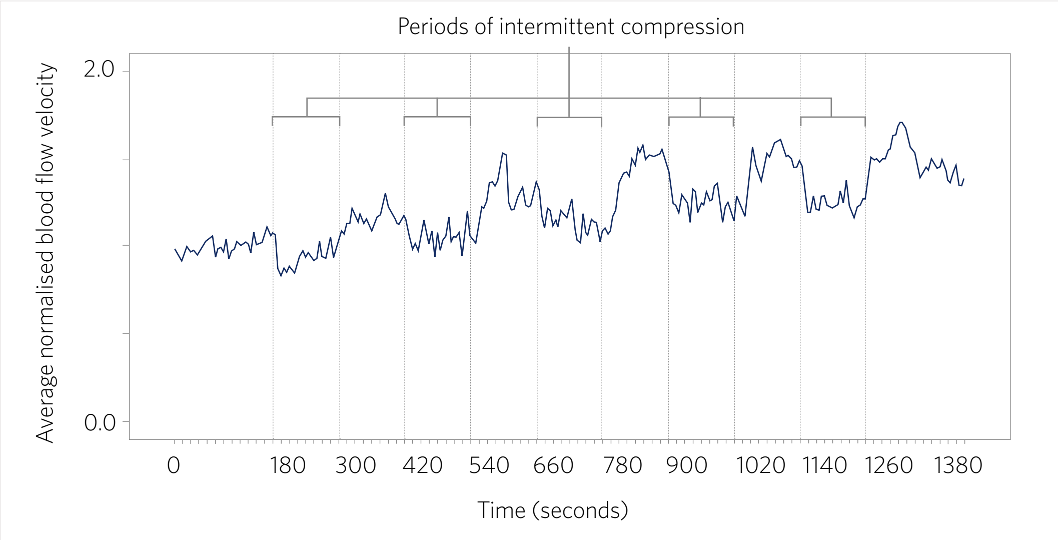

Figure 2. Normalised averaged distal arterial response for seven patients with leg ulcers to five 2-minute applications of Cycle 5 (from Morris et al, 2020; reproduced with permission from International Wound Journal)

of lower limb wounds (4 arterial ulcers, 3 VLUs, 2 DFUs, 2 mixed leg ulcers and 2 patients with systemic lupus erythematosus).

Arterial flow measurements were not performed in six patients due to severe calcification or distal vessel occlusion; where arterial flow was measured, thigh IPC increased arterial flow by 4.76%, with a large hyperaemic response seen following inactivation of the IPC, with a rising baseline over successive cycles of IPC activation (Figure 2); venous velocity increased by an average of 11.6cm/s, non-significantly higher than the increase in venous velocity seen among the healthy volunteers. Clinical experience of the thigh IPC device described by Morris et al (2020) is growing, with the device manufactured and marketed as WoundExpress™ (Huntleigh Healthcare, UK; Figure 3). Naik et al (2019) reported use of WoundExpress in the management of the VLU and mixed aetiology leg wounds experienced by 21 people attending an outpatient clinic. All patients were provided with WoundExpress, in addition to their usual sustained compression bandages and hosiery. The duration of WoundExpress use per day was set pragmatically at 2 hours, allowing time for benefits to accrue, without placing excessive restrictions on the patients' usual activities. The treated wounds were evenly distributed between being a VLU (*n*=11) or mixed aetiology (*n*=10), while the majority had been present for over 1 year (15/21; 71.4%) and on the basis of their long duration could be considered to be 'hard-to-heal'.

Figure 3. WoundExpress device

Ten patients (48%) had leg wounds over 10cm^2. All bar one patient showed progression towards healing over the 8 weeks of WoundExpress treatment, with self-reported pain falling in 15/18 (83.3%) who experienced wound pain. Two patients experienced complete wound healing while, after a wound infection, one patient showed an increased wound surface area. Patient satisfaction with WoundExpress was high after the 8 weeks of WoundExpress treatment; the device was reported to be comfortable or very comfortable to wear (17/18 patients), easy or very easy to apply (16/18) and remove (18/18 patients).

Use of WoundExpress was not considered to be less comfortable than the patients' prior experience of compression, and none were less satisfied with WoundExpress than with their prior compression device. A separate uncontrolled evaluation reported the outcomes of WoundExpress use among 27 patients with hard-to-heal VLUs or mixed aetiology leg wounds (mean wound duration approached 4 years) (Kettley and Turner-Dobbin, 2020). In this evaluation, patients received WoundExpress treatment for 16 weeks; 21/27 (77.8%) completed the 16 weeks of treatment, with 7 patients' wounds healed (33.3%).

All bar one showed progression towards healing, with wound pain reported to have reduced in 6/8 (80%) patients in the study centre where this outcome was measured. Both patients and clinicians reported that WoundExpress therapy was well tolerated. Naik et al (2020) reported that patients maintained the 2-hour WoundExpress treatment duration, with the mean wear time after 8 weeks treatment reported to be 127.35 minutes (95% confidence interval 121.83–132.87). WoundExpress, as with previous prototype thigh IPC devices, should be considered as an adjunct to sustained compression, until such time that evidence is available to compare whether the application of thigh IPC alone matches the effect of applying thigh IPC and sustained compression to the lower limb.

Where new innovations emerge in wound management, there may be a temptation to create labels to describe the new modality as an 'advanced wound therapy' or, in the case of adjunct therapies, as being a 'combination therapy'; ideally such temptation should be resisted in the case of WoundExpress, at least until robust clinical data has outlined the full potential for this therapy, both in management of existing lower limb wounds, and potentially in primary and secondary prevention of new limb wounds. Interestingly, no prior research was identified that explored the use of IPC in wound prevention.

Box 5. Benefits observed from thigh IPC

- The compact size of WoundExpress was found to be easy to apply and remove (Naik et al, 2019)
- Concordance with WoundExpress was high (Naik et al, 2019), which supports patients sharing responsibility with healthcare professionals in the management of their lower limb wounds
- Thigh IPC does not result in direct contact of the inflatable cuffs with the surface of the wound, so potentially reduces pain, folliculitis, inadvertent skin damage and contact dermatitis (Çarli et al, 2014; Marlborough et al, 2014; Oiso and Kawada, 2020), while also reducing the risk of direct deformation damage to the existing wound and surrounding soft tissue.

WoundExpress has already been shown to confer benefits in terms of enhanced arterial and venous blood flow in the lower limb (Morris et al, 2020). Reduced self-reported wound pain would also appear to be a benefit of thigh IPC. Other clinical benefits associated with traditional IPC (oedema reduction, improved lymphatic flow, use in arterial disease, reduced DVT and VTE among others) remain to be elucidated for thigh-administered IPC, but it may be reasonable to expect some or all of these benefits to be realised, given the clear effect of thigh IPC on arterial and venous flow in the lower limb. There may also be benefits from thigh IPC that may not be observed with traditional IPC devices (Box 5).

USING WOUNDEXPRESS IN CLINICAL PRACTICE: CONSENSUS RECOMMENDATIONS

There are a broad range of considerations that need to be addressed to gain maximum value from the use of WoundExpress (Box 6); most of these are not reported in the small but growing literature around thigh-administered IPC. See page 27 for a suggested pathway for use of WoundExpress in practice.

Box 6. Considerations before using WoundExpress

- Patient and environmental assessment before using WoundExpress?
- Which patients will gain the greatest benefit from WoundExpress?
- When should WoundExpress not be used?
- When to stop using WoundExpress?
- How to maximise concordance with WoundExpress through patient education?

WHAT TO DO BEFORE USING WOUNDEXPRESS?

As with any use of therapeutic interventions, there is a requirement to assess both the patient and their immediate environment before instigating a new intervention. For the patient and their environment, consider the following:

- Is their thigh too large for the inflatable cuffs of the WoundExpress?
- Could adipose tissue around the thigh reduce the effectiveness of WoundExpress?
- Have they sufficient manual dexterity to apply and remove WoundExpress?
- Have they capacity to self-manage WoundExpress?
- Are people around the patient to provide support?
- Do they smoke? Risk of fire may be present given air flow into WoundExpress cuffs, although this is likely to be minimal given relatively low air flows during inflation and deflation
- Could use of WoundExpress increase their risk of falling?
- Do they have a pet indoors? Risk of puncture of the inflatable cuffs and presence of animal hairs on fasteners
- Do they have a reliable electricity supply?

WHEN TO START USING WOUNDEXPRESS?

Not every patient with a lower limb wound will be required to use WoundExpress; many uncomplicated wounds will proceed to healing using sustained compression. In principle, many lower limb wounds may be amenable to thigh IPC using WoundExpress including, but not limited to, the following:

- VLUs
- Mixed aetiology leg wounds
- PAD
- Arterial leg wounds
- Lower limb PUs
- DFUs
- Lymphoedema
- Skin grafts
- Pyoderma gangrenosum
- Sickle cell disease
- Skin tears
- General improvement of lower limb skin appearance
- Any lower limb wound where oedema is present
- Connective tissue disorders
- Amputation wounds.

Use of WoundExpress in each of these indications should be associated with frequent assessment of the lower limb wound, skin appearance and condition, to enable therapy to be discontinued where poor or negative outcomes are identified.

Introduction of therapies such as thigh IPC should take place within existing care pathways to avoid confusion and potential errors associated with premature or delayed use of therapy. The current NHS England lower limb wound care strategy (NWCSP Lower Limb Recommendations, 2020) makes no reference to the use of IPC; with the 'best' potential point of thigh IPC introduction being at the proposed assessment of limb wound causation, no later than 14 days after first presentation. This would lead to all patients with lower limb wounds receiving mild to strong sustained compression for 2 weeks, before alternative therapies could be considered. There are several potential indicators that might support thigh IPC introduction at first presentation (see Box 7).

Box 7. Potential indicators that might support thigh IPC introduction at first presentation

- Unable to tolerate sustained compression
- Painful wound
- Poor prior response to sustained compression
- Prior successful IPC use
- Hard-to-heal wounds – fixed ankle, immobile patient, after stroke or presence of extensive venous disease.

Immediate use of thigh IPC may be facilitated by the intervention being so easy to operate, so that no barrier is imposed upon patients while they have to wait to be assessed by a specialist. Regardless of how easy thigh IPC use may be, the likelihood is that most patients with lower limb wounds will be managed in sustained compression, until assessment indicates that thigh IPC use may be beneficial.

WHEN SHOULD THIGH IPC NOT BE USED?

The contraindications for sustained compression reported by Rabe et al (2018) – see page 6 of this document – should also be considered for the use of thigh-administered IPC. Cases of less severe chronic heart failure may require considerable caution, given that IPC use raises right auricular pressure and mean pulmonary artery pressures in combination with reduced systemic vascular resistance to blood flow, due to vasodilation (Urbanek et al, 2020).

The 'red flags' noted in the National Wound Care Strategy Programme (2020) would also contraindicate IPC use in the presence of:

- Acute infection of leg or foot
- Symptoms of sepsis
- Acute or chronic limb-threatening ischaemia
- Suspected acute DVT
- Suspected skin cancer.

Kidney failure should also be considered when assessing patients for the use of IPC. Low inflation pressure IPC (40mmHg) increased urine production due to movement of interstitial fluid during bed rest among spinal cord injured patients and may cause nocturnal polyuria (Viaene et al, 2019). Increased frequency of urination during the first week of IPC treatment was also reported by Young et al (2017).

WHEN SHOULD WOUNDEXPRESS THERAPY BE STOPPED?

In an ideal world with no resource limitations, patients may continue to use WoundExpress beyond wound healing to help prevent recurrence of their wounds. In the absence of evidence that IPC does extend the period of time before a wound may reoccur, it would not be cost-effective to permit open-ended use of therapies such as WoundExpress, with potential points to cease treatment being:

- Recognition of wound healing
- Continued use for 2 to 4 weeks post healing to help prevent early recurrence
- Continued use while waiting for surgery
- Use for 2 to 4 weeks only to initiate healing, with a review of the rate of change in wound size after 4 weeks treatment.

These potential rules for stopping WoundExpress therapy are quite different in nature; in one model, the therapy is used for a relatively short time to initiate healing, while a second model considers use of the intervention to healing and indeed beyond the time of wound closure. The outcomes and costs of both regimens should be considered in a future study.

ENHANCING CONCORDANCE WITH WOUNDEXPRESS

The value of thigh-administered IPC therapy will only be realised where patients understand the potential benefits of the therapy and wear the device for appropriate durations of treatment. Many of the perceived benefits of compression and IPC are challenging for both patients and clinicians, being closely related to the physiology, mechanobiology and blood flow parameters of the circulatory system. Clear, unambiguous explanations of the effect of the inflating cuffs of WoundExpress are required to help patients understand what the therapy seeks to achieve. These can be based on diagrams and videos of the action of the device in moving blood from the lower limb to the trunk, with no return of blood from the device to the lower limb. This peristaltic effect of the blood moving along the veins while the cuffs compress (close) or deflate (open) the veins could be a powerful message explaining the purpose of the therapy. There are clear, positive benefits for

Figure 4. Patient using WoundExpress

patients who use their WoundExpress daily:

- Improvements in wound healing
- Easy to use
- Less wound pain
- Short treatment durations
- Treatment controlled by the patient
- Improved quality of life
- Empowers patient to rest during treatment and gives permission for patient to elevate legs (Figure 4).

Clearly these patient benefits require communication through a wide variety of formats, including video, leaflets, visual information on correct use of the therapy and diversity of languages among some of the tools that could be employed to help patients better understand how squeezing the thigh results in changes in blood supply to the calf and foot.

Patients may also require explanation regarding the best duration of WoundExpress treatment each day; 2 hours treatment per day appears to be a good pragmatic period to allow the intervention to have impact, while not limiting the patient's other daily activities. Herrmann and Reid (1934) initially limited combined IPC and suction to 30 minutes but concluded that 'there seems to be no limit to the length of time the treatment can be carried out without discomfort or untoward effects'. WoundExpress therapy duration may best be explained as causing no problems if patients continue to use the device for longer than 2 hours each day. One potential future development might consider providing individualised treatment durations optimal for each patient. Morris et al (2020) reported a progressively higher baseline arterial flow as thigh compression was applied using WoundExpress; the increased oxygenation of the lower limb due to the enhanced arterial flow will, over time, attenuate the reactive hyperaemic response to IPC (Messere et al, 2017) and the WoundExpress treatment time required to achieve increased tissue oxygenation and reduce the hyperaemic response may indicate the optimal treatment duration for each individual.

WHAT NEXT FOR WOUNDEXPRESS?

WoundExpress has been shown in initial studies to have effects on both arterial and venous blood flow in the lower limb, with positive clinical benefits including reductions in wound size and, importantly, in reducing wound pain. It represents a promising intervention to add to the tools available to apply compression to the leg and help counteract the effects of gravity on leg blood flow.

This is the start of the journey; the next steps lie in obtaining greater understanding of the range of effects WoundExpress may have that would contribute to improving the management of several wound types commonly found on the lower limb. While better understanding of the dose responses provided by the therapy are important physiological and product development issues, the experience of Morris et al (2020) should be borne in mind where subtle changes in the operation of the inflatable cells could not be shown in measured blood flow, with the body responding to the overall effect of compression and deflation rather than each individual compression and relaxation of cells. To achieve wider diffusion across health services, therapies such as WoundExpress will require a number of clinical trials to elucidate the incremental benefits of thigh-applied IPC over sustained compression and other forms of IPC. WoundExpress will also have to be compatible with service pathways, such as the new national strategy for lower leg wounds within NHS England, for the therapy to flourish. Exciting opportunities exist to explore whether WoundExpress has a role in primary or secondary prevention of lower limb wounds. All of these studies will depend upon the development of minimum data sets that allow capture and reporting of the technical operating characteristics of IPC devices, along with robust methods for characterising the impact of WoundExpress upon patient concordance and quality of life. WoundExpress is a therapy with considerable potential; the hard work to demonstrate its modes of action, clinical and cost-effectiveness and, crucially, patient experience begins now.

Pathway for use of WoundExpress in practice

Assess both the patient and their immediate environment before instigating a new intervention

When to use?

WoundExpress is indicated for use on hard-to-heal lower limb venous and mixed aetiology ulcers for only 2 hours per day as an adjunct to standard treatment.

Frequent assessment of the lower limb wound, skin appearance and condition should be carried out within existing care pathways to enable therapy to be discontinued where poor or negative outcomes are identified.

Tips for use

- Secure the garment for a snug fit
- Wear lightweight clothing
- Lie down or sit with the affected leg elevated
- Tubing should face down the leg and not be kinked or obstructed
- Remove all excess air from the tube on removal.

Potential indicators that might support thigh IPC introduction at first presentation

- Unable to tolerate sustained compression
- Painful wound
- Poor prior response to sustained compression
- Prior successful IPC use
- Hard-to-heal wounds – fixed ankle, immobile patient, after stroke or presence of extensive venous disease.

When not to use?

WoundExpress should not be used in the following circumstances:

- Severe congestive cardiac failure
- Acute infection of leg or foot
- Symptoms of sepsis
- Acute or chronic limb-threatening ischaemia
- Suspected acute DVT/skin cancer/kidney failure.

When to stop?

Treatment of WoundExpress may cease in the following circumstances:

- Recognition of wound healing
- Continued use for 2 to 4 weeks post healing to help prevent early recurrence
- Continued use while waiting for surgery
- Use for 2 to 4 weeks only to initiate healing with a review of the rate of change in wound size after 4 weeks of treatment.

If appropriate, patients may continue to use WoundExpress beyond wound healing to help prevent recurrence of their wounds.

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