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Management of Venous Leg Ulcers

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Abstract:

Venous leg ulcers account for approximately 70% of all leg ulcers. After a comprehensive patient and wound assessment, compression therapy remains the cornerstone of standard care. Adjuvant care with topical or systemic agents is used for wounds that do not heal within 4 weeks. Once healed, long-term compression therapy with stockings or surgical intervention will reduce the incidence of recurrence. This review article aims to outline optimal management for patients with venous leg ulcers.

Keywords: Venous Leg Ulcers, Ultrasound Therapy, PRP.

Introduction:

The management of chronic venous ulcer constitute one of major heath challenges aiming at healing, prevent recurrence and minimize social and economic effect. In western world approximately 1% of annual health care balance expended on venous ulcer care. The future world vision directed toward the prevention of venous ulcer more than their management , standing on goal of Pacific Vascular Symposium 2009 that talking on globally decrease the incidence of venous ulcer by 50 % in next 10 years **(1)**

The key for management of venous ulcer is reduce ambulatory venous hypertension (AVH) that lead to decrease of edema and inflammatory reaction in leg result in stimulate healing of ulcer and prevent recurrence if maintained optimum venous pressure. The correction of vein disorder that lead to venous hypertension is the important step beside ulcer care **(2)**

Compression therapy is the basis of VLU treatment. Generally, tension prescription depends on the disease severity and is in the range of 20–50 mmHg. A higher compression pressure (over 45 mmHg) resulted in a higher proportion of healed VLU during a period of 24 weeks**.(3)**

It was demonstrated that the effectiveness of compression therapy might affect the recurrence of VLU. an open, prospective, randomized, single-centre study that included 477 patients (240 men, 237 women; mean age 59 years). After the randomization of patients, they were allocated to wear elastic stockings with different pressure: 18–25, 25–35, and 35–50 mmHg. Within the period of 10 years, recurrence of VLU occurred in 96% of individuals allocated to wear stockings with 18–25 mmHg pressure, 66.9% of those wearing stockings with 25–35 mmHg pressure, and 24.5% treated with multilayer compression system exerting 35–50 mmHg). Thus, the force of the compression can not only affect the healing but also the recurrence of VLU. **(4)**

Compression therapy remains the primary non-operative treatment for chronic venous insufficiency despite progress in both ablative and reconstructive venous surgery.

$$\text{Compression} = \frac{\text{N (No. of Bandage Layer) x t (Bandage Tension)}}{\text{R (Radius of Leg)}}$$

All compression bandage systems must create a pressure gradient from ankle to knee. According to the law of laplace, which mathematically relates bandage tension compression pressure, the shape of leg will create this gradient. Hence compression will be found maximum at the gaiter area just proximal to ankle joint of 30 - 42mm Hg and as we go up the leg it decreases and at the knee it in 17- 20mm Hg

Recommended pressures for the treatment of venous disorder include; ankle pressure of 14-17mm/Hg in superficial or early varices, 18-24mm/Hg in varices of medium severity or with ulcer treatment and prevention of mild edema and 25-35mm/Hg in gross varices, post-thrombotic syndrome, gross edema, ulcer treatment and prevention .

First layer dressing: applied from foot to above knee to absorb the discharge from from ulcers and protect bony prominence Second layer - Banding with cotton bandage to keep the 1st layer in place Third layer - Crepe bandage which applies the compression pressure. Four layer - elastoblast to keep compression bandage in place. **(5)**

The 2LB system components were a padded inelastic bandage with short elongation and an elastic bandage with lengthy elongation. The system provides a visual indicator to facilitate the proper application and achieve the desired pressure. The system can be worn 24 hours a day for up to 7 days per the instructions for use **(6)**

In normal standing patient application an external pressure of 35-40 mmHg will narrow the vein but if pressure excessed 60 mmHg it will lead to occluding of vein, so optimum external graduated pressure between 35-40 mmHg will improve venous pumping function, microcirculation and in last study it lowering the level of inflammatory mediator that lead to tissue damage as tumor necrosis factor alpha and promote ulcer healing . **(7)**

Evidence for effectiveness of multi-layer bandaging comes three randomized controlled trials (RCT), all of which compared 4-layer bandaging with standard care that did not include any compression. The first trial found that significantly more VLUs treated with compression were healed at 12 months risk ratio [RR] 4.0, 95% confidence internal [CI] 1.35 to 11.82, p=0.01). As well as a four times greater likelihood of healing, VLUs treated with compression also healed much faster. The second RCT reported significantly faster healing associated with compression in a survival analysis (adjusted hazard ratio 1.65, 95% CI 1.15 to 2.35, $p<0.05$, median weeks to healing 20 versus 43, p=0.03). However, this trial found no significant difference in number of VLUs healed at 12 months. In the third trial, VLUs treated with 4-layer bandaging were 1.8 times (95% CI 1.2 to 2.9) more likely to be healed at 12 weeks, and healing was at a significantly faster rate (p=0.006). Combined with studies supporting the effectiveness of other compression systems, there is good evidence that applying compression therapy will promote VLU healing. **(8)**

multi-layer bandaging is shown to be as effective as compression stockings for promoting healing, with bandaging achieving results faster in some studies. Ulcers treated with 4-layer bandaging showed a mean decrease in wound area of 58.62%, which was significant compared to 20% reduction (p=0.03) for Unna's boot and 16.66% reduction (p=0.03) for SSBs.[3] In another trial, there was significant difference in VLUs that healed with 4-layer bandaging compared to compression stockings (86% vs 77%, p=0.24), although healing was faster with 4-layer bandaging (10 weeks vs 14 weeks, p=0.08). In another trial comparing 4-layer bandaging,2-layer bandaging with an elastic layer and 2-layer compression stockings, there was no significant difference in time to healing between the three groups (HR 0.99, 95% CI 0.79 to 1.25, p=0.96). Finally, 4-layer bandaging achieved similar results to pneumatic compression therapy when compared on number of ulcers healed after 12 weeks (31.6% pneumatic compression vs 42.3% 4-layer bandaging, p=0.30). **(8)**

Local wound management includes debridement, dressing techniques, and bacterial balance . The occurrence of necrotic tissue detains the healing process of wounds. Debridement as the elimination of necrotic tissue from the area of a wound can reduce the healing time period. There are diverse methods of debridement, such as mechanical or enzymatic removal . After debridement, other therapeutic methods can be applied, including skin transplants, in order to achieve wound closure . The purpose of dressings in the treatment of wounds Is to support healing processes and prevent wound infections. Dressings speed up fluid absorption, re-epithelialization, maintain moisture, and isolate thermal wounds. There are various types of dressings, such as

moist occlusive dressings, hydrogels, or semi-permeable films . Inflammation prolongs the healing process of wounds, which is why VLUs with clinical signs of infection should be treated with antibiotics according to the culture results. Depending on the severity of symptoms, systemic antibiotics or topical antimicrobials can be applied . **(9)**

Despite appropriate treatment, the average time for healing VLUs varies from 6 to 12 months, and one-fifth of VLU cases do not heal within 24 months. If standard treatment fails, advanced therapy methods should be taken into consideration that can be applied as adjuvants to conventional treatment . Another challenge in VLU treatment is frequent recurrence. Relapse after recovery within 5 years is high and reaches almost 70%. Furthermore, VLUs can be resistant to treatment. A lack of inclination to cure between 1.5 and 3 months or lack of healing within 12 months after optimal therapy is referred to as therapy resistance . For these reasons, there is still an unmet need regarding insufficient treatment efficacy. It is thought that the weak healing of venous leg ulcers is caused by topical disturbances as a result of T lymphocytes and the amount Biomedicines of granulocytes increasing, oxygen deficiency, growth factor and cytokine imbalance . **(9)**

The exercise was shown to have a significant effect on VLU healing, particularly when combined with compression therapy. Patients receiving both compression therapy and progressive tailored exercise training have a higher quality of life. The cutaneous microvascular reactivity may facilitate the healing of VLU. They have shown that a 12-week supervised exercise program improved measures of cutaneous microvascular reactivity in people being treated with compression therapy for venous ulceration. It appears that the combination of progressive resistance exercises and aerobic activity (e.g. walking) may be the most effective form of exercise regimen. **(10)**

Phlebotonics represent a heterogeneous group of compounds mostly plant flavonoids, classified as venoactive and vasoprotective agents. Moreover, there are many differing opinions in the literature on the use of phlebotonics, ranging from a beneficial effect in CVI to serious side effects. Micronized Purified Flavonoid Fraction (diosmin) was found to have beneficial effects without serious adverse events and was suitable for reduction in symptoms of chronic venous disease, such as edema. Phlebotonics were reported to slightly reduce edema and also ankle circumference. Flavonoids are rather classified as ‘medical food’ and are suggested for venoprotection instead of the VLU treatment.Pentoxifylline is a xanthine derivative with a variety of beneficial anti-inflammatory and hemorheological properties. Pentoxifylline was shown to have a clear benefit in healing VLU, either alone or in combination with compression therapy. **(11)**

Ultrasound Therapy :

Ultrasound therapy (UT) is pointed as one of the adjunctive treatments used in venous leg ulcers therapy . A mechanical effect is the major result of ultrasound use. There are two types of ultrasound influence on tissues: thermal and non-thermal. The non thermal action of ultrasound is thought to be due to two phenomena: acoustic streaming and cavitation. Acoustic streaming means confluence and movement of particles located inside a fluid medium caused by the physical strength of sound waves. We differentiate two sorts of this streaming: microstreaming, mechanically stronger and bulk streaming **(12)**. The cavitation makes and sets in motion micron-sized bubbles in a fluid medium caused by sound waves **(13).**

Stronger application of ultrasound can cause a tissue temperature increase to around 40 degrees Celsius. This thermal effect induces blood flow rise in tissue and beneficial, physical modifications in collagen structures. It is also reported that ultrasound induces protein synthesis, cell proliferation, angiogenesis, or enzymatic fibrinolysis. Moreover, ultrasound induces fibroblasts for collagen formation, enhances collagen deposition, and speeds up granulation tissue creation. Additionally, ultrasound has an anti-inflammatory effect, reduces tissue edema, and supports the cleansing of necrotic tissue from the wound . On the other hand . There aretwotypesoftherapeuticultrasound, either high-frequency ultrasound (HFU) (1–3 MHz) or low-frequency ultrasound (LFU) expressed in the kilohertz (30–40 kHz), and both kinds are applied in the treatment of VLUs **(12)**.

Ultrasound devices can supply a variety of frequencies in a pulsed, or constant way, and are usually administered for between five and ten minutes each time. Ultrasound can be applied directly to the skin, more

often around the ulceration than to the bottom of the ulcer. Acouplingagentisusually placed between the applicator head of an ultrasound device and the skin surface . Indirectly applied ultrasound is administered through a water bath or saline mist placed on a woundbedbyusing the non-contact ultrasound device . Unfortunately, based on a review of ultrasound randomized controlled trials most of the evidence is of poor quality and it is not clear whether therapeutic UT accomplishes the healing process of venous leg ulcers . **(12)**

Oxygen Therapy:

Several healing processes occurring in tissues such as cell replication, anti-bacterial macrophages act, necrotic tissue removal, or collagen formation are greatly oxygen relative. A commonly known fact is that chronic wound tissues have a too low amount of oxygen, and the healing process of hypoxic tissues is disturbed, especially when a transcutaneous oxygen partial pressure (pO2) is lower than 40 mmHg . It is suggested that oxygen therapy (OT) increases oxygen delivery to wounds, accelerates their healing, and does not reveal relevant cell damage risk **(14, 15).**

Hyperbaric Oxygen Therapy Hyperbaric oxygen therapy (HBOT) is used to increase the oxygen supply to wounds and involves patients breathing with pure (100%) oxygen under increased pressure inside a special compression chamber. The whole treatment cycle usually consists of 15 to 40 therapeutic procedures lasting from one hour to two hours each . These procedures happen in pressure conditions from 2.0 to 2.5 atmospheres absolute (ATA) and are held once or twice a day and lead to increased oxygen accumulation to a wound. **(16)**

As the beneficial results of hyperbaric oxygen therapy are noted: fibroblast activation, antibacterial effect, increase in growth factors, tissue hyper-oxygenation, decrease in inflammatory cytokines, leukocyte chemotaxis reduction, angiogenesis, increased tissue perfusion, and oedema reduction . Clinical implications under the influence of hyperbaric oxygen therapy, noted in trials, are reduction in the size of the venous leg ulcers, and acceleration of the healing process . Nevertheless, there is still a need to conduct high-quality, large randomized, future trials to evidence whether HBOT as an adjunct treatment for non-healing venous leg ulcers improves a long-term disease state **. (17)**

Topical Oxygen Treatment :

Topical oxygen therapy (TOT) is an innovative technology in the management of resistant-to-healing venous leg ulcers. TOT is applied directly to the wound and does not require a full-body compression chamber. That is why TOT has much lower systemic complications and can be the alternative for patients with contraindication to HBOT . Generally, TOT is used once a day for 90 min and supplies pure (100%) oxygen at a pressure of just over 1 atmosphere. New therapeutic methods of TOT supply oxygen continuously for up to 72 h. (**18)**

According to the literature, TOT speeds up wound healing by accelerating epithelialization, MRSA elimination, stimulation of circulation, edema reduction, vascular endothelial growth factor (VEGF) level increase, and stimulation of granulation in the wound**(19).** Nevertheless, most literature data on the TOT mechanism of action refers to HBOT, thus has limited value . Clinical trials confirmed that TOT could influence venous leg ulcers area reduction, pain relief, or decrease ulcer recurrence rate **.(15).** On the other hand, the poor quality of current evidence requires clinical confirmation in the future. Some clinical data suggest that topical oxygen diffuse is too superficial and the oxygen amount absorbed by the wound is insufficient. That is why there are authors who claim that TOT should not be applied nowadays beyond clinical trials . **(18, 19)**

Negative Pressure Wound Therapy:

Negative pressure wound therapy (NPWT) is a technology supporting the standard of care in VLUs. NPWT accelerates the healing process of venous leg ulcers with several mechanisms such as local edema reduction, reduction in bacteria, inflammatory mediators, and wound exudate. Moreover, NPWT provides angiogenesis induction, promotes tissue perfusion, stimulates tissue granulation, causes wound shrinking, and contraction of its edges. These mechanisms improve topical wound state and facilitate the healing process. **(20)**

Other names for this therapy found in the literature are: vacuum assisted closure (VAC), vacuum sealing technique (VST), vacuum pack therapy, sealed surface wound suction (SSS), subatmospheric pressure dressing (SPD), foam suction dress ing, or sealing aspirative therapy**(21).**

The device for negative pressure therapy generates subatmospheric pressure and consists of a special pump linked to a container collecting wound exudation. An airtight dressing surrounds the wound and its exudate is drained into the container through a pipe. The dressing applied to the wounds is usually changed every 48–72 h, and the treatment duration is at least several weeks **.(22)**

Due to the specificity of VAC treatment, com pression therapy as the primary treatment of VLUs is not applied in parallel. Furthermore, the size of conventional NPWT devices means that this therapy takes place primarily in hospital settings. For these reasons, this technology is not widely used in the treatment of VLUs. Anewalternative for negative pressure therapy is ultraportable devices. Their significant innovation is the lack of a container whose function is taken over by absorbent dressings linked to a suction pump that can be placed in the bandage. These ultraportable devices, due to their smaller dimensions than the conventional NPWT devices, do not restrict patients' mobility. The advantage of this new technology is also the possibility of parallel use of compression therapy **(23)**

Platelet-Rich Plasma Therapy:

The wound repair process continues as a result of the interplay of the intercellular matrix, skin cells, and plasma proteins . One type of these proteins, also circulating in the blood, are growth factors (GFs). GFs affect the genes of wound cells, thus modulating the regeneration processes, such as proliferation, differentiation, or migration. Consequently, GFs induce extracellular matrix synthesis and angiogenesis. The inadequate GFs bioavailability is characteristic of chronic wounds. Therefore, the local delivery of growth factors has been identified as a promising therapeutic option . Activated platelets release GFs from their-granules, and together with other plasma proteins, such as fibronectin or fibrin, are significant agents in regenerative processes . Platelets as a natural source of growth factors have been recognized as an excellent material for tissue regeneration . Platelet-rich plasma (PRP) or autologous platelet-rich plasma is platelet suspension extracted from whole blood . The concentration of platelets in PRP is higher from two to six times than that occurring in blood. **(9)**

To form a liquid or a gel containing multiple growth factors, PRP is most often mixed with thrombin. PRP supplies not only numerous growth factors but also signaling cytokines that also play a crucial role in new tissue synthesis, angiogenesis, or regulation of inflammation . PRP is used in various f ields of medicine including chronic wound treatment and is applied in a form of injections or topically in a form of gel on a weekly basis for at least several weeks or months . Published studies in the treatment of VLUs have revealed the effectiveness of PRP therapy in reducing the area of the ulcers, and an improvement in patients' quality of life . Moreover, the antibacterial effect of PRP in wound treatment has been shown. Nonetheless, there are no standardized methods for obtaining PRP, and larger, well-designed clinical trials in this field are needed . That is why autologous PRP therapy is nowadays an alternative treatment method for VLUs, and as a biocompatible procedure, it is considered safe **(9)**

Muscle Pump Activator (MPA):

Muscle pump activator (MPA) device works by neuromuscular electrostimulation (NMES) and stimulates the common peroneal nerve which causes calf muscles isometric activation. Consequently, a stimulated calf muscle pump induces venous return enhance ment, and causes edema and venous stasis reduction. This therapy may be particularly advantageous in patients with limited mobility. **(24)**

Intermittent Pneumatic Compression (IPC) :

Intermittent pneumatic compression (IPC) devices are effective in the process of healing venous ulcers for patients with lymphedema. The advantage of this therapy is the possibility of self-application in contrast to the traditional compression therapy that requires application by a third party. According to clinical trials results, IPC is not more efficient than standard compression . **(25).**

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