© Med Sci Monit, 2005; 11(7): CR337-343
PMID: 15990691

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Clinical Research

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Received: 2004.04.13
Accepted: 2005.03.16
Published: 2005.07.01

Evaluation of two different intermittent pneumatic compression cycle settings in the healing of venous ulcers: A randomized trial

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Source of support: Departmental sources

Summary

Background: Intermittent pneumatic compression (IPC) has been sucessfully used in the treatment of venous ulcers, although the optimal setting of preassure, inflation and deflation times has not yet been established. The aim of this study was to compare the effect of two different combinations of IPC pump settings (rapid vs slow) in the healing of venous ulcers.

Material/Methods: 104 patients with pure venous ulcers were randomized to receive either rapid IPC or slow IPC for one hour daily. The primary and secondary end points were the complete healing of the reference ulcer and the change in the area of the ulcer over the six months observational period, respectively.

Results: Complete healing of the reference ulcer occurred in 45 of the 52 patients treated with rapid IPC, and in 32 of the 52 patients treated with slow IPC. Life table analysis showed that the proportion of ulcers healed at six months was 86% in the group treated with the fast IPC regimen, compared with 61% in the group treated with slow IPC (p=0.003, log-rank test). The mean rate of healing per day in the rapid IPC group was found to be significantly faster compared to the slow IPC group (0.09 cm^2 vs 0.04 cm^2, p=0.0002).

Conclusions: Treatment with rapid IPC healed venous ulcers more rapidly and in more patients than slow IPC. Both IPC treatments were well tolerated and accepted by the patients.These data suggest that the rapid IPC used in this study is more effective than slow IPC in venous ulcer healing.

key words: **venous ulcer • treatment • intermittent pneumatic compression**

Full-text PDF: http://www.MedSciMonit.com/pub/vol_11/no_7/5464.pdf

Word count: 3314
Tables: 3
Figures: 3
References: 29

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Background

Venous ulcers of the leg are chronic wounds associated with long-standing venous hypertension of the lower extremities, secondary to leg veins being blocked or incompetent. In Western countries this condition has a prevalence of approximately 1% of the adult population, and 3% in the population over the age of 65 [1,2]. Management of venous ulcers presents a major health burden and drain on health care resources. A recent estimate of the costs of treatment of venous ulcers and chronic venous insufficiency in the USA was around 1 billion US dollars per annum [3].

Compression treatment, in the form of bandaging or hosiery, represent the cornerstone treatment when venous ulcer occurs in the absence of clinically significant arterial disease. There is a wide consensus in the literature that compression using roller bandages or hosiery improves ulcer healing rates [4,5]. However, a substantial proportion of patients (30% to 60%) are not helped by compression bandaging used for several months, or are unwilling or unable to wear it [6]. In many cases, particularly in older patients, the effective level of compression required is greater than that which the patient can tolerate. Either the bandages are felt to be too tight, or the elastic stockings prove to be difficult to apply, because the patients do not have the strength required to pull them on.

Alternative methods are needed, which facilitate the application of sufficient compression and yet maintain patient compliance and improve the healing rate of venous ulcers. One option is intermittent pneumatic compression (IPC), which uses an air pump that periodically inflates/deflates bladders incorporated into sleeves which envelop the legs. Today, IPC devices are primarily used in the prevention of deep venous thrombosis (DVT) [7], and in the treatment of lymphoedema [8] and arterial occlusive disease [9]. Despite the accepted use of IPC in the treatment of venous disease, there is no solid evidence that IPC improves ulcer healing, nor has the optimal regimen been identified, in terms of the method, period and duration of compression delivered by this technique [10,11]. Moreover, the exact physiological mechanisms of action responsible for its beneficial effects remain unclear.

The present study is a continuation of our previous work evaluating the effects of IPC on venous ulcer healing. In a randomized controlled trial, we previously evaluated the efficacy of a slow IPC regimen in the treatment of venous ulcers, comparing the healing rate obtained with slow IPC to that of local treatment. Our results showed significantly higher healing rates in the IPC group (62.5% vs 27.5%, p=0.002) [12]. The present study, then, aimed to compare the effect of two different combinations of IPC pump settings (rapid inflation, short period of maintained compression and rapid deflation vs slow inflation, long period of compression and slow deflation) on the healing rate and the time need to complete healing of venous ulcers.

Material and Methods

A sequential compression device (Green Press 12, Iskra Medical, Slovenia) consisting of seven overlapping chambers was used. One chamber was over the foot, four chambers were over the calf, and two were over the thigh. It was possible to adjust the pressures in the chambers, the rate of inflation, and the compression and decompression times.

We studied the effects of two different compression cycles during the fixed graduated wave, with the highest pressure of 45 mmHg applied at the lowest chambers at the foot and ankle, 35 mmHg at the calf and 30 mmHg at the thigh. The slow compression cycle comprises a pressure rise time of 60 s, maintains inflation for 30 s and has a 90 s deflation time. In the rapid compression cycle, the air chambers inflate over 0.5 s, remain inflated for 6 s, and then deflate over 12 s.

The experimental design was a prospective, randomized, controlled, parallel group, in a comparative study, and was conducted in outpatient and inpatient settings at the Clinic of Dermatovenerology of the Faculty of Medicine in Skopje, Macedonia.

The local ethical committee approved the study protocol, and informed consent was obtained from the participants.

104 eligible consecutive patients with venous ulcers of the leg were randomized in a 1:1 ratio to receive either slow or rapid-inflation IPC for 1 hour daily. For each participant a computerized random number was generated (Microsoft Excel 97), and then the particular regimen of compression was allocated by opening the correspondingly numbered sealed opaque envelope.

In both groups the ulcers were debrided and cleaned, and then a hydrocolloid dressing (Tegasorb thin, 3M) was applied. All patients in the study were advised to elevate their legs while resting, and to avoid standing.

Only patients with pure venous ulcers attending the clinic for management of their ulcers were considered. All these patients had clinical signs of venous ulcer, such as hyperpigmentation of the surrounding skin, lipodermatosclerosis, varicosities and edema. They were formally assessed for evidence of chronic venous insufficiency with photoplethysmography, defined as venous refilling time less than 25 s and doppler demonstration of venous pathology.

Inclusion criteria were:
1) at least one unhealed venous ulcer;
2) age 18 years or more;
3) willing and able to comply with the study;
4) geographically suitable, meaning with reliable transportation for outpatients to the testing site.

The criteria for exclusion were:
1) edema due to congestive heart failure, renal or hepatic insufficiency;
2) acute thrombophlebitis or suspected DVT of the lower extremities;
3) infected ulcer or cellulites;
4) bone fracture of the lower extremity;
5) peripheral neuropathy;
6) significant peripheral vascular disease, defined as an ankle-brachial pressure index of less than 0.8;
7) systemic medication that could affect ulcer healing, inclusive of corticosteroids, cytotoxic agents, rutozides, pen-

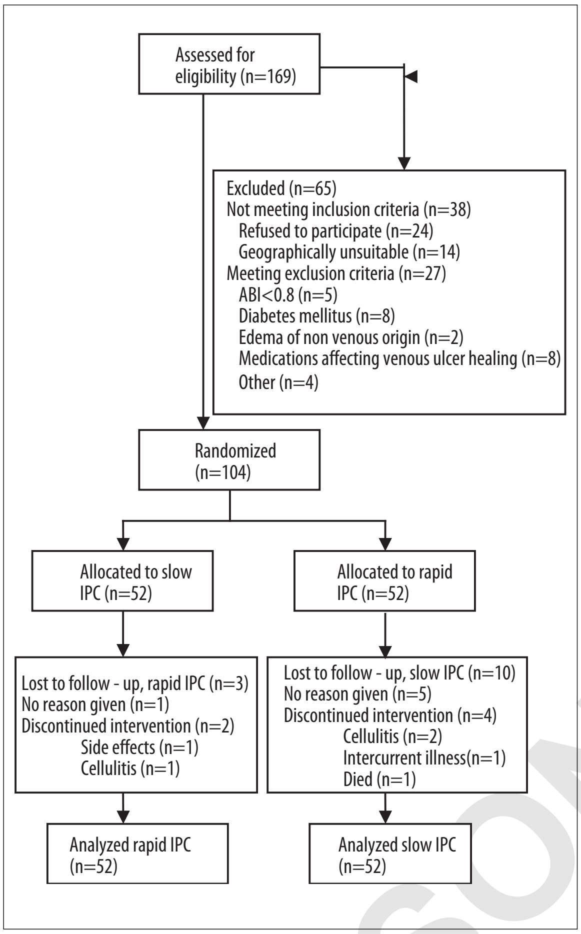

Figure 1. Study CONSORT flow diagram.

toxiphylline, anticoagulant or fibrinolytic agents within the past two months;
8) the presence of diabetes mellitus, malignant disease or connective tissue disorder.

All patients were evaluated for the first four weeks, and afterwards every month for up to six months. The evaluation was made by an observer blinded to the compression regimen used. At each visit, ulcer size was determined by computerized planimetry (AUTOCAD 14) of surface tracings made with plastic film.

The primary efficacy endpoint was incidence of complete healing by six months. A secondary efficacy variable was time to healing. Where the ulcers were multiple, the largest ulcer was selected to be monitored as the reference ulcer. Tolerability of the treatment was assessed by using spontaneous reports of adverse events at each visit.

All statistical calculations were performed using SAS software (version 6.1 for Windows, SAA Inc, Cary, NC). The sample size calculation was based on the proportion of patients achieving complete ulcer healing at 6 months [13]. The rates of healing under IPC quoted in the literature range between 48 and 92% at 6 months [11,12]. Using a conservative estimate of 55% of ulcers healed at 6 months with IPC, and assuming that an absolute increase of 25% in the number of ulcers healed would be worthwhile, we established that 100 patients (50 in each arm) would give us 80% power to detect an increase in healing rates from 55 to 80% at 6 months (α=5%).

Comparisons between treatment groups for demographics and baseline ulcer evaluations were performed using the Fisher exact test or χ^2 analyses. The proportion of ulcer healed at each visit was computed using a survival analysis by the Kaplan-Meier life-table method and long-rank test. In this intention-to-treat analysis all dropouts were retained in the statistical analysis as treatment failure.

Because previous reports have cited indicators of success or failure in the treatment of patient with venous ulcers, we identified duration of the ulcers likely to affect outcome [14]. Therefore, Cox proportional hazards regression analysis was performed on this variable.

Results

A total of 104 patients were recruited to the trial; this represents 60% (169/104) of those approached. A CONSORT flow diagram showing the recruitment and outcome of all patients recruited into the trial is presented in Figure 1. The most frequent reasons for exclusion from the trial were refusal to participate and geographical unsuitability. Thirteen patients were withdrawn from the trial, but were included in the analysis as treatment failures. There was an excess of drop-outs in the slow IPC group [10/52 (19, 23%)] compared with the rapid IPC group [3/52 (5.77)], but this difference was not significant (χ^2=4.3, p=0.04). One patient in the slow IPC group was excluded from the trial because he was found to have diabetes. Two patients in the slow IPC group and one in the rapid IPC group developed cellulites, and one from the slow IPC group was admitted to hospital with pneumonia. Only one patient in the rapid IPC group withdrew from the trial because of paresthesias in the treated leg, but electrodiagnostic studies excluded development of neuropathy as a possible complication associated with IPC (15) (Table 1). Both IPC regimens used in the trial seemed to be safe and acceptable to most patients, as adverse reactions that resulted in discontinuation of the treatment were limited to subjective paresthesias in one patient. The most common complaints were warmth and sweating beneath the vinyl leg sleeves. However, comfort scores were all measured at between 4–5 (maximum score 5).

Table 2 shows the characteristics of the patients in each treatment group at baseline. The patients were quite healthy for their age and enjoyed good nutritional status, as indicated by body mass index. By chance, the patients in the rapid IPC group tended to have larger ulcers and were of more advanced age than those in the slow IPC group, but neither of these differences reached the level of statistical significance. The majority of patients in the rapid IPC group had ulcers of short duration. When the mean values for "duration of reference ulcer" were inspected, there appeared to be fewer long-standing ulcers in the rapid IPC group (mean duration 4.2 months) than in the slow IPC group (5.4 months). The median duration of the reference ulcer was 2 months in both treatment groups. There were no significant differences between the slow compression and fast compression treatment groups for the remaining patient demographics and ulcer duration (Table 2).

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Table 1. Main reasons for withdrawal from the trial (values shown are numbers of patients withdrawn from the study).

Reasons for withdrawal from trial	Slow IPC group (n=52)	Rapid IPC group (n=52)
Side effects		
• Paresthesias	0	1
No reason given	5	1
Exclusion criteria discovered after entry to trial	1	0
Cellulitis	2	1
Intercurrent illness	1	0
Died	1	0
Total drop-outs from the trial	10	3

Table 2. Baseline demographics and ulcer characteristics.

Variable	Slow IPC group (n=52)	Rapid IPC group (n=52)
Sex		
F	28 (54%)	25 (48%)
M	24 (46%)	27 (52%)
Age, y		
Mean (±SD)	56.0±11.81	54.4±13.27
Median	56	55.5
Range	53 (29–82)	56 (28–84)
BMI, kg/m^2		
Mean (±SD)	29.5±6.1	28.6±5.8
Ulcer area, cm^2		
Mean (±SD)	4.47±3.61	4.70±6.25
Median	3.29	2.23
Range	16.42 (0.78–17.20)	37.39 (0.76–38.15)
Ulcer duration (mo)		
Mean (±SD)	4.2±28.74	5.4±16.74
Median	2	2
min-max	(0–60)	(0–36)
Number of		
inpatients	28 (54%)	25 (48%)
outpatients	24 (46%)	27 (52%)
Stratifying variable		
Ulcer duration		
< 6 mo	38 (73%)	41 (79%)
> 6 mo	14 (27%)	11 (21%)

Table 3. Frequency, time and rate of ulcer healing.

	Treatment group		p* value
	Rapid IPC	Slow IPC	
No. (%) of patients with healed ulcer by 6 mo	45/52 (86)	32/52 (61)	p=0.004
Median days to complete ulcer healing (range)	59 (20–160)	100 (13–162)	p=0.001
Rate healing (cm^2 per day) mean ±SD	0.09±0.09	0.04±0.03	p=0.0002

*p values determined using Fisher exact test or log-rank test.

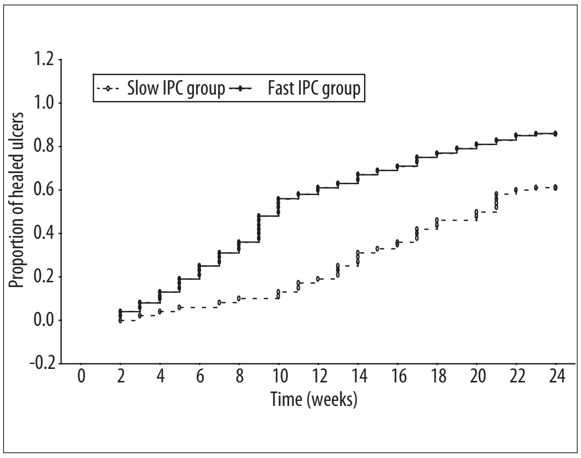

Figure 2. Life table analysis of time to complete healing of reference ulcers.

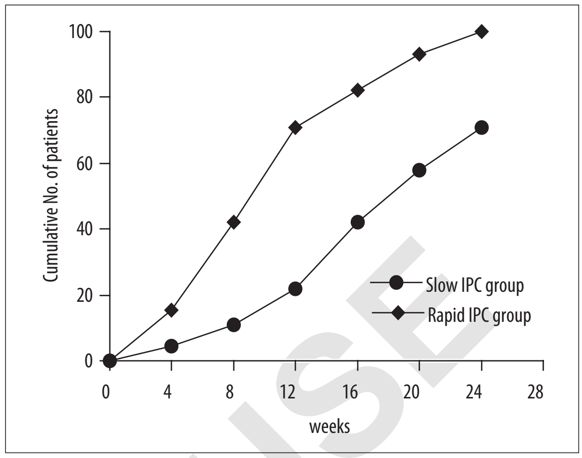

Figure 3. Cumulative proportion of patients achieving complete ulcer healing in the slow IPC and rapid IPC treatment groups.

Treatment with rapid IPC proved more effective than slow IPC in a number of parameters, as shown in Table 3.

Of the 52 ulcers in the rapid IPC group, 45 healed within 24 weeks, as compared to 32 of the 52 ulcers in the slow IPC group (86% vs 61% respectively). The proportion of patients with complete wound closure was significantly greater for patients treated with rapid IPC (χ^2=8.45, p=0.004). The absolute difference in healing rates was 25%.

The results were also analyzed using the life table method, as shown in Figures 2 and 3. This method gives the proportion of reference ulcers healed at each visit, and takes account of drop-outs. During the first 4 weeks there was little difference between slow IPC and rapid IPC groups. After a further week, a significant improvement in healing rates with rapid IPC became apparent. This continued until the end point at 24 weeks, when 86% of the ulcers were healed in the rapid IPC group, compared with 61% in the slow IPC group (p=0.003, log-rank test; Table 3). Moreover, rapid IPC treatment reduced by approximately 2-fold the median time to complete healing when compared with slow IPC treatment at the 6-month time point (p=0.001; Table 3).

After the chances of healing at any point of time for ulcer size and duration had been calculated, there was evidence of a statistically significant treatment effect in favor of the rapid IPC regimen (hazard ratio 0.74, 95% CI 0.56 to 0.90).

The area of the reference ulcer was calculated from the tracings made at successive follow-up visits. These data were studied so that information could be gained about the progress of the reference ulcers apart from their complete healing. The mean rate of healing per day in the rapid IPC group was found to be significantly faster compared to slow IPC group (0.09 cm^2 vs 0.04 cm^2, p=0.0002; Table 3).

Discussion

The results we obtained in this randomized, prospective, comparative study of venous ulcer therapy demonstrate that both the healing rate and the number of ulcers healed completely in a 24-week period were significantly better in the rapid IPC group than the slow IPC group. Moreover, it was shown that the rapid IPC regimen provides complete wound closure in half the time needed by the slow IPC regimen.

Ever since 1981, when McCulloch [16] suggested the use of IPC in the treatment of venous ulcers, evidence has accumulated supporting its use in the healing of venous ulcers. Coleridge Smith et al. [17] randomized 45 patients in an RTC trial to receive either compression stockings (30–40 mmHg compression at the ankle) or sequential IPC as an adjunct to gradient support stockings. In this intention-to-treat analysis they found complete healing of the venous ulcer in 10 of 22 patients in the pneumatic compression group, but only 1 of 24 patients in the control group (p=0.009). The median change in surface area was 19.8% for the IPC group and 2.1% for the control group.

McCulloh et al. [18] compared a single-cell IPC device and Unna's Boots with Unna's Boots alone on 22 patients with venous ulcers. A pressure of 50 mmHg was applied for 90 s followed by 30 s of relaxation. The authors reported no difference in the healing rate in the IPC and control groups. More importantly, the mean healing rate in the control group was 0.08 cm^2/day, while in the IPC group it was significantly higher, at 0.15 cm^2/day.

Schuler et al. [19] compared IPC with standard Unna's Boots among 53 patients with venous ulcers. IPC group wore elastic stockings graded to deliver 30 mmHg at the ankle, which were removed for IPC therapy. The IPC device they used delivered a constant pressure of 10 mmHg to feet and sequentially 50 mmHg to ankles, 45 mmHg to calves and 40 mmHg to thighs. The total compression time of 10 s was followed by 60 s of relaxation. After a follow-up period of 6 months, the healing rates were 76% for the IPC group and 64% for the Unna's Boots group.

Kumar et al. [20] recruited 47 patients with venous ulcers to participate in this RCT. The first group received treatment with four-layer bandaging, and the second group a below-knee single chambered IPC garment (90 s inflation and 90 s deflation) at 60 mmHg as an adjunct to four-layer bandaging. Although there was no difference in the number of ulcers healed between the two groups (87% in IPC vs 92% in control, p>0.05), the rate of healing per day was significantly faster in the IPC group (0.14 cm^2/day in IPC vs 0.05cm^2/day in control, $p<0.05$).

Studies evaluating the effect of IPC on venous ulcer healing are generally extremely small, differing in type and of too uneven quality to draw conclusions. Thus while there are some indications of the beneficial effects of IPC on venous ulcer healing, there is no solid evidence to confirm this claim.

No studies have compared directly the effectiveness of single-chamber devices with gradient multichambered devices. Moreover, none of the studies directly compared the effects of different pressures or cycle times on health outcomes, such as ulcer healing rates.

This study is the first to compare two different IPC regiments in the terms of the compression cycle (slow IPC vs rapid IPC). We ensured that the ulcer disease was clearly defined by recruiting only patients with pure venous ulcers and by rigorously excluding those with serious diseases that could alter healing rates. One hundred and two patients, on the basis of 80% power to detect statistically significant differences if the true healing rates at a fixed time were 80% and 55%, was a sufficiently large number to show better performance in ulcer healing with the rapid IPC regimen, if such existed. The trial duration of 24 weeks allowed sufficient time to show whether there were differences in healing rates between the slow and rapid IPC regimen.

One can speculate that the clinical utility of IPC in the process of venous ulcer healing is due to its mechanical effects exerted on the lower extremity and the subsequent biochemical changes in circulation. When IPC is applied to the lower extremity, the sudden compression increases intravascular flow, shear and compressive starin on endothelial cells, with the resulting release of biochemical mediators such as nitric oxide (NO) [21]. Nitric oxide secreted by endothelial cells (eNO) inhibits the expression of adhesion molecules and chemokines (e.g. monocyte chemoattractant protein-1, MCP-1) from the endothelial cells [22]. This event likely results in diminishing the deleterious consequences of leukocyte adhesion, migration out of the blood vessel and into the interstitium and chronic inflammation, which seems to be a key event in the pathogenesis of venous ulcers [23].

There are data indicating that a shorter inflation rate creates a faster peak flow velocity and consequently increased shear stress on the vascular wall responsible for increased NO production from endothelial cells [24]. It therefore seemed reasonable to compare two different treatment protocols of IPC with a different set-up of cycle times.

We decided to use sequential gradient compression as opposed to uniform, one-chamber compression for number of reasons. In a model of the limb, uniform compression was found to collapse the proximal veins first, with the wave of vessel collapse moving in the distal direction and produced "trapping" of venous blood in the distal veins. On the contrary, Nicolaides et al. [25] showed the sequential gradient compressing, to milk blood from the compressed vessel, beginning distally, with the wave of vessel collapse moving in a proximal direction.

Moreover, the rate of inflation played an important role on the modulation of microcirculation induced by IPC, while peak-pressure duration did not. Shorter inflation rate creates a faster peak flow velocity and increased shear stress on the vascular wall. This is the major impulse that stimulates the vascular wall to release nitric oxide (NO) [26]. The released NO inhibits platelet aggregation [27] and inhibits platelet and monocyte adhesion to endothelial surfaces [28]. These events minimize the deleterious effects of leukocytes in the course of skin damage in chronic venous insufficiency [29]. We expect the rapid IPC regimen to generate greater shear stress on the vascular wall, which has a more beneficial effect on the healing of venous ulcers, reducing inflammation.

Further research is required to give an explanation of the exact underlying physiology responsible for the improved healing rates of venous ulcers treated with rapid IPC regiments. However, these results are aimed to help the clinician choose more effective settings of IPC, to improve patient recovery and ultimately save on treatment costs.

Conclusions

The results of this comparative study suggest that rapid IPC (inflation time 0.5 s, 6 s pressure plateau and 12 s deflation time) healed a significantly greater proportion of patients compared to slow IPC (inflation time 60 s, 30 s pressure plateau and 90 s deflation time). The rapid IPC accelerated the healing of pure venous ulcer, the difference being evident in the first 8 weeks. We recommend this particular pressure, inflation and deflation settings in a rapid IPC regimen for patients with venous ulcers as being efficient, safe and well-tolerated.

Acknowledgments

We would like to thank Ljiljana Atanasova, leg ulcer nurse specialist, for handling the patients and keeping the records. The authors also want to thank Prof. David Margolis for his advice on statistical analysis.

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