Original communication

Intermittent negative pressure (INP) therapy in patients with no-option chronic limb-threatening ischemia

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Summary: *Background:* Aim of this study was to assess the influence of intermitted negative pressure (INP) therapy on the foot microcirculation in patients with no-option CLTI. *Patients and methods:* CLTI patients defined as no option for revascularization on the basis of an interdisciplinary vascular board decision (interventional radiology, vascular surgery) were included in this study. INP therapy was performed at home. Therapy regime was: 1 hour twice daily. Follow-up was after 6 weeks and 3 months. Microcirculation measurement was performed by laser Doppler flowmetry and white light spectrometry (oxygen to see, O2C™). Following parameters were evaluated: oxygen saturation (sO2 in%), relative hemoglobin (rHb) and flow (in arbitrary units A.U.). Additionally the clinical outcome of the patients was assessed. *Results:* From September 2020 to June 2022, 228 patients were screened. In total 19 patients (13 men, 6 women, mean age was 73.95 years) were included. 6 weeks after INP therapy the microcirculation showed a significant improvement for the parameter sO2 (%) (p=0.004). After 3 months a non-significant decrease compared to 6 weeks follow-up was seen for the parameter sO2; however, the perfusion was still improved compared to baseline measurement. With regard to the microperfusion values flow (AU) and hemoglobin (AU), the changes were not significant. Clinically, the patients reported a significant reduction of rest pain after therapy (p=0.005). *Conclusions:* INP therapy in no-option CLTI patients showed a significant improvement of the skin perfusion after 6 weeks. Therefore, INP therapy might have therapeutic potential in these critical ill patients.

Keywords: FlowOx™, microperfusion, chronic limb-threating ischemia, no-option patients, intermittent negative pressure, oxygen to see (O2C)

Introduction

Chronic limb-threatening ischemia (CLTI) represents the endpoint of peripheral artery disease (PAD), and is associated with high mortality and amputation rates. The patients suffer from chronic pain and non-healing chronic wounds, as well as reduction in quality of life [1].

These patients usually require urgent revascularization, otherwise amputation rates are 13–19% within 6 months and up to 23% within 1 year; moreover, CLTI is associated with high mortality (50–60% within 5 years) [2].

However, there is a special group of CLTI patients in whom traditional therapeutic options such as open or endovascular revascularization have been exhausted and no further revascularization options exist. This group of patients is referred to as no-option patients, and this accounts for approximately 14–20% of the total population of patients with CLTI [3, 4]. However, there is no clear definition of what a no-option patient is, although different definitions have been proposed [3, 4, 5, 6].

Various alternative methods have been used in this group of patients to relieve pain or improve foot perfusion such as spinal cord stimulation (SCS), lumbar sympathectomy (LS), pharmacotherapy, endovascular or open deep vein arterialization [1, 3, 7, 8, 9, 10, 11].

A relatively new approach is intermittent negative pressure therapy, that has already been used in patients with peripheral artery disease (PAD) [12, 13, 14, 15].

It has been shown that intermittent negative pressure in healthy volunteers increases blood flow [14]. These physical stimuli can increase expression of endothelial nitric oxide synthase (eNOS), which is known to be a strong vasodilator [16]. Due to vasodilation, collateral vessels can develop, so this can potentially lead to improvement

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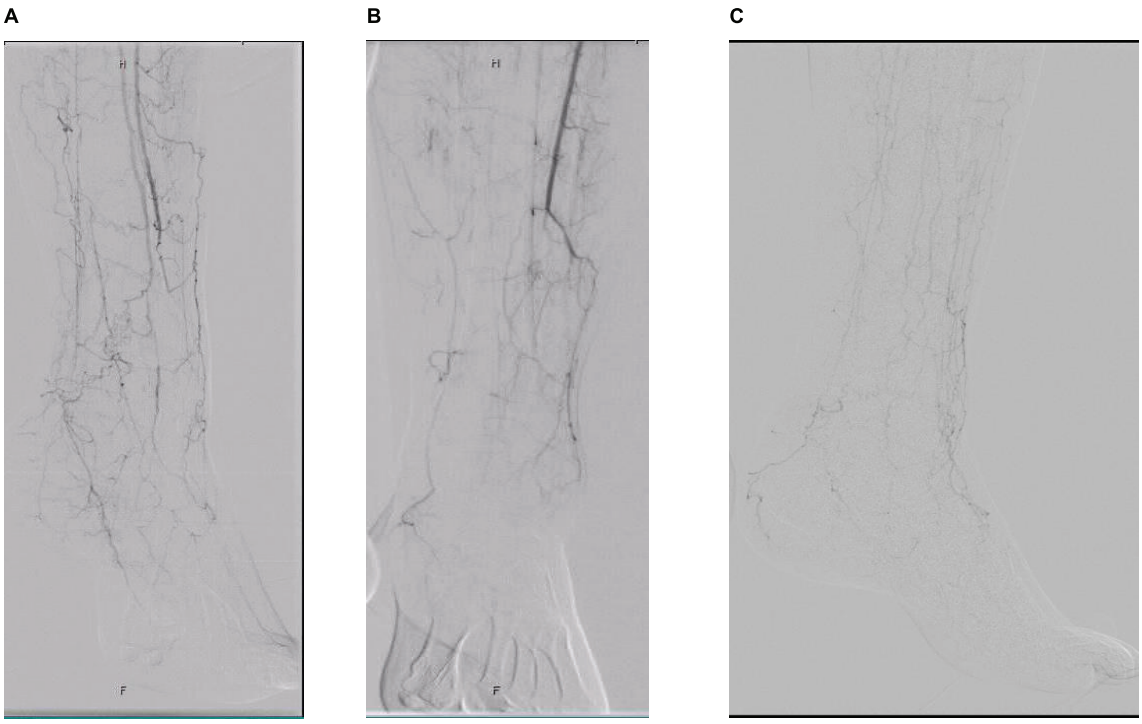

Figure 1. Examples of angiograms of included patients, defined as no-option for revascularization.

of rest pain and wound healing [1, 17]. Therefore, this study aimed to assess the impact of INP on the foots' microperfusion in no-option CLTI patients.

Patients and methods

Patients

No-option CLTI patients were enrolled in the study prospectively between September 2020 and June 2022 at the university hospital Erlangen. The study was conducted in congruence with the Declaration of Helsinki, and was also approved by the ethics committee of the University Hospital Erlangen (number: 258_20 B).

Inclusion criteria

Only no-option CLTI patients were included in this study. Inclusion criteria were as follows: Patients with CLTI Fontaine grade III or IV (Rutherford category 4 or 5) of the lower leg type; Absent of outflow, no distal recipient vessel (Kawarada's pedal arch classification type III) [18]; neither surgical nor endovascular revascularization possible; ulcer smaller than 3 cm, no superinfection of the foot. Therefore, patients at Rutherford category 6 were excluded.

All patients received a diagnostic digital subtraction angiography (DSA). The decision to define these patients as no option for revascularization was made on the basis of an interdisciplinary vascular board decision (interventional radiology, vascular surgery). An example of the angiograms of the included patients is given in Figure 1A–1C.

Intermittent negative pressure therapy

For the intermittent negative pressure (INP) therapy, the FlowOx^{TM} device (Otivio GmbH, Oslo, Norway) was used. The device represents a pressure chamber. After the patient places his affected leg in the chamber, the device is additionally hermitized from the outside with seal. The pressure chamber generates intermittent negative pressure of −40 mmHg. The preset cycle was 10 sec. of negative pressure and 7 sec. of atmospheric pressure. The therapy was performed for 1 hour twice a day and then conducted for 3 months in total.

Study inclusion was conducted routinely together with family members; by this the device handling could be optimized.

Assessments

Different measurements were conducted to assess the peripheral blood flow. The ankle-brachial index (ABI) was used to assess the macrocirculation. For microcirculatory assessment, the combined method of laser-doppler flowmetry and wight light tissue spectrometry was used (Oxygen to see O2C^{TM}, LEA Medizintechnik GmbH, Giessen, Germany). The method can determine several microperfusion parameters: relative blood flow, postcapillary oxygen saturation (sO2), and regional hemoglobin (rHb) [19, 20]. SO2 is measured in %, flow and Hb are measured in arbitrary units (AU). Critical values were defined as sO2 less than 10%, and flow less than 5 AU [21]. The measurement was performed at rest, in the supine position with the legs extended [22, 23]. The investigation was performed at different locations, therefore, the typical angiosomes of the foot

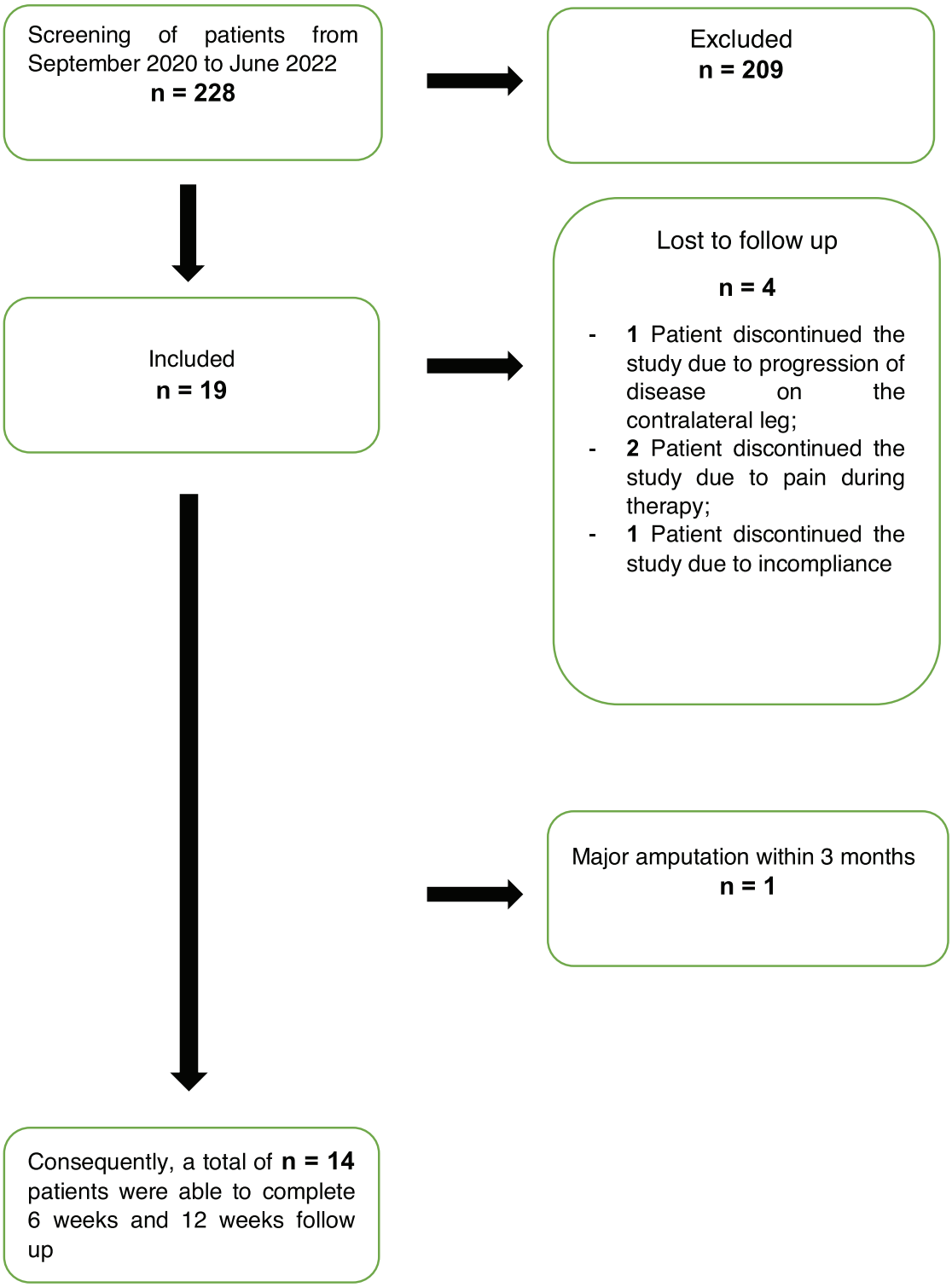

Figure 2. Study flow-chart.

were measured: probe 1 on the dorsum of the foot for the angiosome of the anterior tibial artery, probe 2 above the lateral malleolus for the angiosome of the fibular artery, and probe 3 medial plantar of the foot for the angiosome of the posterior tibial artery [19, 24, 25]. Microcirculation measurements were performed on the day of enrollment in the study before INP therapy (timepoint: BASE), at 6 weeks (timepoint: 6FU), and at 12 weeks (timepoint: 12FU) after INP therapy.

After the study, an additional survey of the patients was conducted regarding usability of the device as well as persisting rest pain. Therefore, a standardized Likert scale was used.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 28.0.0.0 (SPSS Inc., Chicago, ILL).

Microcirculation values were analyzed using the median, maximum, minimum, and standard deviation. A two-connected sample with Wilcoxon test was used as a non-parametric test. Boxplot diagrams were used for graphical representation. The significance level was defined as $p<0.05$.

Results

Patients

From September 2020 to June 2022, 228 patients with PAD Rutherford stage 4 or 5 were screened for study inclusion. A total of 19 patients were identified as no-option for revascularization (compare figure 2) and prospectively included in the study (13 men and 6 women, mean age was 73.95 years). Patient characteristics are shown in Table I.

Table I. Patient characteristics

Patients	n	%
Diabetes Mellitus	8	42.1
Chronic kidney disease	11	57.9
Coronary artery disease	7	36.8
Arterial hypertension	17	89.5
Dyslipidemia	14	73.7
Smoker	8	42.2
Previous surgery	11	57.9
Previous endovascular therapy	9	47.4
PAD Rutherford category 4	5	26.3
PAD Rutherford category 5	14	73.7
Pedal arch classification		
Type 3	19	100

Assessment of macroperfusion during INP therapy

Macrocirculation was assessed before, during and after INP therapy using the ABI. Interestingly, by comparing the mean values before and after therapy, a significant increase of the ABI was recognized (ABI, BASE: 0.35±0.28, 12 FU: 0.57±0.24, p=0.044). However, in total, 6 patients had to be excluded from this analysis due to falsely elevated ABIs by mediasclerosis.

Change of microperfusion during INP therapy

Measurement of microcirculation was performed at study inclusion (BASE), after 6 (6FU) weeks and after 3 months (12FU). The main outcome parameter with respect to microcirculation were sO2, Flow and rHb.

By comparing the changes of sO2 during follow-up, a significant improvement of the microperfusion was recognized between the time points BASE and 6FU (sO2, BASE: 42.9% [18.0–63.0], 6FU: 56.6% [32.0–75.0], p=0.004). At 12FU, a non-significant decrease of the parameter sO2 was recognized (sO2: 6FU: 56.6% [32.0-75.0], 46.8% [10.0–74.0], p=0.068), however, still higher than before therapy (compare figure 3).

With regard to the perfusion parameter flow, a non-significant increase was seen between the timepoints BASE and 6FU (flow, BASE: 31.9 A.U. [12.0–108.0], 6FU: 34.5 A.U. [12.0–95.0], p=0.776). In contrast to sO2, during 12 weeks follow-up, the flow increases during therapy compared to 6FU, however still not significantly (flow: 6FU: 34.5 A.U. [12.0–95.0], 12FU: 38.8 A.U. [12.0–108.0], p=0.509) (compare figure 4).

The assessment of rHb during therapy showed constant values during INP therapy (rHb: BASE: 81.4 A.U. [63.0–100.0], 6FU 86.8 A.U. [71.0–105.0], p=0.080 and 6FU 86.8 A.U. [71.0–105.0], 12FU 83.7 [51.0–100.0], p=0.600) (compare figure 5).

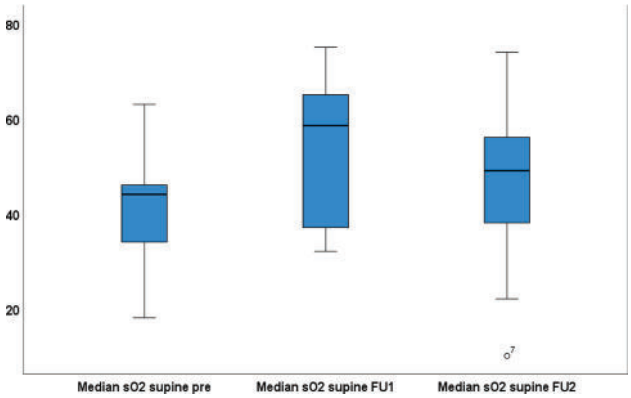

Figure 3. Microperfusion measurement of the parameter sO2 (in %) before, 6 weeks and 12 weeks after therapy with INP.

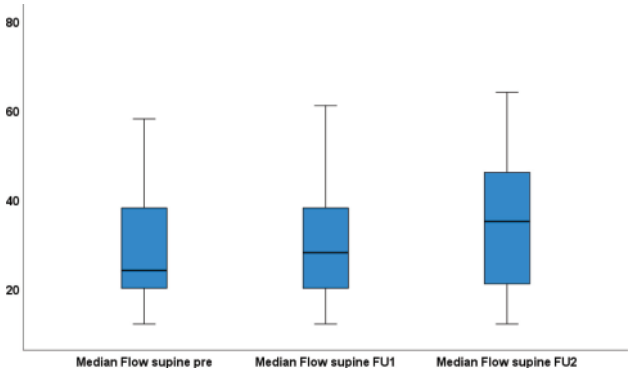

Figure 4. Microperfusion measurement of the parameter Flow (in Arbitrary unit) before, 6 weeks and 12 weeks after therapy with INP.

Clinical results

No study-related adverse events occurred during the entire study. In none of the patients, relevant skin lesions, abrasions, or pressure-related skin damages were seen.

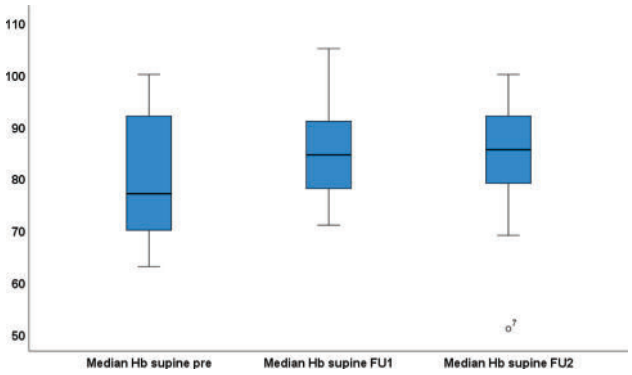

Figure 5. Microperfusion measurement of the parameter rHb (in Arbitrary unit) before, 6 weeks and 12 weeks after therapy with INP.

The patient recorded usability of the device was good, with a mean of 1.5 (±0.53) as was the general satisfaction with the device 1.87 (±0.35) (Likert scale 1–10, 1 indicating best satisfaction possible to 10 maximal dissatisfaction). Additionally, the rest pain was assessed, using a pain scale (0–10, 0 no pain to 10 very severe pain). At time point BASE, the mean pain rating was 3.2 (±1.7) which significantly improved after therapy at time point 12FU 1.2 (±2.4) (p=0.005).

Discussion

In this study, first results of intermittent negative pressure therapy using FlowOx^{TM} device in patients with severe non revascularizable CLTI were presented. Due to the multimorbidity of patients with severe CLTI, non-invasive, low-complicative and easy-to-perform alternative therapy methods are of particular importance.

However, for no-option patients several alternative treatment options have been discussed: spinal cord stimulation (SCS), lumbar sympathectomy (LS), and pharmacotherapy [1], endovascular arterialization or open deep vein arterialization [3]. Some studies assessed the effectiveness of the therapy on base of their influence on microperfusion; for spinal cord stimulation the available data reports controversial results, although a positive effect on pain relief after spinal cord stimulation has been demonstrated [7]. Clayes et al. for example, [7] were able to show a significant improvement in microperfusion after 12 months of therapy with spinal cord stimulation using tcpO2.

However, this effect could not be confirmed in another study by Ubbink et al. [8]. They could generally not find a significant difference in microperfusion between patients treated with spinal cord stimulation and those treated conservatively. In both groups, microperfusion was likewise assessed by tcpO2. In addition, due to its invasiveness, this treatment method is associated with possible complications such as dislocation of the device with subsequent need for re-implantation or the risk of infection [7, 8].

Lumbar sympathectomy is another treatment option in no-option CLTI patients. Patients often report an improvement of the pain situation; however, a significant difference and improvement of the blood flow situation has not been demonstrated [9, 10].

Endovascular arterialization of deep veins is nowadays a newer method for the treatment of these patients. The studies report improved wound healing rates after this therapy, amputation free survival after 12 months is about 70%, but with re-intervention rates of about 50% [3]. In addition, this method is associated with possible complications such as occlusion of the stent with loss of the donor artery [11].

Against this, INP is very easy to use non-invasive method, that can be performed at home by the patient independently. Additionally, the risk of complications associated with that intervention is very low.

After screening 228 CLTI patients from September 2020 to June 2022, a total of 19 patients were identified as no option for revascularization. This represents to 8.3% of the total patient population with CLTI; and is therefore slightly lower than the reported rate in the literature, which varies from 14 to 20% [3, 4].

It was interesting to see that in addition to arterial hypertension and dyslipidemia, which is generally a risk factor for the development of atherosclerosis, the combination with chronic kidney disease and no-option CLTI patients was >50%, specifically 57.9% in this study. The reason for this may possibly be that in this patient population obstructive changes in the foot arteries are more pronounced, which has already been shown by Diehm et al. [26]. They analyzed digital subtraction angiographies of PAD patients in combination with chronic kidney disease (n=15), with chronic kidney disease and diabetes mellitus (n=25), with diabetes mellitus but without chronic kidney disease (n=25), and patients with PAD but without chronic kidney disease or diabetes mellitus (n=25). They found that foot arteries were worst in patients with chronic kidney disease and poorly suited as a recipient vessel for distal bypass anastomosis.

In this study, INP therapy was used twice a day for 1 hour at an intermittent negative pressure of −40 mmHg. The positive effect on the microperfusion was most pronounced at 6 weeks, however still detectable after 3 months. Wound healing rates were not assessable in this study, as the main outcome parameter was microperfusion after 3 months, which is too short time for wound follow-up in no-option CLTI patients. However, other studies assessed wound healing after INP therapy. Kavros et al. for example, [27] observed complete wound healing in 58% of cases of 24 patients with CLTI in the group with negative pressure therapy compared with 17% of cases of 24 patients in the group without negative pressure therapy with follow-up period of 18 months. The study by Montori et al. [28] observed complete wound healing in 40% of the cases after at least 6 months of negative pressure therapy. However, these were retrospective studies and none of these studies focused on no-option patients.

Other studies showed positive effects of INP therapy in patients with symptomatic PAD. The study by Hoel et al. [13] demonstrated that at 12 weeks after INP therapy,

a significant improvement in pain-free walking distance was seen in patients with intermittent claudication. In addition, studies by Hoel and Sundby et al. [12, 15] showed the beneficial effects of negative pressure therapy on macro- and microcirculation. However, the main outcome parameter was improvement of walking distance in claudicants in this study. Interestingly none of these studies recognized improvement of the ABIs in their study, which we did in the present study [27, 29]. A possible explanation might be that the improvement of microcirculation in very severe no-option patients might lead to a better outflow of the microcirculation, and therefore indirectly influences macrocirculation. However, the improvement of the ABI in our study cohort is not completely explainable by physiological changes, and might be further influenced by a high rate of masked mediasclerosis. As the rate of patients with diabetes and chronic kidney disease is high in this study cohort, the ABI results should be interpreted with caution. Overall, patients in this study reported uncomplicated use of the device. Subjectively, patients also reported an improvement of the rest pain.

This study has several limitations. The study was conducted using a single-center design, revealing in a small sample size, in this carefully selected patient cohort. Additionally, the follow-up period was short, as the primary outcome of this study was the investigation of microcirculation after 3 months. For a better understanding of the meaning of the observed changes in blood flow, a longer follow-up including a control cohort would be useful in future studies. In addition, the patients with very severe PAD Rutherford category 6 were not included in this study, as the general knowledge of the applicability of INP in no-option at study inclusion was limited. Therefore, critically ill patients who were at very high risk of amputation were not included in this study cohort. Taking all these limitations into account, the study at hand reports first results of the applicability and the potential influences of INP in no-option patients. These results can serve as a basis for upcoming controlled multicenter studies.

Conclusions

INP therapy in no-option CLTI patients showed a significant improvement of the skin perfusion after 6 weeks. Advantages of this therapy are non-invasiveness, ease of use, flexibility as well as revealing independence for the patient. Therefore, INP therapy might have therapeutic potential in no-option CLTI patients. This, however, has to be proven in further large-scale studies, ideally including a control cohort.

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