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Effects of Shock Waves on the Microcirculation in Critical Limb Ischemia (CLI) (8-Week Study)

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ABSTRACT

Shock waves (SWs) are used to control and decrease pain in several clinical conditions (eg, painful elbow and shoulder, etc). This clinical effect may be due to cellular stunning of the tissues (particularly nervous components) in the area treated with SW. It may also be the consequence of unknown metabolic actions on tissues, which may include changes in cellular permeability and the liberation of proteins and mediators locally acting on pain and nerve endings. The aim of this study was to evaluate the reduction in pain and the microcirculation improvement induced by SWs treatment in an 8-week study in patients with chronic limb ischemia (CLI). Patients with CLI (15 with rest pain only and 15 with rest pain and limited distal necrosis) were included. The treatment was based on a 30-minute SWs session, three times weekly for 2 weeks. Clinical and microcirculatory evaluation were performed with laser Doppler PO_2 and PCO_2 measurements. Pain was

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(Abstract continued)
measured with an analogue scale line. A Minilith SL1 (Storz Medical, Switzerland) litotriptor was used. The parabolic reflector is coupled to the skin with a silicon water cushion. Focal pressure was adjusted between 6 and 70 Mpa in eight steps. The energy flux density was variable from 0.03 to 0.5 mJ/mm^2. Focal diameter and distance were defined (depth of target within the patient's foot of about 70 mm). The coded intensity used in this study was between 6 and 8 and the application time was 20 min (at four impulses per second). Twenty-eight of the 30 patients with CLI (15 with rest pain only and 13 with necrosis) completed the study. The treatment was well tolerated. Blood pressure was unchanged after 8 weeks while the increase in laser Doppler flux was significant ($p < 0.05$) (at all measurements after treatment). The ORACLE score at 1 and 8 weeks was decreased ($p < 0.05$). The same trend was observed with the analogue scale line for pain ($p < 0.05$). Po_2 increased ($p < 0.05$) and Pco_2 decreased ($p < 0.05$). Tibial pressure did not change. All patients observed an increase in their subjective pain-free walking distance. The improvement was still present after 8 weeks. In a separate subset of 37 patients (mean age 60 ±9 years; males) with CLI, a SWs dose-finding evaluation was performed. Flux changes were measured at the dorsum of the foot. Three treatment plans were used: (a) 20-minute SW treatment only once; (b) 20-minute SWs treatment every 2 days for 1 week; (c) 20 minutes every day for 1 week. Treatments were well tolerated. A different increase in flux was observed on the basis of different treatments. Flux variations generally indicated that increased SWs dosage was associated with proportional flux increase. Flux improvement was still present after 4 weeks. SWs treatment in CLI produced changes both in the microcirculation and on pain. These preliminary results are comforting and open new research options to be explored in the near future.

Introduction

Shock waves (SWs) are used to control and decrease pain in several clinical conditions (eg, painful elbow and shoulder, etc). This clinical effect may be due to cellular stunning of the tissues (particularly nervous components) in the area treated with SW. It may also be the consequence of unknown metabolic actions on tissues, which may include changes in cellular permeability (shown in previous studies[1]) and the liberation of proteins and mediators locally acting on pain and nerve endings.[2,3]

In peripheral vascular disease and critical limb ischemia (CLI), rest pain and any type of pain associated with distal ischemia and necrosis are clinically very important.[4-7] The control of pain significantly affects the effects of treatments and outcomes. Also the effective, continuous control of pain with treatment is considered an important therapeutic target.[4-7]

At present cyclic prostaglandin E_1 (PGE_1) treatment is effective in controlling the level of ischemia, and indirectly pain in CLI, by an improvement of perfusion and by reduction in the levels of ischemia.[4,5]

It is theoretically possible that treatment with SWs may also induce a local reduction in pain, in patients with CLI both in association with PGE_1 treatment and when used as the only treatment.[1,2]

It has recently been shown in pilot clinical experiments that SWs can be used to improve microcirculation in ischemic areas including the perfusion of ischemic coronary territories.[3]

The aim of this pilot study was to evaluate the reduction in pain and the microcirculation improvement induced by SWs treatment in an 8-week study in patients with CLI.

Table I

Inclusion and Exclusion Criteria

Inclusion Criteria
1. Rest/night pain
2. Walking distance <50 m (treadmill)
3. Tibial pressures <40 mm Hg (Doppler)
4. Localized necrosis/gangrene (not more than 1–2 toes)

Exclusion Criteria
1. Major cardiovascular, renal or lung disease
2. Neoplastic disorders and/or chemotherapy
3. Recent vascular procedure/surgery
4. Neuropathy
5. Diffuse infection

Patients and Methods

The study was conducted according to the Good Clinical Practice rules. Informed consent was required by all patients before treatment. Thirty patients with CLI (15 with rest pain only but not necrosis and 15 with rest pain and limited distal necrosis involving not more than two toes were included. The inclusion criteria are shown in Table I. Diabetic patients were excluded, since the pain component in these patients is variable and more difficult to assess. Also patients who had surgery or any vascular procedure, or signs of neuropathy, severe localized or diffuse infections, and neoplastic diseases were excluded. Treatment was based on 30-minute SWs sessions, three times weekly for 2 weeks (Table II). Clinical and microcirculatory evaluation were performed by experienced angiologists. Laser Doppler (Vasamedics, St. Paul, USA) measurements and transcutaneous P_{O_2}, P_{CO_2} measurements (Kontron, Switzerland) were recorded in a room at controlled temperature (21 ±1°C). The study was conducted according to the Good Clinical Practice and to E.U. guidelines for testing medical devices.

Table II

Study Plan

Run-in 1 week	Week 1 Treatment	Week 2 Treatment	Week 3 Follow-up	Week 4 Follow-up	Week 8
Measurements					
1. LDF	X	X	X		X
2. Doppler pressures	X	X	X		X
3. ORACLE score	X				X
4. Pain, ASC	X				X
5. Transcutaneous P_{O_2}/P_{CO_2}	X				X
6. Clinical evaluation	X	X	X	X	X

LDF = laser Doppler flowmetry, ASC = analogue scale line (0–10),
ORACLE score = score relative to critical ischemia.

Shock Waves

A Minilith SL1 (Storz Medical, Kreuzlingen, Switzerland) litotriptor was used. The parabolic reflector is coupled to the skin with a special soft silicone water cushion. The focal pressure may be adjusted between 6 and 70 Mpa in eight steps. The energy flux density is variable from 0.03 to 0.5 mJ/mm^2. The focal diameter is 3 mm and the focal distance is fixed, relative to the reflector rim, and adjusted to the patient's area to be insonated by inflating or deflating the water cushion. This gives a depth of target area within the patient's foot (the area to be treated) of about 70 mm. The coded intensity used in this study was between 6 and 8 and the application time was 20 minutes (at four impulses per second). The target area could be monitored on-line during the procedure with a coupled B-mode ultrasound system (Kontron, Switzerland) using a 7.5 MHz, convex probe, coaxially in-built in the SWs reflector, which can be rotated and adjusted for aiming. The SWs focus is marked on the ultrasound screen by an electronic view finder (cross-hair).

Doppler pressures were obtained with a pocket Doppler. Both tibial pressures (if detectable) were recorded at the anterior and posterior tibials. The higher pressure of the two was considered for ORACLE score[8] (see below).

Microcirculatory measurements were performed as recently described[9,10] (recorded at the dorsal part of the foot, at least 3 cm away from ulcerations, necrosis, and toes and after 20 minutes' acclimatization and rest).

Transcutaneous partial pressure of oxygen and carbon dioxide P_{O_2} and P_{CO_2} were measured with a Kontron (Kontron, Switzerland) P_{O_2}/P_{CO_2} analyzer using a CombiSensor probe for combined detection of the two parameters.[5] The probe head was heated to 44°C. Measurements were read after 20 minutes of capillarization at 44°C.[9,10]

Pain was subjectively measured on an analogue scale line 0 to 10 (where 0 indicated no pain and 10, unbearable pain).

Patients included in the study had been previously treated with PGE_1 short-term treatment. However, for at least 2 weeks before the study and for the 8 weeks during the study, no other treatment was used, excluding antibiotics, antiplatelet agents, and antihypertensive agents. Smoking had been forbidden in all patients at least 4 months before inclusion.

The microcirculatory parameters were compared by use of the Mann-Whitney U-test within a Sigma-Plot software application.

The Dose-Finding Study

In a separate subset of 37 patients (mean age 60 ±9 years; all males) with CLI, a SW dose-finding evaluation was performed. Flux changes were measures at the dorsum of the foot with LDF. Three treatment plans were used: (a) 20-minute SW treatment only once, (b) 20-minute SW treatment every 2 days for 1 week, (c) 20 minutes every day for 1 week.

The ORACLE Score in Critical Limb Ischemia

To evaluate CLI in a simple, repeatable, semiquantitative and objective way, a prospective analysis of a group of patients with CLI was performed and the ORACLE score devised (ORACLE is an acronym for Occlusion Revascularization in Atherosclerotic Clinical Limbs.[8] E stands for European study group). A series of 22 parameters were originally considered in subjects with CLI and eventually six parameters, considered essential, were prospectively monitored (Table III):

1. the highest tibial pressure (including posterior and anterior tibial pressures)
2. the presence and grading of diabetes
3. the presence of localized or systemic infections
4. the presence of localized or extended necrosis
5. the presence and grading of neuropathy
6. the presence and grading of pain

These parameters were chosen because they could be evaluated easily, quickly, anywhere, without any technical support (except a pocket Doppler) even by nonspecialized staff or in a general practitioner's office. Originally the score was devised on an analogue scale line and then simplified to four classes (Table III) from D (normal) to A severe clinical condition. Each class of severity of limb ischemia ranged from class D, relative to very mild, mostly subclinical vascular disease

Table III

ORACLE Score Nomogram for Critical Limb Ischemia

Class	A	B	C	D
Score	3	2	1	0
Highest tibial pressure, mm Hg	<40	41–80	81–120	>121
Diabetes	Severe, insulin	Moderate, oral antidiabetics	Mild, diet only	No
Infections	Severe, systemic	Moderate	Localized	No
Necrosis	Severe, foot/leg	Localized, 1–2 toes	Minimal	No
Neuropathy	Severe	Moderate	Mild	No
Pain	Severe, continuous, unbearable	Moderate (mainly at night)	Mild, transient	No
Score	18	12	2	0

Each class of severity of limb ischemia (from D, relative to very mild, mostly clinically asymptomatic vascular disease to A, corresponding to very severe limb ischemia associated with > 90% of risk of amputation in 12 months) is associated with a score (from 0 in class D to 3 in class A). The total score is obtained by adding the scores relative to the single items.

to class A corresponding to very severe limb ischemia (associated with > 90% risk of amputation in 12 months). Each class is correlated to a score (from 0 in class D to 3 in class A). The total score is obtained by adding the scores relative to the single items (Table III). The score can be easily obtained by nurses or vascular technicians and requires only 5–6 minutes. The only technical parameter is Doppler tibial pressures, which may be obtained by a pocket Doppler and a standard blood pressure cuff.

Meaning of the ORACLE Score

The presence of arterial calcification (eg, in diabetics) may alter the score (ie, a higher tibial pressure value than the real one may be obtained and a potentially lower score may be given). However, this is usually compensated by the score relative to the presence of diabetes and its semiquantification.

Preliminary evaluation of the ORACLE score for CLI in a group patients and a follow-up of 12 months (these patients were managed without PGE_1 treatment) indicated that the rate of major amputations (thigh or below knee) was comparable to the ORACLE score measured at inclusion. An ORACLE score of 18 at inclusion was associated with a 100% rate of amputation, a score of 10, with a 50% rate.

Results

Twenty-eight of the 30 patients with CLI (15 with rest only and 13 with necrosis) completed the 8-week study. Details of patients are shown

Table IV

Details of Patients

Age	61 ±11
Sex	Men, 20; women, 28
Rest pain	15
Necrosis/gangrene	13
Dropouts	3 (with necrosis)

in Table IV. There were three dropouts due to nonmedical factors (patients preferred to be treated in another vascular center closer to the place where they lived). There were no deaths and the treatment was well tolerated by all patients. There were no significant differences in macrocirculatory or microcirculatory parameters between patients with rest pain only and those with necrosis. The only (not significant) difference between the groups was in the inclusion ORACLE score (average 13 ±6 in all patients, average 12 ±5 in the rest pain group, and 14 ±7 in the necrosis group; $p < 0.05$). Therefore, the pooled

Table V

Parameters

	Run-in 1 Week	Week 1 Treatment	Week 2 Treatment	Week 3 Follow-up	Week 8	Normal Values
Measurements						
1. LDF						
	0.33 ±0.1	X 0.64 ±0.1	X 0.73 ±0.12	X 0.78 ±0.11	X 0.56 ±0.1	0.8 ±0.1
2. Doppler pressures						
	34 ±7	X 33 ±8	X 34 ±6	X 38 ±8	X 38 ±8	110% of brachial pressure
3. ORACLE score						
	13 ±6	X 8 ±4			X 7 ±5	0
4. Pain, ASC						
	8 ±5	X 4 ±4			X 5 ±5	0
5. Transcutaneous						
		X			X	
PO_2	44 ±8	51 ±8			53 ±7	>63
PCO_2	34 ±7	30 ±5			26 ±6	<28

LDF = laser Doppler flowmetry, ASC = analogue scale line (0-10), ORACLE SCORE = score relative to critical ischemia.

data presented in Table V and in the figures include all patients completing the study.

Table V shows the variation in the study parameters. Blood pressure was on average 156 ±12 (systolic) over 89 ±8 (diastolic) at inclusion, and comparable values were measured at the end of the 8 weeks (157 ±8 over 87 ±9). No alteration in other cardiac parameters was observed (ie, heart rate) during the study.

Figure 1 shows the variations in the average skin flux (laser Doppler flowmeter output) before inclusion and after 1, 2 (treatment) and at 3 and 8 weeks (follow-up). The increase in flux was significant ($p < 0.05$) at all measurements after SW treatment.

Figure 2 shows the decrease in the ORACLE score at 1 and 8 weeks (the decrease was significant; $p < 0.05$). The same trend (Figure 3) was observed with the analogue scale line measuring pain ($p < 0.05$).

The improvements in Po_2 and Pco_2 are shown in Figure 4. Po_2 increased ($p < 0.05$) and Pco_2 decreased ($p < 0.05$) as a consequence of treatment. Normal values are shown for Po_2 and Pco_2 and LDF data.

Tibial pressure did not change (Table IV), but all patients observed an important increase in their subjective pain-free walking distance (however, this was not measured with a treadmill in this pilot study). All measured parameters improved after SW treatment, and the improvement was still present after 8 weeks. This indicated that the effect of treatment is not transient.

The Dose-Finding Study

In the separate, comparable subset of patients, treatments were well tolerated. A different increase in flux was observed (Figure 5) on the basis of different treatments.

The flux variations generally indicate that increased dosage is associated with a proportional increase in flux. Flux improvement was still present after 4 weeks, confirming that the effect of SW treatment is not transient. Average values are shown in Figure 5.

Discussion

As tibial pressure did not change during the study, the effects on the foot microcirculation may involve both an action on pain and an im-

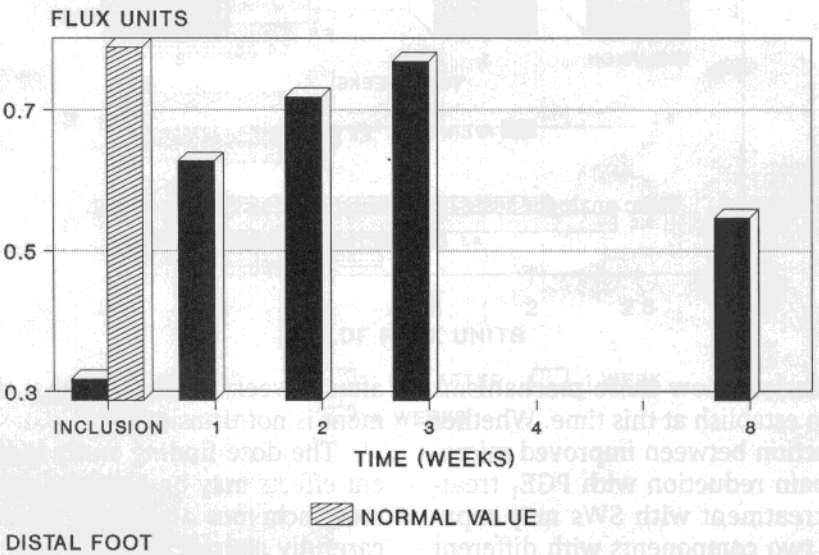

Figure 1. Laser Doppler evaluation after SW treatment.

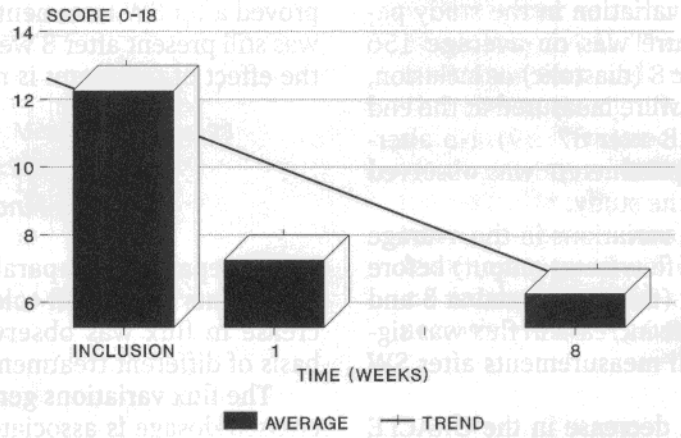

Figure 2. ORACLE score: evaluation after SW treatment.

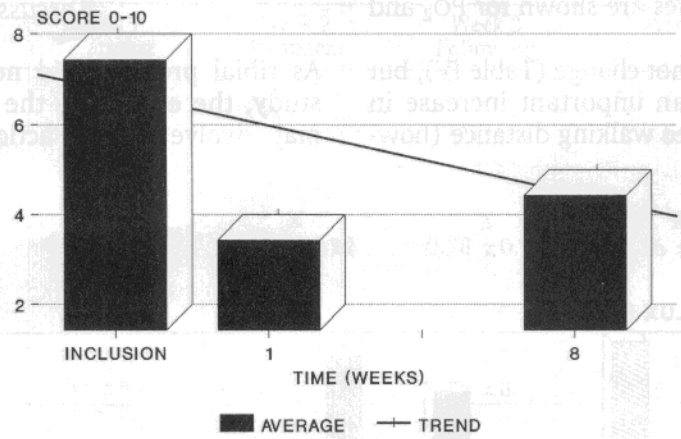

Figure 3. Pain: analogue scale line evaluation after SW treatment.

pact on skin perfusion. How these mechanisms work is difficult to establish at this time. Whether there is an interaction between improved microcirculation and pain reduction with PGE_1 treatment, the local treatment with SWs may separately act on the two components with different pathways.[1-4] It is also very important to observe that all measured parameters improved after the treatment and the improvement was still present after 8 weeks, indicating that the effect of treatment is not transient.

The dose-finding study indicated that different effects may be obtained with different treatment schemes and these observations must be carefully considered to evaluate the best therapeutic options.

Several experiences have recently been reported indicating that SWs treatment acts on pain

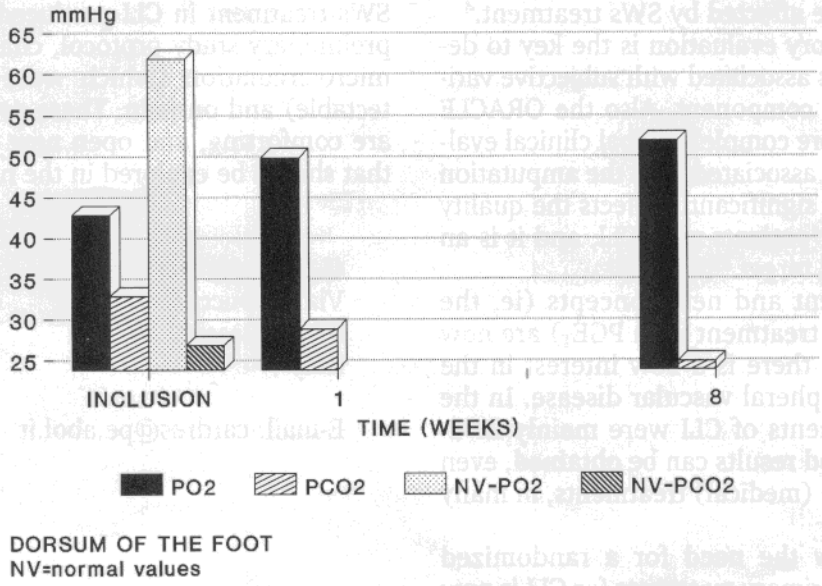

Figure 4. Transcutaneous P_{O_2} and P_{CO_2} evaluation after SW treatment.

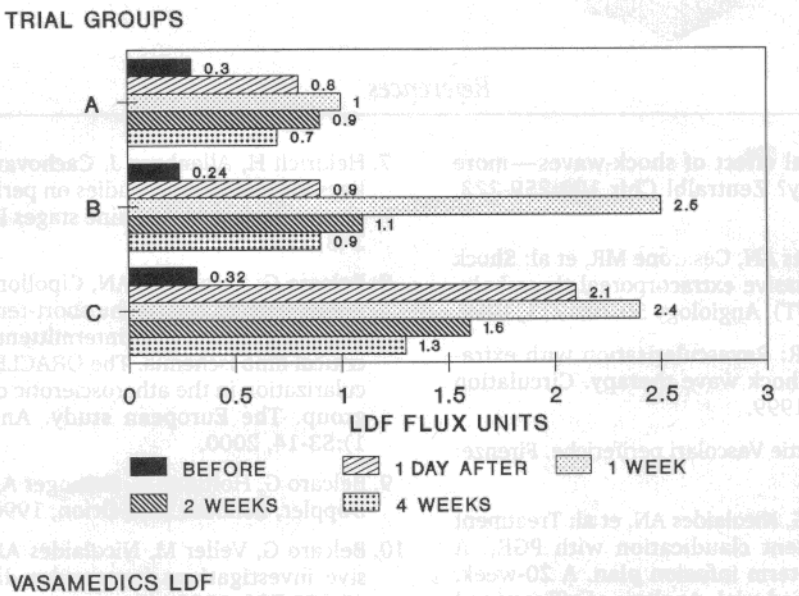

Figure 5. Flux changes with treatment. **A.** Once 20 minutes. **B.** 20 minutes every 2 days for 1 week. **C.** 20 minutes every day for 1 week.

in several different clinical conditions.[1,2] Also it has been shown that perfusion (ie, myocardial perfusion) may be affected by SWs treatment.[4]

Microcirculatory evaluation is the key to detect these changes associated with subjective variation in the pain component. Also the ORACLE score allows a more complex, global clinical evaluation and, being associated with the amputation rate, its variation significantly affects the quality of life of vascular patients with CLI, and it is an important clinical target.[11]

New treatment and new concepts (ie, the cyclic short-term treatment with PGE_1) are now emerging[8-10] and there is a new interest in the treatment of peripheral vascular disease. In the past most treatments of CLI were mainly invasive, but now good results can be obtained, even with conservative (medical) treatments, in many patients.

There is now the need for a randomized study. Since the primary treatment for CLI is now cyclic short-term PGE_1 therapy (in association with invasive procedures in selected patients and clinical conditions), it would be very interesting to evaluate treatment with SWs in patients treated with PGE_1 (ie, one group treated with PGE_1 and SW and one group treated with PGE_1 only).[11]

Conclusion

SWs treatment in CLI produced, in this limited, preliminary study protocol, changes both in the microcirculation (which were objectively detectable) and on pain. These preliminary results are comforting, and open new research options that should be explored in the near future.

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