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EFFICACY OF 904 NM LASER THERAPY IN ACUTE LATERAL ANKLE SPRAINS

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EFFICACY OF 904 NM LASER THERAPY IN ACUTE LATERAL ANKLE SPRAINS

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan
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Robert Adriaan de Bie

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Opgedragen aan Hannerieke: “Light and joy of my life”

1 INTRODUCTION

One of the highlights of living in the countryside, apart from enjoying the good life and the tranquillity, is catching sheep that have run away or that need to be moved to another part of the meadow. It invokes hilarious scenes with all collected neighbours trampling around like madmen, desperately trying to herd the sheep to their new location. Lack of co-ordination on behalf of the herdsmen and stubbornness of the sheep often results in both sides milling around for hours. But in the end we mostly succeed in our goal. One night, after another sheep hunt, one of my neighbours, a retired engineer, was so elated that he jumped over the fence and sprained his ankle and started calling for help. For some reason everyone pointed at me, saying; "He's the one doing something with ankles at the university, so ask him what to do."

My neighbour looked at me suspiciously and asked; "Do you really know something about ankles?" "No", I said jokingly, "but I'm going to help you anyway. Let's see if you can manage to walk" I continued.

"Why?"

"So we can get back to our shed and I can do some first aid, that's why."

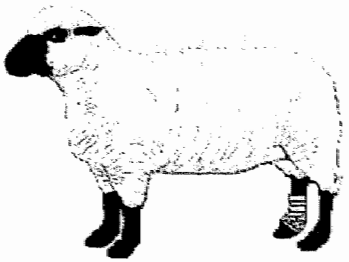
My neighbour now made some serious efforts of standing upright, and with some grunts and curses he managed to do so.

"It doesn't seem too bad" I said to encourage him, while he stumbled back to the shed.

"I don't agree" he said. "It hurts like hell, and it is starting to swell enormously."

When we had reached our shed I urged my neighbour to sit down: "Take your shoe off, and we'll put your foot under the running tap to cool it."

"Ah, that feels good" he said "but what is it good for?"



"This is what you could call first aid in ankle sprains. It's called RICE,[1,2] meaning rest, ice, compression and elevation. Since we don't have any ice available, 10 minutes under the running tap should do just as well. After that I'll put an elastic wrapping around your ankle and you go home where you put your foot up and take it easy for a day or two."

"I'll be bored to death" he complained. "And although you think it's not serious I want to be sure. So can you take me to the hospital where the doctors can take some X-rays and tell me how bad it is?"

"Sure, but I don't know if the X-ray is telling you anything else than that the ankle isn't broken.[3]"

"Okay, but what about all those other new imaging techniques. Surely they can tell me how serious it is and how long this is going to take?" he wondered.

"Well, I'm not so optimistic. Routine stress tests and arthrography have a low reproducibility and do not correlate well with complaints and objective findings.[4,5] Other diagnostic imaging techniques such as CT-scan or ultrasonography are very hard to interpret and Magnetic Resonance Imaging is way too expensive. Besides, there is this underlying idea in all these diagnostic techniques that the extent of the tissue damage

reflects the severity of the injury; you could question whether this is correct. Besides, some people make a lot of noise when in pain, but the amount of noise doesn't reflect the amount of pain. And for prognosis, well, most doctors just tell you to go home and wait and see."

"So, you're telling me there's no way to inform me how serious it is?" he asked incredulously.

"Yep" I replied.

"I don't like it. And what about this new laser therapy? My cousin is a physiotherapist and has bought a new laser apparatus the other week. He says it is very good at healing sports injuries such as ankle sprains."

"Well", I said, trying to distract my neighbour from his painful foot; "actually, since the 1980s laser therapy is being used in physiotherapy. Laser therapy in a physiotherapeutic setting is defined by an average power output with a maximum of 50 mW per square centimetre.[6,7] So, it's a very low dose laser. Already in 1987 we performed a pilot study about the efficacy of 780 nm laser therapy on ankle sprains.[8] We then found a 23% difference in pain reduction within five days in favour of the laser group compared to placebo. Yet, the findings of our study need to be interpreted carefully since we had few patients in the trial."

"I don't understand it" he said. "It works, and yet you doubt it."

"Because the number of patients is small, it could have been just a chance finding. To be more sure one would need to do a larger trial with at least 50 persons per group."

My neighbour nodded in consent. "Is there really a need for an evaluation in such a rigorous way? Surely, everyone sprains his ankle at sometime during his life, but how serious can it be?"

"Just to give you an idea, in the Netherlands one in every four sports injuries concerns the ankle, while in hospitals four out of 1000 Dutch people are treated for ankle sprains every year. Ankle sprain injuries are responsible for 10 to 15% of all absenteeism from work, and the average duration of absenteeism is about 7.3 days.[9] Some 20% of all ankle sprain injuries lead to chronic instability. Medical costs, expenses on sick leave and (semi)-permanent invalidity are high.[10] Thus, finding new or better therapies for treating ankle sprains in a cost-effective way might be very relevant.

And another thing comes up as well. We studied the literature to gain more insight into the efficacy of laser therapy in musculoskeletal disorders. We performed two systematic reviews. These early reviews, done in 1990 on 35 randomised clinical trials,[6,7] concluded that laser therapy for musculoskeletal disorders seems promising, when compared to placebo laser therapy. In rheumatic diseases and post traumatic injuries randomised clinical trials showed a swift pain reduction and a quicker functional recovery. However, trials of LT in the treatment of soft tissue injuries, like your ankle, gave conflicting results. And besides, the quality of the research in those trials was not very good. Moreover, there is also a lot of uncertainty what dose is the most adequate."

"And what about other therapies for ankle sprains?"

"Again, I don't know" I admitted lamely. "They use taping nowadays, since they believe it's better than a plaster cast,[12-14] but all kinds of other therapies are used as well. There's hardly any evidence on the efficacy of these therapies."

"My faith in medical science has gone down the drain" my neighbour said. "You don't know my prognosis, you don't know if laser therapy works, and even worse, the quality of

research in this area is no good."
"Cheer up" I said. "I have just started my PhD thesis investigating these questions of yours, and I'll let you know the answers in a few years."
"Nice going" my neighbour remarked sourly. "You don't really expect me to wait a few years with my ankle until you know the answers, do you?"
"No, we're going to get you to the hospital right now."

SOME YEARS LATER.....

"Hi neighbour."
"What's up son?"
"I'm bringing you some answers to your questions."
"Oh, but I already know what to do about white fly on my cabbage leaves...."
"No, no" I said "It's about your ankle."
"What about my ankle" he said. "It's fine."
"No, I mean the questions you had a couple of years back, when you sprained it."
"Ah, so, err..." He seemed confused. "Eh, what did I ask, again?"
"You wanted to know about the best therapy for sprained ankles, the prognosis of sprained ankles and whether laser therapy was any good."
"I did?"
"Yes, and I have the answers right here" and I handed him my thesis.
"This is a book" he said.
"I know, and it systematically describes everything you wanted to know. After the introduction, which is chapter 1, chapter 2 presents a systematic review on the efficacy of physiotherapy interventions in acute lateral ankle sprains. It describes 81 studies that investigated the effects of physiotherapy interventions versus other interventions or placebo interventions, in subjects with acute lateral ankle sprains. Of these, 44 fulfilled our entry criteria, and were assessed on methodological criteria.
Chapter 3 describes a systematic review on the efficacy of 904 nm low level laser therapy in musculoskeletal disorders. We found 25 studies that investigated the effects of 904 nm laser therapy versus placebo or another intervention, in subjects with a condition for which LT was thought useful. Of these, 21 fulfilled our entry criteria, and were assessed blindly on methodological criteria.
In chapter 4 we write about the prognosis of ankle sprains. We developed a new tool for predicting the severity of ankle sprains just after injury. Since hard data obtained by diagnostic imaging techniques are still imperfect,[3,4] we decided to use data from history taking and signs and symptoms that are part of the intake routine. During a three month period data were collected of 35 patients with lateral ankle sprains who visited the first aid department of the University Hospital Maastricht. Assessments took place at intake and at two and four weeks after injury. From these data we tried to learn about the best predictors for fast recovery."
"I'm speechless" my neighbour said. "But what about the laser therapy?"
"In chapters 5 to 7 we describe the design of the trial and the putative biological mechanisms of laser therapy, as well as, the short and the long term results of a randomised, double blind, clinical trial, in which dosimetric questions are addressed as well."
"I see. And what is your opinion about all this research on ankle sprains?"
"Well, chapter 8 discusses the relevance of our research in the ankle sprain business."
"But tell me, is this thesis not far too complicated for me to read?"

"No, there is also an extended summary of it all in Dutch."
"You seem to have an answer to everything."
"Well, only to acute lateral ankle sprains. So, happy reading! And, you know what, I'll bring you a bottle of home made wine as well."
"Now that's something" he said. "Perhaps science isn't so bad after all!"

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2 EFFICACY OF CONSERVATIVE INTERVENTIONS IN THE TREATMENT OF ACUTE LATERAL ANKLE SPRAINS: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: This systematic review summarises the efficacy of conservative interventions in acute lateral ankle sprains.

Method: We performed computer aided searches of databases and of bibliographic indexes. Furthermore, we checked congress reports, reviews and relevant citations. Subsequently, all retrieved empirical studies were scored on methodological quality and effect sizes were calculated for pain, swelling and days of sick leave.

Results: We found 81 studies that investigated the effects of physiotherapy interventions versus other interventions or placebo interventions, in subjects with acute lateral ankle sprains. Of these, 44 fulfilled our entry criteria.

Study quality ranged from poor (9 points) to rather good (70 points). Only two studies scored more than 60 points (both on pulsed shortwave therapy) and they showed no effect. Tape was found to be superior over other types of treatment, in effect shortening the duration of sick-leave, while plaster of Paris treatment seemed to prolong sick-leave. Placebo therapies delivered no positive results.

Further and improved research is needed to shed more light on efficacy of other treatment interventions.

Keywords: systematic review, acute ankle sprains, conservative interventions

Introduction

Ankle sprains are one of the most common injuries of the ankle, and are most often reported in relation to sports participation.[1] They relate to the lateral ligament complex of the ankle, and are reported on as sprains, strains, inversion injuries, lateral ankle injuries and lateral ligament injuries.

There is still much debate about which therapy is most effective in the treatment of ankle sprains. There are many treatment options available, but there is little consensus which treatment is the most efficacious. Many choices regarding therapy seem to be driven by tradition or fashion rather than efficacy. Adequate initial treatment for ankle sprains is thought to consist of rest, ice, compression and elevation (RICE)[2,3] while treatment after the initial phase can consist of plaster of Paris, taping, braces or special orthoses, often combined with all kinds of adjunct therapies. In the case where the ankle is being surgically treated, one often chooses for a plaster of Paris approach afterwards.

To shed some light on the efficacy of conservative treatment approaches for ankle sprains, we performed a systematic review to evaluate the effects of the provided therapies on the outcome measures pain, swelling and sick-leave.

Method

Trials on interventions for lateral ankle sprains were identified by Medline and Embase searches (both up to 1996) and by checking the Database of the Cochrane 'Rehabilitation & Related Therapies Field' at Maastricht University, the Netherlands. Additionally, we checked Current Contents, Physiotherapy Index, reviews, congress reports and handbooks. Retrieved references were followed-up by citation tracking. Papers published in English, French, German, Dutch, Spanish, Italian, Norwegian, Swedish and Danish were eligible for inclusion. Languages outside the above mentioned range, as well as abstracts and unpublished studies were not included. The search strategy was derived from the search strategy described by Dickersin[4] which is now widely being used by Cochrane reviewers. Keywords used to describe the design were: randomised controlled trials, controlled clinical trials, random allocation, double blind, single blind, experiments and evaluation studies. Keywords used to identify the illness were: ankle, sprain, inversion, lateral ankle sprain, lateral ankle ligament injury and strain. Keywords to identify the interventions were: therapy, exercise, rehabilitation, bracing, taping, cast, plaster of Paris, orthosis and all physical therapy modalities known to us ((pulsed) ultrasound therapy, laser therapy, (pulsed) short wave therapy, electro therapy, thermo therapy and cryo therapy).

The selected studies had to fulfil the following criteria for inclusion in the review. The subjects in the study had to suffer from a lateral ankle sprain. The therapy should consist of conservative treatment approaches and had to be contrasted with placebo, no treatment, physiotherapeutical or other interventions, while studies comparing various surgical techniques were excluded. The study design had to be a randomised clinical trial.

The papers eligible for reviewing were given to two reviewers (APV and AFL) who independently assessed the quality of all retrieved studies. In a consensus meeting they tried to reach agreement on items on which

they had different opinions. If consensus could not be reached, a third reviewer (RAB) made the final decision.

Table 1 shows the criteria for assessing the methodological quality of the trials. The list was originally designed by Ter Riet et al.[5], and modified over the years by Koes et al.[6], De Vet et al.[7] and Assendelft et al.[8]. It is based on generally accepted principles of intervention research.[9,10] The criteria list was adapted for ankle sprains with respect to the intervention and relevant outcome measures. Studies could earn points for methodological quality in five categories. These categories were study population, interventions, blinding, outcome, and data presentation and analysis. A maximum score of 100 points could be obtained.

Table 1: Criteria for assessing methodological quality in randomised clinical trials of low level laser therapy.

Methodological criteria		Weights
Study population (total points=48)		
A	Homogeneity	4
B1	Randomisation procedure mentioned	10
B2	Concealed method of randomisation	10
C	Comparability of relevant baseline characteristics	6
D	Numbers of patients	8
E	Dropouts described for each study group separately	7
F	Loss to follow up not leading to bias	3
Intervention (total points=12)		
G	Intervention adequately described and performed	10
H	Co-interventions avoided or equal in study groups	2
Blinding (total points=21)		
I	Patients blinded	7
J	Therapist blinded	7
K	Observer blinded	7
Outcome (total points=12)		
L	Adequate outcome measures	5
M	Adequate follow up period	5
N	Description of side effects	2
Data presentation and analysis (total=7)		
O	Mean or frequencies of most important outcome measures presented for each group	1
P	Intention to treat analysis	3
Q	Adequate correction for baseline differences or drop outs	3

To synthesise the data we pooled the data using a random effects model.[11] All outcomes are reported as effect sizes with 99% confidence intervals. Effect sizes allow comparisons among studies that address the same research hypotheses but use somewhat different manipulations and/or outcome measures. The thus obtained effects are measured in terms of their own standard deviations. Effect sizes were calculated by

using Cohen's *d* or Hedges's *g*.[11,12] Tests for heterogeneity in pooled estimates were done by using chi-square statistics.[11]

Results

81 Trial reports were identified that use some form of randomisation and study various interventions for the treatment of ankle sprains and contrast them with a different intervention, placebo therapy or no therapy. Of these, 27 were excluded from further reviewing (references can be obtained from the authors): 10 studies use medication versus placebo, 8 describe preventive effects, 6 study biomechanical aspects of ankle orthosis and braces, 1 incorporates multiple foot injuries, 1 studies healthy subjects and 1 reports only 2-years results. Of the remaining 54 studies[1,2,3,14-58], 4 were reported more than once[19,24,27,30] and two 3 or 5 times.[54,58] Of duplicate trials the most complete descriptions were used in this review.

The methodological characteristics of 44 trials are presented in Table 2. They are ranked according to their methodological score.

The methodological score ranged from 9 to 70 points. Only 2 studies scored more than 60 points, implying the methodological inadequacy of 95% of the material. There was no apparent relationship between the year of publication and the methodological quality. The average methodological score for negative trials was 35 points (SD 14), and the average methodological score for positive trials was 29 points (SD 10). The blanks in the table give insight in methodological aspects of the reviewed trials that were not reported.

Only three studies reported to have used a concealed randomisation method (item B).[18,36,42] Many studies were hampered by large numbers of drop outs and losses-to-follow up (items E and F). A few studies even lost over 50% of the population during follow up.[21,22,33] Blinding of patient, therapist or observer occurred seldom (items I, J, K). Side-effects were scarcely reported upon (item N). Finally, presentation of data and analyses was inadequate in many cases (items P and Q).

Table 3 gives a short description of the study design, participants, interventions and outcome measures for all studies. The studies are ranked alphabetically. The 44 reviewed trials contained in total 4646 patients with ankle sprains. In total 35 interventions were studied, among which 5 larger subgroups could be detected. 13 Trials reported on plaster of Paris (cast) versus another intervention. Tape was studied in 19 trials, whereas a form of bracing or bandage was studied in 10 and 7 trials respectively. 11 Studies used placebo therapy as a contrast to another intervention, that mostly consisted of a physical therapy modality such as laser, ultrasound or pulsed shortwave therapy.

The column 'participants' describes the number of participants per group, and provides demographic data. The column interventions gives insight into the specific treatment modalities that were used. The column on outcome measures shows the timing of measurement. The last column (notes) provides additional data on drop outs and number of patients that were lost during the intervention period or during follow up as well as other remarks.

Table 2: Methodological scores of the reviewed trials

Author	Year	A† 4	B 20	C 6	D 8	E 7	F 3	G 10	H 2	I 7	J 7	K 7	L 5	M 5	N 2	O 1	P 3	Q 3	Total 100	Outcome
barker	85	4	20	2	6	2		10	2	7	7		4	5		1			70	negative
mcgill	88	4	20		8	6	1	10	2		3		3	5		1			63	negative
zeegers	95	4	10	4	4	5		6	2				5	5	2	1			48	negative
o'hara	92	4	10	6	4	7		6	2				4				3		46	positive
bie	88	4			6	7		10	2	3	3	3	2			1	3		44	positive
klein	91	2	20	2	4			6					1	5		1			41	negative
sloan	89	4	10	4	6			6	2			3	5						40	positive
pennington	93	4		2		5		10	2	3		3	5			1	3		38	positive
oostendorp	87	4			4	7	3	6				3	4	5		1			37	positive
wester	96	4	10	2	2			8					5	5		1			37	positive
pasila	78	2	10	6	6			8					4			1			37	positive
konradsen	91	2		2	8	7	2	6					2	5	2	1			37	positive
johannes	93	4	10	4	4	2		6	2				1		2	1			36	negative
williamson	86	2	10	4	4	2		6	2			3	1			1			35	negative
scotece	92	4		4	2	7	3	6	2				1	2		1	3		35	positive
nilsson	83	4		4	2	6	1	6					5	5		1			34	negative
axelsen	93	4	10		6	1		10					2			1			34	positive
bradnock	95	4				7		10	2	3			1	2		1	3		33	negative
cetti	84	4		4		7	3	6						5		1	3		33	positive
dettori	94	4			8	1	1	6				3	4	5		1			33	positive
sommer	93	4		2	4	7	1	6					2	5		1			32	positive
clark	91	2			4			10	2	3	3		2	5					31	negative
eiff	94	4		2			2	10	2				5	5		1			31	positive
hedges	80	4		4	8			6					3	5		1			31	negative
holmer	91	4		6	4	1		6	2				5	2		1			31	negative
cotee	88	2			6	7		10					1			1	3		30	positive
leanderson	95	4		2	6			6	2				3	5		1			29	positive
korkala	87	4		4	2			6					4	5	2	1			28	negative
moller-larson	88	4		4	4		1	6					2	5		1			27	positive
brakenbury	83	2		6	6			6	2				4			1			27	positive
rucinski	91	2			2	7		8	2				1			1	3		26	positive
michlovitz	88				2	7		10					3			1	3		26	negative
jongen	92	4		4	2	1	1	6					1	5		1			25	negative
gronmark	80			2		7	3	6					1	2		1	3		25	negative
muwanga	86	4		2	8		2	6	2				1						25	positive
airaksinen	90				6			8					4	5		1			24	positive
lelieveld	79				2	5		10	2				1						20	positive
zwipp	92			2	2			6	2				1	5		1			19	positive
allen	85	4			4			6					2			1			17	negative
wilkerson	93	4			2			6	2				1			1			16	negative
freeman	65							6					3	2					14	positive
caro	64			2				6	2				2			1			13	positive
makulowu	77			2				6					1						9	positive
brooks	81	2						6					1						9	positive

† See Table 1 for explanation of categories A to Q

Table 3 Description of studies and outcomes

Study	Participants	Intervention
Airaksinen et al, 1990	44 patients with ankle sprains, in previous 24 hours, divided over two groups of 22 patients each Mean age 32.1 (SE 1,8) and 31.6 (SE 2.2) Gender: 14 and 12 male Prognostic variables given	• Intermittent pneumatic compression (60mm Hg 20 min, pulse cycle 30 secs) for 5 consecutive days and elastic bandage • Elastic bandage
Allen et al, 1985	57 patients with inversion injuries, divided over three groups of 19, 20 and 18 patients Mean age 31, 28 and 32.5 years Gender: 14, 17 and 11 males Prognostic variables given	• No treatment • Weave strapping • Stirrup strapping All patients: elevate leg first 24 hours, ankle mobilising exercises, keep record of drug intake
Axelsen et al, 1993	48 patients with acute ankle sprains, within previous 24 hours, divided over two groups of 26 and 14 patients Mean age (range): 25 (16-48) and 25 (15-50) years Gender: 13 and 7 men Prognostic variables given	• Laser (830 nm, 30 mW, 4 J/cm^2, 30 sec) until pain free • Placebo laser until pain free
Barker et al, 1985	82 patients with lateral ankle sprains in previous 36 hours, divided in two groups of 34 and 39 patients Median age 28 (16-55), 30 (16-56) years Gender: 23 and 24 males Prognostic variables given	• Low power pulsed shortwave therapy (640 burst/ sec, high intensity, continuous magnetic field) for 45 minutes, on 3 consecutive days • Placebo shortwave therapy for 45 minutes, on 3 consecutive days All patients: Tubigrip, elevate leg, elbow crutches, analgesics, no co-interventions
Bie de et al, 1988	38 patients with lateral ankle sprains grade 1 and 2 in previous 48 hours, divided over three groups of 12, 11 and 15 patients Mean age: 26, 27 and 26 years Gender: 8, 7 and 10 men Prognostic variables given	• Laser (780 nm, 180 sec, 5 mW, 80Hz; 10 treatments in 14 days) and tape • Placebo (10 treatments in 14 days) and tape • Tape
Brudnock et al, 1993	47 patients with acute ankle sprains divided over three groups of 17, 13 and 17 patients No prognostic variables given	• Longwave therapy (45 kHz, 5 min, continuous output, 0.95 Watts) • High Frequency Ultrasound (3MHz, 5 min, pulse ratio 1:2, 2 Watts) • Sham Ultrasound , (5 min, Watts) All patients: active mobilisation during therapy, one treatment session only!
Brunkenbury et al, 1983	400 patients with ankle sprains divided over four groups containing 70, 60, 42, 40 patients direct after randomisation Gender: all male No prognostic variables given	•Chymoral* and cast for seven days, followed by tubigrip when necessary (CC) •Placebo and cast for seven days, followed by tubigrip when necessary (PC) •Chymoral and tubigrip (CT) •Placebo and tubigrip (PT) (oral enzyme preparate containing 100.000 armour units of proteolytic activity)

OUTCOME MEASURES	NOTES
Assessments at intake, 1 and 4 weeks • Decrease in oedema: at 1 week 72 ml vs 29 ml, at 4 weeks 104 ml and 85 ml • ROM: 12° vs 4° at 1 week, and 20° vs 16° at week 4 • Pain relief (VAS): 14 mm vs 26 mm at week 1, and 44 mm vs 36 mm at week 4 • Limb function (VAS): 30 mm vs 10 mm at 1 week, and 48 mm vs 34 mm at 4 weeks	no information on drop outs intention to treat?
Assessments on intake and at 10 days • ROM improvement in %: No treatment 33.8%, Weave 28.6%, Stirrup 22.1% • Distance walk in sec.: No treatment 13.6, Weave 12.7, Stirrup 10.9 • Pain (severe/ moderate/ none): No treatment 3 /2 /3, Weave 0 /10/ 3, Stirrup 1 /6 /5 • Requiring analgesics: No treatment 7, Weave 9, Stirrup 4	42% drop outs no intention to treat analysis
Assessments at intake and at 1 week • Swelling in ml (graph); laser -1.53 (0.76) , placebo -1.5 (1.41) • Pain free in days (range); laser 5 (2-50), placebo 14 (1-20) • Sick leave in days (range): laser 1.7 (2.34), placebo 5.4 (5.4) • Analgesic consumption: no data	24% drop outs no intention to treat analysis
Assessments on days 1, 2, 3, 8 and 15 • ROM (graph): ratio's on all days p>0.35 • Average walking velocity (graph): all days p>0.35 • Average length of two steps (graph): all days p>0.35 • Foot timing data (graph): all days p>0.35, except day 3, p= 0.28 • Symmetry of foot position (graph): all days p>0.35, except day 2 and 8 p=0.21 • Pain (VAS) (graph); all days p>0.35 • Swelling (graph); all days p>0.35, except day 2 p=0.21 Assessments on 5 and 17 days • Difference in pain during the day compared with baseline; at 5 days: laser 71%, placebo 48%, tape 53%; at 17 days: laser 90%, placebo 78%, tape 91% • Difference in pain during the night compared with baseline; at 5 days: laser 98%, placebo 76%, tape 60%; at 17 days: laser 97%, placebo 95%, tape 94% • Hindrance in sports activities compared with baseline; at 5 days: laser 8%, placebo 0%, tape 4%; at 17 days: laser 42%, placebo 37%, tape 18%	9.7% drop outs 12% loss to follow up no intention to treat analysis
Assessments at intake, after 1 treatment and at 3 days • Mean stride length improvement ratio (SD): LWT 1.64 (26.8%), HF US 1.19 (12.3%), Sham 1.2 1 (12.6%) • Mean swing phase duration improvement (SD): LWT 1.34 (23%), HF US 1.06 (12.8%), Sham 1.16 (13.2%) • Double support duration ratio (seconds) (SD): LWT 0.74 (30.3%), HF US 0.83 (16.9%), Sham 0.88 (10.9%) • Cadence ratio (steps/minute) (SD): LWT 1.17 (18.7%), HF US 1.04 (12.3%), Sham 1.09 (9.3%) • Walking speed (metres/second) (SD): LWT 2.08 (32.6%), HF US 1.27 (16.8%), Sham 1.34 (17.2%)	Only 1 treatment given
Assessments at intake and at 3, 7 and 14 days • Bruising on day 7 (worse, same, better): CC (12/19/39), PC (18/18/24), CT (10/12/20), PT (4/5/31); on day 14: CC (3/7/57), PC (7/10/34), CT (2/6/28), PT (2/2/33) • Oedema on day 7 (worse, same, better): CC (5/22/49), PC (6/20/45), CT (3/16/25), PT (1/9/42); on day 14: CC (3/2/70), PC (1/6/64), CT (1/4/38), PT (0/3/49) • Changes from initial in plantar flexion: on day 3 (better/same/worse); CT (16/13/17), PT (29/10/14) (CC and PC missing); on day 7: CC (39/14/24), PC (37/7/30), CT (20/6/20), PT (31/8/14); on day 14: CC (55/6/16), PC (45/8/21), CT (24/9/14), PT (37/9/7) • Changes in power of dorsal flexion (SEM) on day 7: CC 17.2 (2.6), PC 10.8 (3.3), CT 23.2 (5.2), PT 15 (3.9); on day 14: CC 29.8 (3), PC 30.8 (4), CT 34.3 (5.3), PT 31.5 (4) • Changes in degrees of dorsiflexion (SEM) on day 7: CC 3.7 (2.3), PC 3.1 (1.7), CT 7.3 (3.8), PT 6.3 (3.2); on day 14: CC 10.4 (2.2), PC 9.8 (2.8), CT 9.5 (3.9), PT 13.5 (3.9) • Global response at 14 days (none/moderate/complete): CC (0/40/37), PC (0/47/25), CT (0/17/29), PT (0/21/33) • Mean time off work in days (SEM); CC 16.3 (0.8), PC 16.2 (0.8), CT 11.6 (1.1), PT 11.2 (1.1)	47% drop outs 53% loss to follow up no intention to treat analysis

STUDY	PARTICIPANTS	INTERVENTION
Brooks et al, 1981	205 patients with lateral ankle sprains in previous 48 hours, divided over four groups of 27, 21, 28 and 26 patients (direct after randomisation) No prognostic variables given	• No treatment but minimal bandage • Physiotherapy: ice, mobilisation, walking instruction, wobble board exercises • Double tubigrip during daytime • Cast with weight bearing after 48 hours
Caro et al, 1964	132 patients with inversion injury of the ankle, divided over three groups of 33, 42, 37 patients. Prognostic variables not given	• Hydrocortisone (injection of 50 mg into site of maximal tenderness). Application of crepe bandage, weight bearing and gentle exercises. • Eversion strapping. Weight bearing, gentle exercises, elevate leg while at rest • Cast for two weeks. Full weight bearing after 48 hours.
Cetti et al, 1984	130 patients with acute sprain of the ankle and positive stress radiogram, divided over two groups of 65 each Gender: 69 men Mean age 26 years, range 13-76 Prognostic variables given	• Cast for 6 weeks • Pliton-80 cast brace with shoe insert for 6 weeks
Clark et al, 1991	55 patients with lateral ankle sprains in previous 72 hours, divided over three groups of 22, 16 and 17 patients Mean age: 31.3, 30 and 29.4 years Gender: 17, 12 and 13 males Prognostic variables given	• Low laser (820 nm, 50 mW, 2.28 Hz) • High laser (820 nm, 50 mW, 5000 Hz) • Placebo laser Irradiation of 5 most tender points of the ankle for 2 min each for 5 treatment sessions within 8 days; ankle exercise regimen, elbow crutches for 3 days, tubigrip throughout trial period
Coté et al, 1988	30 patients with 2nd and 3rd degree ankle sprains, divided over three groups of 10 patients each Age range 18 - 22 years Prognostic variables not given	• Cold treatment (20 min, 50-60°F by cold immersion cylinder) • Heat treatment (20 min, 102-106°F by warm whirlpool submersion) • Contrast Bath Treatment (alternate immersions, staring with heat (see above) for 3 min, then cold (see above) for 3 min, and so on for 20 min) All treatments on days 3, 4, 5 post injury, active pain free ROM during immersions
Dettori et al, 1994	64 patients with moderate and severe ankle sprains, divided over three groups of 18, 22 and 24 patients Mean age 25.4 (5.4), 24.2 (5.8) and 25.9 (4.8) years Number of males per group: 17, 20 and 23 Prognostic variables given	• Cast • Elastic Wrap • Air stirrup All patients: first two weeks: progress to full weight bearing, active ROM exercises (CAST group: isometric exercises hourly), ice and elevation as needed; third week: resistive ankle exercises and proprioceptive exercises 3 times per week, tubing and active ROM exercises daily; week 4 and 5: functional ankle exercises 3 times per week, tubing and active ROM exercises daily

OUTCOME MEASURES	NOTES

Assessment after 48 hours and weekly
• Clinical score (15 points max.):
  • First visit: no treatment 6.2, physio 6.5, tubigrip 7.1, cast 7.1
  • Second visit: no treatment 2.8 , physio 4.9, tubigrip 5.1, cast 6.2
  • Third visit: no treatment 1.0, physio 1.2, tubigrip 1.0, cast 1.6
  • Fourth visit: no treatment 2.0, physio 0.4, tubigrip 0.5, cast 0.8
  • Fifth visit: no treatment 0.2, physio 0.5, tubigrip 1.0, cast (missing)
	50% loss to follow up
	no intention to treat analysis

• Time to cure: hydrocortisone 14.4 (var 66.8) days, eversion strapping 20 (var 121.2 days) and cast 25.3 (var 68.44) days • Frequency of residual symptoms after three months	15.2% loss to follow up no intention to treat analysis

Assessments at 2 and 6 months
• Sports activity (in 80 sport performers) after 6 months (same/lesser/stopped): Cast (34/4/2), Pliton (38/2/0)
• Sick leave by severity of employment;
  • heavy; cast 43.1 days, Pliton 13 days
  • fairly heavy; cast 44.2 days, Pliton 13 days
  • light; 31.5 days, Pliton 10 days
  • overall mean; cast 37.5 (range 2-63) days, Pliton 12.2 (range 0-44) days
• Clinical assessment (excellent/good/poor); cast (37/21/7), Pliton (47/14/4)
• Treatment assessment (excellent/good/poor); cast (43/15/7), Pliton (56/7/2)
	24 weeks table on relapses and residual symptoms unclear

• Assessments on visits 1, 3, 5, 6 and 15 • Swelling (anova p= 0.35) • ROM (anova p= 0.319) • Pain (anova p=0.347) • Contact time (anova p=0.664) • Step length (anova p=0.84) • Velocity (anova p=0.139)	5 extra patients in results section no intention to treat analysis
Assessments given as differences over 3 days • Volumetry: Cold - 37.5 ml, Heat -12.4 ml, Contrast - 0.1 ml	15.6% drop outs 28% loss to follow up no intention to treat analysis
Assessments at 2, and 5 weeks • Median number of days before re-uptake of work: Cast 32.4 days, Elastic wrap 29.6 days and Air Stirrup 29.4 days • Decrease in swelling; at 2 weeks: Cast 2.6%, Wrap 4.5%, Air Stirrup 4.8%; at 4 weeks: Cast 5.6%, Wrap 5.5%, Air Stirrup 6.5% (estimated from graph) • Mean functional pain index difference (0-4); at 2 weeks: Cast 0.7 points, Wrap 1.9 points, Air Stirrup 1.8 points; at 5 weeks: Cast 2.8 points, Wrap 2.9 points, Air Stirrup 2.7 points (estimated from graph) • ROM: 28% of the cases for each group missing and data unclear • Active ROM: unclear	

Study	Participants	Intervention
Eiff et al, 1994	82 patients with acute lateral ankle sprains within previous 48 hours, divided over two groups of 40 and 37 patients No prognostic variables given	• Early mobilisation; 48 hours elastic wrap, 10 days Aircast, resume activities as tolerated • Immobilisation; plaster splint for 10 days, crutches, no weight bearing All patients: application of ice and elevate leg in first 48 hours, standard rehabilitation program
Freeman, 1965	45 patients (with 46 complete ruptures of the lateral ligament of the ankle), divided over three groups of 12, 18 and 16 patients Prognostic variables not given	• Strapping and mobilisation • Cast for 6 weeks • Operation and immobilisation All patients: physiotherapy
Grommark et al, 1980	95 patients with lateral ankle ligament rupture, divided over three groups of 32, 30 and 33 patients Gender: 67 men Mean age 26.2 (14-53) years	All patients: ice, elevation and compression • Operation and 4 weeks of cast after removal of stitches at 2 weeks • Plaster cast for 6 weeks • Strapping for 6 weeks, changed every 1 or 2 weeks
Hedges et al, 1980	121 patients with ankle sprains divided over two groups of 44 and 49 patients Mean age (SD) 29.3 (11.9) and 32 (13.2) years Gender: 16 and 18 males Prognostic variables given	• Plaster splint (non weight bearing) • early mobilisation (elastic bandage and partial weight bearing while using crutches and additional ice pack)
Holmer et al, 1991	200 patients with acute ankle sprain, divided over two groups of 106 and 94 patients Gender: 47 and 41 men Mean age: 30.2 and 32.5 years No prognostic variables given	• Compression anti-embolic stocking (CS) • Ace bandage (A) All patients: crutches, elevate leg
Johannes et al, 1993	136 patients with ankle ligament ruptures, divided over two groups of 59 and 57 patients Mean age 28.5 (13-60) and 28 (15-54) years Gender: 56 men	All patients: daily exercise instructions, no walking aids permitted • Semi rigid bandage • Tape (renewed every 2 weeks) All treatments continue until patients is free of complaints
Jongen et al, 1992	100 patients with recent ankle sprain, divided over two groups of 44 patients each Mean age 28 years Man: woman ratio = 3:1 No prognostic variables given	All patients: 1 week plaster cast • Taping for 2 x 3 weeks • Malleotrain for 6 weeks

OUTCOME MEASURES	NOTES
Assessments at 3 and 10 days, 3 and 6 weeks, and 3, 6 and 12 months • Residual pain at 10 days; Mobilised (M) 81%, Immobilised (I) 78%; 3 weeks, M 57%, I 87% (P<0.05); 6 weeks M 48%, I 62%, 3 months M 26% I 24%, 6 months M 10%, I 12%, 12 months both 0% • Residual swelling at 10 days; M 85%, I 84%; 3 weeks M 55%, I 68%; 6 weeks M 32, I 44%; 3 months M 11%, I 15%; 6 months both 3%, 12 months both 0% • Impaired activity at 10 days; M 69%, I 84%; 3 weeks M 29%, I 39%; 6 weeks M 18%, I 18%; 3 months M 3%, I 6%; 6 months M 0%, I 3%; 12 months both 0% • Return to full work at 10 days; M 54%, I 13% (P<0.001); 3 weeks M 75%, I 79%; 6 weeks M 97%, I 96%; at 3 and 6 months both 100% • Relapses at 3 weeks (no of patients) ; M 1, I 0; 6 weeks M 2, I 1; 3 months M 0, I 1; 6 months M 0, I 1, 12 months both 0 • Functional instability at 3 weeks; M 20%, I 22%; 6 weeks M 13%, I 19%; 3 months M 8%, I 14%; 6 months both 8%, 12 months both 3%	6% drop outs 6% loss to follow up
Assessments at 3, 6 and 12 months • Free of symptoms (mean duration in weeks (range)): Strapping 12 (2-20), Cast 22 (8-40), Operation 26 (16-46) • Pain after 1 year: Strapping 0/12, Cast 1/17, Operation 1/16 • Swelling after 1 year: none • Pain and Swelling: Strapping 0/12, Cast 0/17, Operation 5/16 • Functional instability: none • Functional instability, pain and/or swelling: Strapping 5/12, Cast 7/17, Operation 6/16 Assessments at 6 weeks • Hospital stay; operation 4.2 days, cast 1.6 days and strapping 1.2 days • Free of symptoms (pain and ankle tilt): operation 31/32, cast 23/30, strapping 22/23	2% loss to follow up no intention to treat analysis

Assessments at 1 week, and at 8 months (on average)
• Mean weight bearing improvement (0-4) (SD): Plaster 2.04 (1.54), Early mobility 2.2 (1.39)
• Mean pain improvement (0-4) (SD): Plaster -2.08 (1.26), Early mob -1.84 (1.22)
• Mean swelling improvement (0-4) (SD): Plaster -0.51 (0.58), Early mob -0.34 (0.64)
• Long term:
  • Symptom free: 5 vs 8
  • Disability, pain or swelling when very active; 3 vs 4
  • Disability, pain or swelling with normal activities; 6 vs 5
	23% drop outs
	74% loss to follow up
	no intention to treat analysis

Assessments at 2, 4 and 6 weeks • Mean days till weight bearing (SD): CS 1.8 (2), A 1.8 (2.7) • Mean days till normal walking (SD): CS 11.5 (10.3), A 10 (9.3) • Mean days till normal ADL (SD): CS 7 (10), A 7 (8.6) • Mean days till normal leisure activities (SD): CS 23 (20.5), A 19.4 (18.2) • Mean days off work (SD); CS 5.2 (7.5), A 3.6 (4) • Mean days till disappearance of swelling (SD): CS 27.4 (25.8), A 25.9 (21.3) • Mean days till pain free (SD); CS 23 (24.5), A 19.9 (17.7)	26% drop outs no intention to treat analysis
Evaluation at 2 and 4 weeks • patient assessment: no differences (no data as well)	15% loss to follow up no intention to treat analysis
Assessments at 3, 5, 7, and 15 weeks • Clinical evaluation (very good/good/satisfactory/bad): Tape (22/12/7/3), Malleotrain (25/10/4/5) • Patient satisfaction (very satisfied/satisfied/neutral/unsatisfied): Tape (12/25/6/1), Malleotrain (22/16/3/3) • Re-uptake of work: Tape 20 days, Malleotrain 22 days • Re-uptake of sports activities (yes/no/not applicable): Tape (36/6/2), Malleotrain (32/7/5)	12% loss to follow up no intention to treat analysis

STUDY	PARTICIPANTS	INTERVENTION
Klein et al, 1991	60 patients with ankle sprains, divided over two groups of 27 each Median (range) age 22 (16-45) and 21 (16-35) years Gender: 18 males in each group Prognostic variables given	Al patients: ice, elevation of leg and crutches • Aircast for 10 days, as little weight bearing as possible; 6 weeks wear in shoe • Plaster for 10 days; 6 weeks circular cast
Konradsen et al, 1991	80 patients with grade 3 lateral ligament ruptures within previous 24 hours, divided over two groups of 36 and 37 patients Mean age (range) 24 (17-48) and 22 (18-38) years No prognostic variables given	• Aircast for 6 weeks, with exercise instruction • Cast for 1 week, 5 weeks walking cast
Korkala et al, 1987	150 patients with severe lateral ligament sprains, divided over three groups of 50 each Prognostic variables not given	• Semi-elastic bandage for 1 week, followed by elastic bandage for 1 to 3 weeks. Full weight bearing allowed • Plaster cast for 4 weeks. Full weight bearing after 1 week. • Operation and 4 weeks plaster cast. Full weight bearing after 1 week.
Leanderson et al, 1995	73 patients with grade 2 and 3 ankle sprain, divided over two groups of 39 and 34 patients. Mean age 28 years 48 men, 28 women Grade 2 to grade 3 ratio = 2:1 Type of employment similar per group	• Air stirrup ankle brace • Compression bandage All patients: weight bearing and early motion when comfortable
Lelieveld, 1979	60 patients with ankle sprains, divided over three groups of 20 patients each Mean age 22.9, 28.8 and 25.8 years Gender: 25 men No prognostic variables given	• Electric stimulation (sinus current, 10 ms, 50/100 Hz, CP form) for 4 - 8 min • Ultrasound (continuous, 0.5 W/cm^2) for 5 - 10 min • placebo ultrasound for 5 - 10 min All patients: elevate leg, crutches, eight bearing when possible, elastic bandage
Makuloluwe et al, 1977	80 patients with mild or moderate ankle sprains, divided over two groups of 40 patients each. Prognostic variables not given	• Immobilisation with elastoplast • Ultrasound (1.5 W/cm^2 x 4 minutes) and sometimes ice (5 minutes before first treatment)
Mc Gill, 1988	37 patients with lateral ligament sprain of the ankle, in previous 48 hours, divided over two groups of 18 and 18 patients Mean age 22.9 (SD 6.3) and 26.8 (SD 9.7) years Number of males per group 8 and 2	• Pulsed short-wave therapy with circuplode (82 Hz; intensity 19.6 W, 3 sessions of 15 minutes each on 3 consecutive days) • Placebo pulsed short-wave therapy All patients: tubigrip, elevate leg while at rest, axillary crutches, bear weight when possible, 500 mg Paracetamol, avoid co-interventions.

OUTCOME MEASURES	NOTES

Assessments at baseline, and at 3, 5 and 7 weeks; median follow-up 15 months
• Relapses: Aircast 8/27, Plaster 10/27 (unclear when measured)
• Instability: Aircast 9/27, Plaster 12/27 (unclear when measured)
• Pain free: Aircast 18/27, Plaster 19/27 (unclear when measured)
• After 15 months
  • Swelling: Aircast 1/27, Plaster 3/27
  • No sports limitation: Aircast 17/27, Plaster 7/27
  • Complete re-uptake of sports: Aircast 17/27, Plaster 10/27
  • Talar tilt: Aircast 3.82 (n=22), Plaster 3.35° (n=20)
  • Anterior draw sign: Aircast 6.32 mm (n=22), Plaster 6.15 mm (n=20)
	Loss to follow up ranges from 10 to 30%
	no intention to treat analysis

Assessments at 1 and 7 weeks and 3 months and 1 year • Injury score (0-48 points)(graph); at 1 week; Aircast 30 points, Cast 33 points; at 7 weeks; Aircast 7, Cast 17; at 3 months; Aircast 6, Cast 8 points • Natural walk at 1 week; Aircast 22%, Cast 0%; at 7 weeks: Aircast 100%, Cast 11%, at 3 and 12 months both 100% • Days off work at 1 week; Aircast 17%, Cast 19%; at 7 weeks; Aircast 100%, Cast 81 %, at 3 and 12 months both 100% • Days off sport at 1 week; Aircast 0%, Cast 0%; at 7 weeks; Aircast 11%, Cast 0%; at 3 months; Aircast 86%, Cast 49%; at 1 year; Aircast 86%, Cast 89%	9% loss to follow up no intention to treat analysis
Assessments after 2 years • Recurrent sprains: Bandage 6/36, Cast 10/47, Operation and Cast 8/34 • Reduced sporting activity: Bandage 8/36, Cast 7/47, Operation and Cast 4/34 • Fear of giving way (none/on flat surfaces/on rough surfaces): Bandage 17/6/13, Cast 32/0/15, Operation and Cast 31/0/3 • Tenderness: Bandage 7/31, Cast 4/42, Operation and Cast 2/26 • Talar tilt >11°: Bandage 9/30, Cast 5/40, Operation and Cast 3/26 • Anterior draw sign more than 6 mm: Bandage 7/30, Cast 9/40, Operation and Cast 3/26	Drop outs range from 22% to 36% no intention to treat analysis

Assessments at 3-5 days, 2, 4 and 10 weeks
• active ROM in dorsal flexion-plantar flexion in % of the uninjured ankle
  • Air stirrup 65, 77, 84, 95%
  • Compression 58, 77, 86, 87%
• SIP score: no data given
• Sick leave from work: Air stirrup 5.3 (range 0-26) days, Compression 9.1 (range 0-21 days)
• Karlsson's score ($p< 0.05$)
  • Air stirrup 23, 53, 63, 71
  • Compression 20, 57, 64, 73
	21% loss to follow up
	no intention to treat analysis

Assessments every day for 15 days • Swelling (graph) • Pain (graph) • Mobility (graph) • Normal walking pattern (graph)	5% drop outs no intention to treat analysis
Assessments at 1 and 2 weeks • Recovery rate at one and two weeks: ultrasound 46.2% and 86.4% recovered at one and two weeks resp., eversion strapping 26.6% and 58.6% at one and two weeks resp.	co-intervention: ice no intention to treat analysis
Assessments at 1, 2, 3, 8 and 15 days • Mean number of Paracetamol tablets taken 0.44 (0.51) vs 0.29 (0.55) • Number of hours spent with ankle elevated 1.87 (0.77) vs 1.77 (0.57) • Pain 2.37 (1.19) vs 2.34 (1.47) • Time to weight bearing 3.78 (3.20) vs 2.88 (1.5) days • Volumetry of the foot (graph only)	13.5% loss to follow up no intention to treat analysis

STUDY	PARTICIPANTS	INTERVENTION
Michlovitz et al, 1988	30 patients with grade 1 or 2 ankle sprains within previous 28 hours, divided over three groups of 10 each Age range 18-38 years Prognostic variables not given	• Ice for 30 minutes and placebo high voltage pulsed stimulation (HVPS) • Ice and (HVPS) (28 pps without contraction) for 30 minutes • Ice and (HVPS) (80 pps without contraction) for 30 minutes All treatments once a day for three days
Møller-Larsen et al, 1988	200 patients with verified rupture of ankle ligament(s), divided over two groups of 55, 55 and 65 patients Median age 25, 23 and 23 years Gender: 108 males	• Operation and walking cast for ten days, no weight bearing. After 10 days plaster cast for 5 weeks • Sent home for 5 days, leg elevated Followed by 5 weeks walking cast, weight bearing allowed • Sent home for 5 days, leg elevated. Followed by 5 weeks taping, weight bearing allowed
Muwanga et al, 1986	144 patients with acute ankle injury, divided over three groups of 48, 50 and 46 patients. Mean age per group 24.9, 25.9 and 26,9 years Number of males per group 32, 28 and 34	• Double tubigrip in the daytime, removal at night • Eversion strapping until next visit • Nottingham ankle support in the daytime, removal at night All patients: elevate leg while at rest, static ankle exercises, crutches when necessary, walk a.s.a.p.
Nilsson, 1983	180 patients with ankle sprains within previous 6 hours divided over three groups of 59, 59 and 60 patients Gender: 105 men Mean age: 32.6 years	• Elastic wrapping (E) • Elastic wrapping and cold pack for 45 min and elevated leg (EC) • Elastic wrapping and cold pack for 45 min and elevated leg, additional 1 ml Xylocain injection and 1 ml Decadron (ECI) All patients: do not walk and groups 2 and 3 receive additional physiotherapy
O'Hara et al, 1992	220 patients with acute ankle injuries, divided over two groups of 118 and 102 patients Gender: 153 men Mean age 35.2 (14-78) years Prognostic variables given	• Malleotrain every day • Standard therapy advice on resting the affected joint and as simple support (e.g., tubigrip) All patients: analgesia when required (paracetamol 1 g, up to 4 times per day)
Oostendorp, 1987	24 patients with ankle sprains within previous 24 hours divided over two groups of 12 patients each Gender: 16 men Mean age 22 years	All patients: in first week ice, compression bandage and reduced weight bearing. • taping for 6 weeks (T) • taping and standardised exercise programme (TE) for 6 weeks, 3 times a week

OUTCOME MEASURES	NOTES
Assessments at 1 and 3 days • Volumetric measurements; differences between day 1 and 3 in ml (sd); Ice 20 (28), Ice + HVPS (28) 16 (56) and Ice + HVPS (80) 7 (39) • ROM dorsal flexion; differences between day 1 and 3 in degrees (SD); Ice 6 (2), Ice + HVPS (28) 7 (7) and Ice + HVPS (80) 4 (3) • Pain on day 1 (pre and post treatment); differences on VAS: Ice 2.5 (1.43), Ice + HVPS (28) 3.65 (2.1), Ice + HVPS (80) 3.7 (2.36)	
Assessments at 5 weeks and one year • Satisfaction (no data) • Mechanical stability (no data) • Other outcomes unclear	12.5% loss to follow up no intention to treat analysis
Assessments at intake and at 10 days • Bear weight on injured foot (increase at 10 days: tubigrip 40%, eversion strapping 62% and Nottingham ankle support 67%) • ROM: Nottingham ankle support superior over other two (p=0.00174) • Confidence: Nottingham ankle support superior over other two (p=0.02) • Convenience and hygiene: Nottingham ankle support and tubigrip superior to eversion strapping	7.7% loss to follow up no intention to treat analysis

Assessments at 1, 3, 7, 14 and 21 days
• Skin temperature
• Swelling (graph): on day 3: (E) 86 ml, (EC) 73 ml, (ECI) 55 ml; on day 7: (E) 55 ml, (EC) 35 ml, (ECI) 40 ml
• Pain:
  • after 1 day: constant (E) n=24, (EC) n=14, (ECI) n=2; when walking (E) n=35, (EC) n=44, (ECI) n=46; none (E) n=0, (EC) n=1, (ECI) n=9
  • after 7 days: constant (E) n=7, (EC) n=1, (ECI) n=0; when walking (E) n=31, (EC) n=30, (ECI) n=17; none (E) n=21, (EC) n=28, (ECI) n=40
• Analgesics used: (E) n=59 (mean 4 tablets), (EC) n=59 (mean 2.9 tablets), (ECI) n=57 (mean 1.4 tablets)
• Walking ability after 7 days: normal (E) 14, (EC) 24, (ECI) 34; limp (E) 38, (EC) 35, (ECI) 21; unable to walk (E) 4, (EC) 0, (ECI) 1
• Limitation of ankle movements (graph);
  • at 3 days (E) 14°, (EC) 11.5°, (ECI) 8.5°
  •at 7 days (E) 12°, (EC) 8.5°, (ECI) 6°
• Cessation of treatment:
  • at 7 days (E) n=16, (EC) n=21, (ECI) n=29
  •at 14 days (E) n=24, (EC) n=28, (ECI) n=21
  • at 21 days (E) n=16, (EC) n=10, (ECI) n=6
• Days off work (E) 12.6, (EC) 11.3, (ECI) 9.5
Follow-up between 3 and 6 months (mean 4.3 months) and at 3 years (mean 32.6 months)
	Not all patients received the same injection therapy; 10 patients received Celostone instead
	Between 5% and 10 % missing
	no intention to treat analysis

Assessments every day for 14 days • Pain (7 cm VAS)(graphs): at rest, at night, during activity (endpoints p<0.05 for all three) • Limitation of activity (7 cm VAS) • Ability to work (differences): Malleotrain 49%, Control 45% • Improvement (6 point scale): Malleotrain 4.37 units, Control 3.94 units • Medication during 14 days (median): Malleotrain 11, Control 25.6 pills	
Assessments at 6, 12 and 24 weeks. Data are presented graphically only. • Pain (VAS): 6 weeks (T) 25 mm, (TE) 18 mm; 12 weeks (T) 15 mm, (TE) 10 mm; 24 weeks (T) 10 mm, (TE) 5mm • Fear of giving way (%): 6 weeks (T) 65, (TE) 30; 12 weeks (T) 45, (TE) 20; 24 weeks (T) 40, (TE) 10 • Re-uptake of work (%): 6 weeks (T) 85, (TE) 86; 12 weeks (T) 90, (TE) 93; 24 weeks (T) 93, (TE) 95 • Re-uptake of sports training (%): 6 weeks (T) 30, (TE) 63; 12 weeks (T) 45, (TE) 90; 24 weeks (T) 75, (TE) 95 • Re-uptake of competition sports (%): 6 weeks (T) 20, (TE) 50; 12 weeks (T) 40, (TE) 80; 24 weeks (T) 70, (TE) 95	% in graphs do not correspond with numbers of patients in groups no intention to treat analysis

STUDY	PARTICIPANTS	INTERVENTION
Pasila et al, 1978	321 patients with ankle sprain in previous 4 days, divided over three groups of 107 each Mean age 30.3, 29.8 and 32.6 years Gender: 50% men	• Diapulse (D) (38 W/sec) • Curapulse (P) (40 W/sec) • Placebo (P) All patients: treatment for 20 minutes on 3 successive days, 60° elevation, avoidance of medication, elastic bandage after treatment
Pennington et al, 1993	50 patients with grade 1 and 2 ankle sprains in previous 72 hours, divided over two groups of 25 each Prognostic variables not given	• Diapulse for 70 minutes • Placebo for 70 minutes
Rucinski et al, 1991	30 patients with grade 1 and 2 ankle sprains in previous 24 hours, divided over three groups of 10 each Prognostic variables not given	• Elastic wrap for 30 minutes and 45° elevation • Intermittent compression (40-50 mm HG, 60 sec on, 15 sec off) for 30 minutes and 45° elevation • 45° Elevation for 30 minutes
Scotece et al, 1992	184 patients with grade 1 and 2 ankle sprains in previous 24 hours, divided over three groups of 60, 60 and 64 patients Prognostic variables not given	• Athletic tape for 72 hours • Gel cast for 72 hours • Daily new strapping All patients: NSAIDS for 5 days, ice bath for 5 min, walk on involved ankle until sensation returned (3 times), balance board, weight bearing when possible, stretching exercises, resistive exercises: home program; resistive ankle exercises, walking exercises
Sloan et al, 1989	143 patients with ankle sprains, in previous 24 hours, divided over two groups (numbers unknown) Median age 24 years Gender: 113 men	• Immediate cold therapy by inflated cooling anklet for 30 min, elevate leg while supine at 45° • Simulated therapy with non inflated anklet for 30 min, while supine but not elevated All patients: high dose NSAIDS (2400 mg daily), elastic support co-intervention: paracetamol 500 mg
Sommer et al, 1993	120 patients with fresh ankle sprain, divided over three groups of 40 patients Mean age (SD) 25.9 (7.8), 24.9 (8.6) and 24.5 (5.5) years Gender: 23, 27 and 25 males Prognostic variables given	• Cast for 3 weeks, 2 weeks no weight bearing, last week partial weight bearing • Aircast splint up to 6th week, no weight during 1st week • Unna's paste dressing with partial weight for two weeks, then tape up to 6 weeks
Wester et al, 1996	61 patients with partial sprains of lateral ankle ligaments, divided over two groups of both 24 Mean age 25 (7.2) years Gender: 19 women, 29 men	• Training on wobble board: 15 minutes a day, 12 weeks • No training All patients: 1 week compression bandage, 2 days immobilisation, elevate leg, avoid straining of ligaments, avoid resumption of sports until pain free in activities of daily life

OUTCOME MEASURES	NOTES

Assessments at 1 and 3 days
• Strength measurement: changes between day 1 and 3
  • abduction: (D) 21 N, (C) 21 N, (P) 20 N
  • adduction: (D) 17 N, (C) 21 N, (P) 20 N
• Weight bearing; changes between day 1 and 3
  • heel: (D) 9.5 kg, (C) 10.6 kg, (P) 9.5 kg
  • toes: (D) 11.1 kg, (C) 10.4 kg, (P) 8.8 kg
• ROM: change between day 1 and 3
  • dorsal flexion: (D) 5.1°, (C) 6.3°, (P) 5.1°
  • plantar flexion: (D) 5.6°, (C) 4.8°, (P) 3.4°
  • eversion: (D) 3.1°, (C) 3.4°, (P) 2.6°
  • inversion: (D) 2.9°, (C) 4.0°, (P) 2.8°
• Swelling (circumference): change between day 1 and 3
  • (D) 4.5 mm, (C) 5.0 mm, (P) 2.6 mm
• Volumetric measurement: change between day 1 and 3
  • (D) 30 ml, (C) 40 ml, (P) 36 ml
• Walking impairment: change between day 1 and 3
  • (D) 1.0, (C) 0.9, (P) 0.7
	7% drop outs
	no intention to treat analysis

Assessments before and after treatment • Volumetric differences in % (sd) of total foot volume: diapulse 4.7 (1.4), placebo 0.95 (0.8) • Pain reduction (0-10 scale): diapulse 16 / 25, placebo 8 / 24 • Ability to bear weight or walk: no data	one treatment only no intention to treat analysis
Assessments before and after treatment • Volumetric differences in ml (sd): pump 7.4 (5.9), wrap 3.7 (14.6), control 14.9 (13.7)	one treatment only

Assessments at 3, 13 and 21 days
• Return to duty;
  • 3 days: 3-day strap n= 24, 3-day gel cast n= 20, daily strap n= 36
  • 13 days: 3-day strap n=30, 3-day gel cast n=32, daily strap n= 24
  • 21 days: 3-day strap n=6, 3-day gel cats n=12, daily strap n=0
• Swelling by figure of 8 measurements: no data	

Assessments at intake and at 7 days • Soft tissue swelling at day 7: 46% vs 40% improvement • Severity of injury at day 7: 88% vs 79% improvement • Ability to bear weight: 36% vs 29% • ROM: no differences • Pain relief: no differences	18% loss to follow up co-intervention: paracetamol no intention to treat analysis
Assessments at 6 weeks and 6 months • Pain free weight bearing in weeks (SD); Cast 4 (1.5), Aircast 3 (1.5), Unna's 3.8 (2.3) • Circumference: no data • Mobility: no data • X-ray stability in degrees: Cast 4.8 (3.5), Aircast 2.6 (2.3), Unna's 3.6 (3.8) • Gain in stability in degrees (SD): Cast 7.6 (3.1), Aircast 9.7 (3.6), Unna's 10.5 (3.9) • Days off work (SD): Cast 27.3 (13.7), Aircast 23.1 (14.6), Unna's 23.9 (13.2)	3% drop outs 14 % loss to follow up no intention to treat analysis
Assessments at intake, 4-7 days, 6 and 12 weeks • Volume reduction in ml: week 1; 58 (14) vs 64 (14), week 6; 15 (18) vs 20 (10), week 12; 9 (10) vs 10 (10) • Pain at rest: week 1 (12 vs 7), week 6 (1 vs 0), week 12 (0 vs 1) • Pain during walking: week 1 (20 vs 20), week 6 (6 vs 5), week 12 (1 vs 1) • Pain during sports activities: week 1 (23 vs 23), week 6 (18 vs 18), week 12 (4 vs 7) • Relapses at 12 weeks: 6 vs 13 • Feeling of giving way: 0 vs 6 • Use of brace or tape: 4 vs 5 • Change in sports habits: not reported	21% loss to follow up no intention to treat analysis

Study	Participants	Intervention
Wilkerson et al, 1993	34 patients with an inversion injury, in previous 24 hours, divided over three groups of 12, 12 and 10 patients Mean age 20.35 (sd 1.8) years Gender: 28 males	• Elastic tape + Air Stirrup • Aircast Cryo /Strap at room temperature followed by modified Air Stirrup • Aircast Cryo /Strap frozen followed by modified Air Stirrup All patients: some form of cryo therapy once a day during acute phase
Williamson et al, 1986	154 patients with an inversion injury, in previous 48 hours, divided over two groups of 74 and 80 patients Prognostic variables not given	• Ultrasound • Sham ultrasound (no blinding procedures described) All patients: local ice packs, exercises and wobble board training, tubigrip and crutches when necessary
Zeegers, 1995	264 patients with X-ray confirmed ankle sprain, divided over four groups of 59, 60, 62 and 62 patients Mean age (range): 26.7 (15-49), 25.2 (15-50), 26.6 (15-50) and 23.9 (15-46) years Gender: 37, 46, 48 and 39 males Prognostic variables given	• Taping (Coumans) for 3 weeks, followed by 2 weeks of tubigrip • Adidas Adimed Stabil shoe combined with tubigrip for the night for 5 weeks • Aircast with tubigrip for 5 weeks • Elastic sock for 5 weeks All patients: walking instructions
Zwipp et al, 1992	100 patients with lateral ankle sprains, divided over four groups of, 52, 50, 48 and 50 patients Prognostic variables not given	• Surgery and cast immobilisation, NSAIDS, active ROM exercises, after 5-8 days application of walking cast for 5 weeks • Surgery and early functional orthotic treatment, NSAIDS, active ROM exercises, after 8-10 days fitting orthosis • Conservative management and cast for 3-5 days, walking cast for 5 weeks • Conservative management and cast for 3-5 days, followed by early functional orthotic treatment (see group B) All patients: after removal of cast/orthosis: 6 physical therapy sessions

Outcome measures	Notes
Assessments on ankle function (100 point scale) each day post injury: no difference	co-intervention: cryo therapy in all groups 29% drop outs no intention to treat analysis
• Combined 15 -point measure of swelling, discomfort, degree of limp, pain on inversion, pain on plantar flexion: no data provided: results reported as no difference	31% drop outs in ultrasound group, 29 % drop outs in sham ultrasound group no intention to treat analysis
Assessments at 1, 3 and 5 weeks, 3 months, 1 and 5 years • Normal walking after 1 week: Tape 81%, Adidas 91%, Aircast 76% and Elastic sock 72%; after 5 weeks: Tape 98%, Adidas 100%, Aircast 98% and Elastic sock 97% • Normal walking on stairs: no data • Normal cycling: no data • Stability after 1 week: Tape 65%, Adidas 83%, Aircast 76% and Elastic sock 65%; after 5 weeks: Tape 97%, Adidas 97%, Aircast 98% and Elastic sock 89% • Painfree at 1 week: Tape 49%, Adidas 60%, Aircast 41% and Elastic sock 42%; after 5 weeks: Tape 86%, Adidas 83%, Aircast 76% and Elastic sock 80% • Days off work: Tape 15, Adidas 17.1, Aircast 17.1 and Elastic sock 15.5 • Swelling at 5-6 weeks; Tape 16%, Adidas 5%, Aircast 21%, Elastic sock 26%	8% drop outs 42% loss to follow up at 3 months 25% loss to follow up at 1 year 39% loss to follow up at 5 years no intention to treat analysis
Assessments at 3 and 12 months • Ankle performance: unclear and no difference • Joint stability: unclear and no difference	7% loss to follow up at 3 months 16% loss to follow up at 1 year 20% loss to follow up at 2 years no intention to treat analysis

The two best studies are the ones by Barker et al[18] (70 points) and McGill et al[42] (63 points). Both study pulsed short wave therapy (PST) versus placebo.

Barker et al.[18] randomise patients with lateral ankle sprains over 2 groups of 34 and 39 patients. They administer PST on 3 consecutive days for 45 minutes to both groups, either in a verum or a placebo fashion. Additionally, all patients receive tubigrip, elbow crutches and analgesics. Assessments on 1, 2, 3, 8 and 15 days after randomisation show no efficacy of PST over placebo on range of motion, walking velocity, step length, pain, swelling or other walking indices. Methodological points were lost by the lack of an intention to treat analysis and a 10% drop out rate.

McGill et al.[42] randomise patients with lateral ankle sprains over 2 groups of 18 patients each. They administer PST on three consecutive days for 15 minutes in a verum and a placebo fashion. All patients receive additional tubigrip, crutches and analgesics. Assessments at 1, 2, 3, 8 and 15 days after randomisation show no effects on number of analgesics taken, pain, time to weight bearing on injured foot or swelling. Also here no intention to treat analysis was performed and on average 13.5% of patients were lost during follow up.

As can be seen from Table 3, quite a number of outcome measures per study have been used. Outcome measures that were most prominently reported upon were pain, swelling and days of sick leave. Since the format of most outcome measures differed, we used an effect size calculation to make the outcomes comparable over studies. Most of the studies failed to provide adequate data to calculate effect sizes. For these studies results are expressed as positive (+), negative (-) or undecided (?).
In table 4 the outcomes on pain, swelling and sick leave during the first six weeks are reported for the five previously detected subgroups.

Table 4: Effects of interventions in acute ankle sprains in the first six weeks

Intervention	Qualitative analysis Outcome according to reviewer *by study*	*conclusion*	Quantitative analysis Outcome according to data *difference (99% CI)*	*conclusion*	*combined outcome*
Brace vs other					
pain	+[27], ?[29], ?[36], +[54], -[57], +[57]	pain relief	1.03 (-0.40/2.46)[27,29,54]	no pain relief	undecided
swelling (in ml)	+[27], ?[29], -[57], +[57]	reduction	no data		reduction of swelling
days of sick leave	+[27], ?[37], +[39], ?[54], -[57]	undecided	0.55 (-0.64/1.74)[39,54]	no reduction	undecided
Tape vs other					
pain	-[16], -[19], -[48], -[57]	no pain relief	no data		no pain relief
swelling (in ml)	+[57]	reduction	no data		reduction of swelling
days of sick leave	?[14], ?[48], +[52], +[57]	reduction	-2.97 (--4.31/1.63)[48,52]	reduction	reduction
Bandage vs other					
pain	-[15], +[27], -[33], +[34], -[46], +[47]	undecided	0.72 (-295/4.38)[5,27,33,34]	no pain relief	undecided
swelling (in ml)	+[27], +[48], -[57], -[51]	undecided	-14.8 (20/-9.58)[51]	no reduction	undecided
days of sick leave	+[21], -[23], +[27], +[34], -[39], -[46], +[59]	undecided	-0.38 (-0.59/-0.17)[21,23,34,39]	reduction	reduction
Cast vs other					
pain	-[27], ?[29], +[33], ?[36], -[54]	undecided	-0.29 (-1.64/1.06)[27,33,36,54]	no pain relief	undecided
swelling (in ml)	?[21], -[27], ?[29], +[33]	undecided	0.17 (-0.06/0.27)[33]	no reduction	undecided
days of sick leave	-[21], -[23], -[27], -[29], ?[37], -[52], -[54]	increase	4.52 (3.94/5.1)[21,23,54]	increase	increase
Placebo vs other					
pain	-[17], ?[18], -[19], ?[25], ?[40], ?[42], -[50], ?[53]	no pain relief	-3.59 (-1.16/6.00)[17,42]	no pain relief	no pain relief?
swelling (in ml)	?[17], ?[18], ?[21], ?[40], -[42], -[49], -[50]	no reduction	-3.38 ml (-3.679/3.081)[17,50]	no reduction	no reduction
days of sick leave	-[17]	no reduction	no data		undecided

+ reduction compared to other intervention(s); - no reduction; ? no difference

From both the qualitative as well as the quantitative analysis brace therapy seems to provide some pain relief, although not statistically significant (quantitatively) nor consistent (qualitatively). The qualitative analysis regarding tape shows no pain relief. However, quantitative data supporting this claim are lacking. The other interventions do not show clear benefits. Placebo therapy shows no pain relief, both quantitatively as well as qualitatively.
Both quantitative as qualitative analyses show no clear evidence in reduction of swelling by the studied interventions, although brace shows some swelling reducing properties.
Reduction of sick leave is best accomplished by taping. Both quantitative and qualitative analyses show this. Cast therapy seems to prolong sick leave significantly (quantitatively). For the other interventions the efficacy of the studied therapies remains undecided. Few studies reported side effects. Complications due to surgical therapy were reported as deep venous thrombosis in 4 patients[32, 38], loss of sensation in 6 cases[58] or infection (2 cases).[58] Deep venous thrombosis also occurred in 2 patients treated with plaster of Paris[38], while severe dermal lesions were found in 3 patients treated with tape and in 1 patient treated with a bandage.[35] Tape was also mentioned to be more painful in some cases.[45]

Discussion

The value of a literature review depends on the success in obtaining the results of all trials that have been conducted on the issue of interest. Despite the intensive search strategy it is possible that relevant studies reported in fora not accessible to us or in languages incomprehensible to us were missed in this review.

When one assesses the methodological quality, the primary goal is to achieve an estimate of both the effects and the chance of bias in the results of the performed studies.
One method of assessing quality is by using a criteria list which tries to measure internal validity, precision of the study and relevance of the choices with respect to population, interventions and measures of effect. Assigning weights to the criteria anticipates the argument that some errors in trial design are more crucial than others. Although controversial, weighting does give some insight into the quality of the performed studies and provides an overview of the credibility of the results. It also enables the reviewed studies to be ranked to some extent, according to their methodological quality. Another advantage of our scoring system is that it is already well known[5-8, 60] and transparent. It permits the reviewer to allocate the distribution of methodological points elsewhere or to adjust scores if this is felt necessary.

The fact that systematic reviews use reported material to judge the quality of the trials under consideration is a consequence of this type of research, but is also cause for concern. It might very well be that the quality of the reported material does not reflect the quality of the primary research. Especially in trials where more reports of the same research question were generated, one tends to find differences, which in the end translate into differences in methodological scores.

We did not blind the reviewing procedure. From previous investigations[59] we found that blinding is not likely to bias the findings or results of the methodological score when articles are evaluated by skilled and trained people.

The 44 trials in this review can be considered the best available evidence when one studies the efficacy of conservative treatment regimens in ankle sprains. Because of the use of random allocation of the patients and the use of control treatments, their potential to supply valid answers is much larger than that of uncontrolled or non-randomised controlled studies. Nevertheless, the observed study quality ranged from very poor (9 points) to rather good (70 points). Many (avoidable) errors in design and data-analysis were noted. In the studied trials, also the more recent ones, there is still a reluctance (or sloppiness) to assure proper blinding. Of course, some interventions are hard to blind due to the nature of the intervention. However, in the here studied trials many interventions that used apparatuses could have been blinded and in all trials at least attempts could have been made to blind the assessors and data-analysts.

A considerable number of randomised clinical trials studies the efficacy of conservative treatment regimens in ankle sprains. However, many of the reviewed studies showed serious methodological flaws, and much information was lacking in the publications. In fact only two studies score above 60 points. There seems to be no relationship between methodological quality and year of publication, although trials reporting positive effects were of lower methodological quality. Apparently one continues to repeat methodological flaws over time, and low quality trials are still accepted by indexed (and peer reviewed) journals.
Therefore, we suggest that in the future more attention should be paid to appropriate blinding procedures (where feasible), avoiding drop outs or adjusting for these problems by using intention to treat analysis, to avoid or standardise co-interventions and to ensure better data representation.

We did try to pool the results of the trials on outcome measures as pain, swelling and days of sick leave. However the pooled results should be interpreted carefully. As can be seen from table 4, in many of the findings rather a small amount of trials contribute to the pooled measure of effect, since a large part of the studies did not present data that allowed pooling. Therefore, also a qualitative assessment of the data was performed, resulting in an overall assessment combining both quantitative and qualitative methods. As can be seen there is much uncertainty about the efficacy of the studied interventions.
Pooling of the two best trials on pulsed shortwave therapy (PST) was impossible; qualitative assessment showed no results of PST.

Larger and methodologically more adequate trials are called for in future to provide more definite and satisfying answers.

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3 EFFICACY OF 904 NM LASER THERAPY IN MUSCULOSKELETAL DISORDERS: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: This systematic review summarises the efficacy of 904 nm low level laser therapy (LT) in musculoskeletal disorders.
Method: In order to retrieve randomised trials computer aided searches of databases and of bibliographic indexes were performed. Furthermore, congress reports, reviews and handbooks were checked for relevant citations. Subsequently, all retrieved studies were scored on methodological quality.
Results: We found 25 studies that investigated the effects of 904 nm LT versus placebo or any other intervention, in subjects with a condition for which LT was thought a feasible intervention. Of these, 21 fulfilled our entry criteria, and were assessed in a blinded manner on methodological criteria. Overall, study quality ranged from poor to reasonable. Classification of the material into diseases studied, yielded no clear evidence for the efficacy of LT, except perhaps for knee problems and myofascial pain.
Conclusion: We conclude that 904 nm LT does not seem to be efficacious in the treatment of musculoskeletal disorders, but that further and improved research is needed to shed more light on its efficacy.

Keywords: systematic review, laser therapy, musculoskeletal disorders

INTRODUCTION

Laser therapy (LT) is a very young treatment modality. Medical lasers were first introduced in the early 1960's. Favourable results in surgery on humans were reported around 1965.[1,2] About 15 years later the first reports on LT in physiotherapy[3] and in acupuncture[4] appeared. The first randomised clinical trials were published in 1981 by Gallachi et al.[5] and Lewith et al.[6] Gallachi described the effects of LT in the treatment of cervical and lumbar pain, whereas Lewith conducted a randomised trial to evaluate the effect of infrared stimulation of local trigger points on the pain caused by cervical osteoarthrosis.
In the treatment of musculoskeletal disorders, lasers with varying wavelengths are used, mostly ranging from 632 to 904 nm. The use of LT has increased rapidly over the last few years, despite the lack of adequate insights into the biological working mechanisms and the extent of its effects.

The physical properties of the interaction between laser light and tissue can be divided into two processes; absorption and scattering. Absorption can be seen as the transformation of light energy into another form of energy, ultimately resulting in warmth dissipation. Absorption of laser light occurs mainly at a molecular level where three mechanisms can be distinguished. Either i) atoms are excited to higher modes of oscillation or ii) electron bonds are excited within the biomolecule or iii) rotation of (parts of) the biomolecule takes place.[7] Scattering, due to differing relative refractive indices of the various cellular substances and molecules, may be defined as a change in the direction of light propagation. Both absorption and scattering are wavelength dependent, and result in the loss of laser power into the irradiated tissue.
The aforementioned physical properties of laser irradiation have led to a series of theories, in which the term biostimulation occurs predominantly. During the past 15 years biostimulative effects of LT have been described by several authors. Biostimulation refers to the application of electromagnetic energy by LT to body tissues, supposedly influencing all kinds of cell functions.[8,9,10] The effects are thought to consist of stimulation or inhibition of biochemical, physiological and proliferative activities. The magnitude of the effect is reported to be dependent on wavelength, dosage and dose-intensity of LT.[11]
The "cellular communication" theory, which tries to explain the bio-effectivity of LT claims that, in case of an impairment or disorder, the energy state of a cell is changed, consequently altering the electromagnetic communication between cells. LT is thought to influence this communication in a positive way.[7,12] The "photochemical theory" offers an alternative explanation. The absorption of laser light takes place in tissue chromophores (photo acceptors). These chromophores may either be enzymes, membrane molecules or any other cellular or extracellular substances. Activation of these chromophores by LT is considered responsible for the postulated bioeffects.[13]

Neither theory has been thoroughly confirmed in research and the supposed underlying mechanism remains unclear. Moreover, recent research with 904 nm laser on tissue samples has failed to show any effects on cell metabolism, and hence has not provided corroborative evidence.[14] The lack of a convincing biological basis that explains the clinical effects induced by LT, serves to maintain the conflicts about proper dosage and treatment indications. Musculoskeletal disorders are thought to be influenced positively by LT in five main areas; analgesic effects, anti-inflammatory effects, nerve regeneration, regeneration of muscular tissues and of bone tissues.[12,13] Thus, a further analysis of the potential effects of LT on each of these areas seems imperative.
We decided to perform a systematic review to evaluate the efficacy of 904 nm LT.

Methods

Trials on 904 nm low level LT were identified by Medline and Embase searches (both up to 1996) and by checking the Database of the Cochrane 'Rehabilitation & Related Therapies Field' at Maastricht University, the Netherlands. Keywords used for the intervention under study were laser, low level laser therapy, infra red, light therapy in combination with rehabilitation, exercise therapy, physiotherapy and physical therapy.
Keywords used to describe the design were: controlled trials, experiments, clinical trials, randomised and evaluation studies. Additionally, Current Contents and Physiotherapy Index, reviews, congress reports, and handbooks on LT were checked. Retrieved references were followed-up by citation tracking. Papers published in English, French, German, Dutch, Spanish, Italian, Norwegian, Swedish and Danish were eligible for inclusion. Abstracts and unpublished studies were not included.

The selected studies had to fulfil the following criteria for inclusion in the review. The subjects in the study had to have a condition for which LT was thought a feasible treatment option and this had to be contrasted with placebo, no treatment or other interventions. The treatment regimen had to consist of 904 nm LT and the study design had to be a randomised clinical trial. This design is considered the paradigm for intervention studies because of its potential to provide a valid assessment of the efficacy of an intervention.[15,16]
The papers eligible for reviewing were blinded for author(s), journal and references and the lay-out of the original papers was changed. They were distributed to two reviewers (APV and AFL) who independently assessed the quality of the studies. They tried to reach consensus in a subsequent meeting on the items, on which they disagreed. If consensus could not be reached, a third (not blinded) reviewer (RAB) made the final decision.
Table 1 shows the criteria used for assessing the methodological quality of the trials. The list was originally designed by Ter Riet et al.,[17] and modified over the years by Koes et al.,[18] Van der Heijden et al.[19] and Assendelft et al..[20] It is based on generally accepted principles of intervention research.[15,16] The criteria list was adapted for LT, with respect to the intervention, laser parameters, and relevant outcome measures. Studies could earn points for methodological quality in five categories. They dealt with study population, interventions, blinding, outcome and data presentation and analysis. A maximum score of 100 points could be obtained. With respect to the evidence on efficacy of LT, a study was considered 'positive' if its author(s) concluded that laser treatment was more effective than the reference treatment. This usually corresponded with a statistical signi-ficant difference between treatments. However, a number of studies also reached this conclusion on pre-post group comparisons. In the results section we corrected for this. A study was labelled 'negative' if no difference between the study treatments was reported or if the reference treatment showed better results.

Results

Twenty-five trials[21-45] were identified that used some form of randomisation and compared 904 nm LT with a different intervention or placebo therapy. Of these, four papers were excluded from further reviewing; three were controlled clinical trials but not randomised[42,43,44] and one trial used healthy individuals, instead of patients.[45] One author[40,41] presented different arms of the same trial in separate articles. Since the methodology was reported differently as well, we describe the results of each arm (article) separately. The methodological characteristics of the remaining 21 trials are presented in Table 2, ranked according to their methodological score.

Table 1: Criteria for assessing methodological quality in randomised clinical trials of low level laser therapy.

Criterion *		Weighting
Study population (total points=49)		
A	Homogeneity	4
B	Randomisation procedure mentioned	10
	Concealed method of randomisation	10
C	Comparability of relevant baseline characteristics	6
D	Numbers of patients	9
E	Dropouts described for each study group separately	7
F	Loss to follow up not leading to bias	3
Intervention (total points=14)		
G	Intervention adequately described and performed	12
H	Co-interventions avoided or equal in study groups	2
Blinding (total points=18)		
I	Patients blinded	6
J	Therapist blinded	6
K	Observer blinded	6
Outcome (total points=12)		
L	Adequate outcome measures	5
M	Adequate follow up period	5
N	Description of side effects	2
Data presentation and analysis (total points=7)		
O	Mean or frequencies of most important outcome measures presented for each group	3
P	Intention to treat analysis	1
Q	Adequate correction for baseline differences of drop outs	3
		100

* Further details given in appendix

The methodological score ranged from 6 to 65 points. Seven out of the 21 trials used a cross-over design.[21,26-29,36,38] The descriptions of inclusion and exclusion criteria (A), the intervention (G) and blinding of the patient, therapist and/or observer (I, J, K) were in general satisfactory. The descriptions of prognostic comparability (C), drop outs (E), co-interventions (H) and side effects (N) were rather disappointing.

Quite a number of studies mentioned that the allocation procedure was randomised, but failed to mention how this was done or if the method of randomisation was concealed.

Some studies showed obvious flaws in their design leading to bias. Vasseljen[41] mentioned that patients and physiotherapists were 'fully aware of the treatment being given', whereas in the study of England et al.[25] the therapist was not blinded 'for reasons of safety and

practicality'. Rather large drop out rates were reported in the studies of Flöter et al.[26] and Lucas et al.,[32] where more than 15% and 27% of the patients dropped out, respectively.

Table 2: Methodological item scores per study

maximal score per item	A 4	B 20	C 6	D 9	E 7	F 3	G 12	H 2	I 6	J 6	K 6	L 5	M 5	N 5	O 3	P 1	Q 3	Total 100
Olavi, 1988 [36]							5								1			6
Beard, 1990 [21]							8						2					10
Gobelet, 1986 [27]							2		4	4					1			11
Dolan, 1988 [24]							8			4					1			13
Meier, 1988 [34]	4		2	3			6											15
Bihari, 1989 [22]							6	2	4		4			2				18
Longo, 1988 [31]	2		2				4	2			4		5					19
Seichert, 1987 [38]							9		4					2	3	1		19
Jensen, 1987 [29]	2				5		10		4	4								25
England, 1989 [25]	2			3			9		4		4	2			1			25
Ceccherelli, 1989 [23]	4			6			6		4	4			5		1			30
Flöter, 1988 [26]		10	2				10		4	4		1						31
Nivbrant, 1989 [35]	2	10		3	1		10		4	4		3	2		1			40
Lucas, 1995 [32]	2			9	2		8	2	4	4	4	2			3	1		41
Hansen, 1990 [28]	4	10					7		6	6	6	3		2				44
Rogvi, 1991 [37]	4	10		9	1		7	2		4	4	2	5					48
Siebert, 1986 [39]	2	10	2	9			10	2	4		4	5	5					53
Lundeberg, 1987 [33]	4	20					8		4	4	4	4	5		1			54
Vasseljen, 1992 [40]	4	10		9	7	3	10	2					5		3	1		54
Klein, 1990 [30]	4	10		9			10	2	4	4	4	5		2	3	1		58
Vasseljen, 1992 [41]	4	10		9	5	3	10	2	4	4		5	5		3	1		65

In correct allocation procedures were suspected in the studies by Longo et al.[31] and Dolan et al..[24] In the latter study the person who was responsible for the randomisation had experienced 'serious ethical problems' when he had randomised patients to the control group. This study also allowed for many co-interventions and groups were prognostically not comparable. Taken together the reviewed studies used 70 measures of effect in total, of which 30 were related to pain and 3 to the use of analgesics. Five studies reported on range of motion (ROM) and five on influence of LT on activities of daylife. Table 3 gives a short description of the study design, participants, interventions and outcome measures. Additional measures of outcome were very diverse, and made an estimate of the overall effect of LT difficult. The studies are arranged in alphabetical order by first author.

As can be seen from Table 3, quite a number of outcome measures per study has been used. However, comparison of outcomes between studies was hampered by incomparability of patient groups or diseases studied.

Table 3: Description of studies and outcomes

Study	Method	Participants	Intervention
Beard et al, 1990	Randomised cross-over trial, inadequately blinded, no intention to treat analysis	10 men and 4 women with symmetrical rheumatoid arthritis of the PIP joints No duration of illness No mean age	Six treatments in a two week period on index and middle fingers with laser (904 nm, peak power 1W; dose 0.5 J/cm^2) or sham
Bihari et al, 1989	Randomised trial, patient and observer blinded, no intention to treat analysis	45 patients with crural ulcers No duration of illness No mean age	Once per week treatments with IR laser (904nm, 4800 Hz), He-Ne laser (632.8 nm) and non coherent light. Average dosage 4 J/cm^2 per session
Cecherelli et al, 1989	Randomised trial, patient and therapist blinded, no intention to treat analysis	27 women suffering from painful myofascial syndromes in the cervical region Mean age 46 years Mean pain duration 73 months	Twelve treatment sessions 3 times a week on alternate days with laser (904nm, freq 1000Hz, peak power 25W, pulse duration 200ns, 1 J/cm^2 per treated area) or placebo laser
Dolan et al, 1988	Randomised trial, therapist blinded, no intention to treat analysis	33 patients with ulcers (stage 3 or 4) No duration of illness No mean age	Ultraviolet irradiation (235 mW/cm^2 UVA and 137 mW/cm^2 UVB and UVC), laser (904nm, pulse duration 200 ns, freq 1000 or 5000Hz, beam divergence <1 or 15°, 0.45 J/cm^2), placebo laser, control group. Each group was treated daily. The experiment was halted after 147 days
England et al, 1989	Randomised trial, patient and observer blinded, no intention to treat analysis	15 men and 15 women with supraspinatus or bicipital tendonitis. Mean age 48 years (range 18-78) Mean symptom duration 12.5 weeks (range 5-56)	Treatment for two weeks three times per week with laser (904nm, freq 4000Hz, pulse duration 180 ns, peak power 10 W, dose 3 mW for 5 mins: calculated dose 0.9 J/cm^2), dummy laser and drug treatment (naproxen sodium)
Flöter et al, 1988	Randomised cross-over trial, patient and therapist blinded, no intention to treat analysis	25 men and 35 women with chronic pain Mean pain duration 12.3 years (SE 12.9) Mean age 62.2 years (SE 12.4)	Twelve treatments of 10 minutes, 6 with laser (904 nm, peak power 80 W, freq 1000 Hz, pulse duration 120 ns, 0.038 J/cm^2) and 6 treatments with placebo
Gobelet et al, 1986	Randomised cross-over trial, patient and therapist blinded, no intention to treat analysis	16 patients with soft tissue rheumatoid arthritis in acute phase No duration of illness No mean age	Six treatments with He-Ne and IR laser (904 nm, peak power 60 W, freq 800 Hz, 9.6 mW; dose calculation not possible) and 6 sham treatments with He-Ne laser (632.8 nm, 1 mW)
Hansen et al, 1990	Randomised cross-over trial, patient, therapist and observer blinded, no intention to treat analysis	3 men and 37 women with chronic oro-facial pain Mean age 59 years (range 25-80) Mean pain duration 4.9 years (range 0.5-42)	Eight treatments during 4 weeks with 2 weekly sessions; per point 2 treatments of 60 seconds with laser (904 nm, pulse duration 200 ns, mean output 30 mW, beam diameter 7 mm, 4.7 J/cm^2) or sham

OUTCOME MEASURES	NOTES
Measured at initial assessment and after 2 and 4 weeks. Mean differences between laser and sham not given, only p-values; • joint range (p=1.02) • joint size (p=0.15) • joint tenderness (measurement failed)	No effect Data do not allow for pooling
Measured at initial assessment, last measurement at 9 months, other measurements unclear. Ratios given on; • wound healing; effective/not effective (IR laser 14/1, He-Ne laser 14/1, light 8/5)	Positive effect Data do not allow for pooling
Measured at initial assessment, at four weeks and at three months. • At 4 weeks mean difference between laser and placebo 12.2 (p=0.008)	Positive effect
Measured at initial assessment and every week for 22 weeks: • wound surface area; impossible to capture data	Positive effect Incorrect allocation procedure, prognostically inhomogeneous groups, many co-interventions Data do not allow for pooling
Measured at initial assessment and after 2 weeks: Mean differences between laser and dummy laser on; • range of movement; Ext 6°(p=0.005), Flex 15°(p=0.005), Abduction 20°(p=0.005) • pain (VAS) 2.5 cm (p=0.001) • stiffness (VAS) 1 cm (P=0.05) • function (VAS) 1.5 cm (p=0.05) • mobility (VAS) 2 cm (p=0.005)	Positive effect Data do not allow for pooling
Measured at initial assessment, and after 6 and 12 treatments. Mean differences between laser and placebo after 12 treatments on; • pain intensity (VAS) 1.07 cm • mood (VAS) 0.46 cm • duration of pain episodes; no data • number of pain episodes; no data	Positive effect Selective drop out rate of 15% Data do not allow for pooling
Measured at initial assessment, and after 6 and 12 treatments. Mean differences at 12 treatments on; • combined index for pain, mobility, sports capacity and work; 11.6 (p=0.005)	Positive effect Pre-post comparison of data Data do not allow for pooling
Measured during every treatment session. pain intensity; no data • analgesic consumption; no data • influence of pain during ADL; no data • pain duration; no data	No effect Data do not allow for pooling

STUDY	METHOD	PARTICIPANTS	INTERVENTION
Jensen et al, 1987	Randomised cross-over trial, patient and therapist blinded, no intention to treat analysis	3 men and 26 women with arthrosis of the knee Mean age 72 years (range 55-82) No duration of illness	Four weeks of treatment, 5 times per week, consisting of 2 weeks of laser treatment (904 nm, freq 190-250 Hz, pulse duration 200 ns, beam divergency 9-15°; calculated dose 0.397 J/cm^2) and two weeks of placebo treatment
Klein et al, 1990	Randomised trial, patient, therapist and observer blinded, no intention to treat analysis	15 women and 5 men with chronic low back pain Mean age 42 years (SE 9) Mean pain duration 8.7 years (SE 7)	Twelve treatments for 4 weeks, 3 times per week with laser (904 nm, freq 1000 Hz, pulse pause 200 ns, dose 1.3 J/cm^2, 20 minutes per area) or placebo laser
Longo et al, 1988	Randomised trial, observer blinded, no intention to treat analysis	120 patients with acute lumbago Age range (40-65) years No duration of illness	Laser (904 nm, freq 3000 Hz, pulse duration 200 ns, peak power 72 W; dose calculation not possible) placebo laser or 10,600 nm laser (freq 5500 Hz, 30% duty cycle, peak power 150W, divergence 1.5 rad)
Lucas et al, 1995	Randomised trial, patient, therapist and observer blinded, no intention to treat analysis	39 patients with crural ulcers (stage 3) Mean age 85 years No duration of illness	For a maximum of 6 weeks, 5 treatments a week with laser (904 nm, peak power 12 x 70 W,freq 830 Hz, pulse duration 150 ns, mean power 8 mW, 125 sec, dose 1 J/cm^2), placebo treatment, control treatment
Lundeberg et al, 1987	Randomised trial, patient, therapist and observer blinded, no intention to treat analysis	31 men and 26 women with tennis elbow Mean age 43 years (range 25-62) No duration of illness	Ten treatments, 2 per week with a duration of 300 sec with IR-Laser (940 nm, freq 73 Hz, dose 0.07 mW; calculated dose 0.021 J/cm^2), He-Ne laser (632.8 nm, peak power 1.56 mW) or no treatment
Meier et al, 1988	Randomised trial, not blinded, no intention to treat analysis	30 men and 28 women with infrapatellar tendinitis Mean age 34 years 42 men and 10 women with achilles tendinitis Mean age 38 years No duration of illness	12 treatments, for 3 weeks, 4 times per week with laser (632.8 nm, peak power 6 W + 904 nm, peak power 7 W, mean power 25 mW, pulse duration 180 msec; calculated dose 1.19 J/cm^2) or sham (632.8 nm, peak power 6 W). Treatment prolonged when not improved
Nivbrant et al, 1989	Randomised trial, patient and therapist blinded, no intention to treat analysis	30 patients with arthrosis of the knee Mean age 67 years no duration of illness	Six treatments, once a week with laser (904 nm, freq 5000 Hz, mean output 4 mW, beam diameter 0.07 cm^2, dose 0.7 J/point) or placebo laser

OUTCOME MEASURES	NOTES
Measured at initial asessment, after 2 and after 4 weeks: • pain during rest; period index, no data • pain during movement; no data • analgesic consumption; no data	No effect Data do not allow for pooling
Measured at initial treatment and after treatment. Mean differences between laser and placebo • range of motion; differences in degrees • rotation 0.1°; flexion 3.3°; extension 0.1°; lat. flexion 0.2° • isometric torque differences in foot pounds • isometric rotation 0.1°; isometric flexion 7.5°; isometric extension 3.3°; • isometric lat. flexion 3.2° • maximum velocity differences in degrees/sec • rotation 11.3; flexion 4.9; extension 1.2; lat. flexion 9.5 • pain (VAS) difference 0.4 cm • disability (VAS) difference 0.7 cm	No effect Co-intervention: active exercise programme for both groups. Pre-post comparison of data
Measured at initial treatment, after 3 and 5 treatments, 1 and 6 months, after 1 year • combined measure of effect on pain, antalgic posture and functional limitation; data unclear • relapses; no data	Positive effect Incorrect allocation procedure suspected Data do not allow for pooling
Measured at initial assessment and once a week • wound surface area difference in % (pre-post comparison); • laser 66.5% ± (9.6); control 19.6% ± (22.5); placebo 6.8% ± (37.2) • wound healing process; no data	Positive effect Selective drop out rate of 27%
Measured at initial treatment, after treatment series and after 3 months; mean differences between groups • pain (VAS) 0.4 cm • pain on resisted wrist dorsiflexion (VAS) 0 cm • pain on weight test (VAS) 0.1 cm • grip strength 3.3 cm • differences in nerve conduction • latency 0 msec; amplitude 3 V; temperature 1°C	No effect
Measured at initial assessment and every treatment week; combined index on pain and mobility. Ratios on; • knee after 3 weeks • laser cured/not cured 17/8; placebo cured/not cured 11/14 • achilles after 3 weeks • laser cured/not cured 16/9; placebo 7/18 • re-uptake of sports: knee • laser 62%; placebo; no data • re-uptake of sports: achilles • laser 70%; placebo no data • total improvement; no data	Positive effect Data do not allow for pooling Pre-post comparison of data
Measured at initial assessment, after treatment series; follow up after 1 week and after 4 weeks Mean differences between laser and placebo after treatment series, 1 week and 4 weeks • pain at rest (VAS) 1.3 cm, 1.3 cm and 1.2 cm • pain during movement (VAS) 1 cm, 0.8 cm and 0.7 cm • ability to walk (VAS) 1.2 cm, 1.1 cm, 0.2 cm • stiffness; no data; • sleep; no data • analgesic consumption; no data • general improvement; no data	Positive effect

Study	Method	Participants	Intervention
Olavi et al, 1988	Randomised cross-over trial, inadequately blinded, no intention to treat analysis	11 men and 7 women with 31 active trigger points. Mean age 36.8 years (SE 1.46) No duration of illness	Three minute laser irradiation at each trigger point on two different days, with laser (904 nm, pulse duration 150 ns, freq 1400 Hz, peak power 72 W, beam divergency 70 mrad, beam diameter 0.8 mm; calculated dose 2.7 J/point, actually measured 1.5 J/point) vs placebo
Rogvi et al, 1991	Randomised trial, therapist and observer blinded, no intention to treat analysis	20 women, 16 men with arthroscopic confirmed chondromalacia patella. Mean age 33 years (range 17-56) Mean complaint duration 5 years (range 1-22)	Eight treatments during five weeks with laser (904 nm, mean power output 17 mW, freq 1000 Hz) or sham
Seichert et al, 1987	Randomised cross-over trial, patient blinded, therapists unblinded, no intention to treat analysis, adequate base-line corrections	6 men and 9 women with soft tissue rheumatoid arthritis. Mean age 42.8 years No duration of illness	Ten daily treatments of 10 minutes consisting of 5 laser treatments (904 nm, peak power 5 x 5 W, freq 1200 Hz, pulse duration 200 ns, dose 5 x 1.2 mW; calculated dose 0.125 J/cm^2) and 5 sham treatments (632.8 nm, 6.5 mW); distance to skin was 15 cm and irradiated area 6 cm^2
Siebert et al, 1986	Randomised trial, patient and observer blinded, no intention to treat analysis	32 women and 32 men with epicondylopathy (n=41) and other tendinopathies (n=23) Mean age 47 years No duration of illness	Ten treatments on consecutive days, with a pause at the weekends with a duration of 15 min per treatment with IR-laser (904 nm, freq 1200 Hz, pulse duration 200 ns, mean power output 30 mW, dose 7.5 W/cm^2; calculated dose 6.7 J/cm^2) or He-Ne laser (632.8 nm, 10 mW)
Vasseljen, 1992	Randomised trial, patient, not blinded, no intention to treat analysis, adequate baseline corrections	17 women and 13 men with tennis elbow Mean age 45.5 years (range 25-70) No duration of illness	Eight treatments, thrice weekly with laser (904 nm, freq 880 Hz, pulse duration 175 ns, power output 1.5 mW per diode (12 diodes in total), skin dose 3.5 J/cm^2), for ten minutes, placebo-laser or traditional physiotherapy (ultrasound; 1.6 W/cm^2 for 7 minutes and deep friction massage as described by Cyriax for 10 minutes)
Vasseljen et al, 1992	Randomised trial, patient and therapist blinded, no intention to treat analysis, adequate baseline corrections	15 women and 15 men with tennis elbow Mean age 45.5 years (range 25-63) Mean symptom duration 3.5 months (range 1-12)	Eight treatments of 10 min three times per week with laser (904 nm, freq 880 Hz, pulse duration 175 ns, power output 1.5 mW per diode (12 diodes in total), skin dose 3.5 J/cm^2) or placebo

OUTCOME MEASURES	NOTES
Measured directly after last treatment: and at 15 minutes after last treatment • pain threshold (kg/cm²), mean differences between laser and placebo • 0.31 after treatment; 0.91 after 15 minutes	Positive effect Data do not allow for pooling
Measured at initial assessment and after the treatment series; mean differences between laser and placebo • pain intensity (VAS); 1 cm • pain location; no data • disability score; 1 point out of 20 • overall effect • laser cured/not cured 10/9; placebo 3/14	Positive effect, not significant 10% drop out rate Data do not allow for pooling
Measured at initial assessment, after 5 and after 10 treatments Mean differences between laser and placebo after 5 and 10 treatments respectively; • pain during rest (VAS) 0.1 cm, 0 cm • pain during movement (VAS) 0 cm, 0.2 cm • pressure pain (VAS) 0 cm, 0 cm	No effect Pre-post comparison of data Data do not allow for pooling
Measured at initial treatment, tenth treatment and 2 weeks after conclusion of treatment. Mean differences between laser and placebo on a 0-3 point scale on treatment 10 and after two weeks; • pain at rest; 0, 0 points • pain during movement; 0, 0.3 points • pressure pain; 0.1, 0.1 points • range of movement; no data • sensations during laser therapy; no data	No effect Data do not allow for pooling
Measured at initial treatment, at the end of treatment period, at 4 weeks and 5-6 months after treatment. Mean differences between laser and physiotherapy at end of treatment and at 4 weeks • grip strength (bar) 0.05, 0.1 • weight test (kg) 0.3, 0.1 • range of motion; no data • pain intensity (VAS) 1.2 cm, 1.1 cm • general improvement; no data	Positive effect Patients and therapists were fully aware of treatment given Data do not allow for pooling Many co-interventions
Measured at initial treatment, at end of treatment and at 4 weeks. Mean differences between laser and placebo at end of treatment and at 4 weeks • grip strength (bar) 0.05, 0.1 • weight test (kg) 0.3, 0.5 • range of motion (degrees) 3°, 1° • pain intensity (VAS) 0.2 cm, 0.4 cm • general improvement; no data	No effect Data do not allow for pooling

As can be seen 904 nm laser was used for the treatment of various diseases.

Three studies reported on the efficacy of LT in rheumatoid arthritis,[21,27,38] of which two studies reported no effect and only Gobelet et al.[21] found a positive effect using a pre-post comparison of the data. No between groups effect was present.

Two out of three studies[23,26] reported positive effects regarding the efficacy of LT on myofascial pain; the other study[28] reported negative effects. The positive study by Floter et al.[26] was hampered by a drop out rate of 15%.

Four studies[24,34,35,37] reported on the efficacy of LT in knee problems. Nivbrant et al.[35] and Rogvi et al.[37] found a positive, although not significant, trend towards efficacy, whereas Jenssen et al.[24] found no effect. The positive results from Meier et al.[34] were due to a pre-post comparison of the data, and disappeared in a between groups analysis.

Only the study by Olavi et al.[36] reported on the efficacy of LT on trigger points and showed favourable results, but this study was hampered by a rather large amount of non-informativeness (see Table 2).

Three studies[22,24,32] reported on efficacy of LT in the treatment of (pressure) ulcers. Although all three studies were positive, no firm conclusions about efficacy could be drawn here. The positive trend noted by Bihari et al.[22] was due to an incorrect analysis procedure, whereas the positive study by Dolan et al.[24] was hampered by an incorrect allocation procedure, many co-interventions and prognostically incomparable groups. The positive study by Lucas et al.[32] was flawed by a drop out rate of 27%.

Five studies reported on the efficacy of LT in tennis elbow[33,39-41] or tendonitis.[25] The study on tendonitis[25] and one study on tennis elbow[40] reported positive results, whereas the remainder noted no effects.

Finally, two studies reported on the efficacy of LT in low back pain.[30,31] Klein et al.[30] observed no effect but used a pre-post comparison analysis procedure, whereas Longo et al.[31] found an effect but an incorrect allocation procedure was suspected in this study.

Table 4 summarizes the available evidence per disease. As can be seen from this table there is no apparent disease in which LT excels in efficacy.

Table 4: Summary of the results of the review per disease

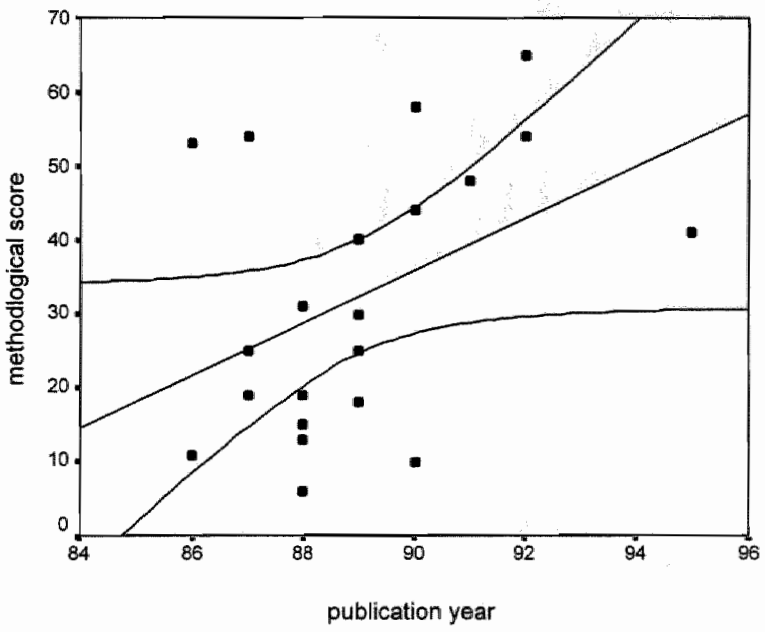
Disease (number of studies)	Outcome according to author(s)	Outcome according to reviewers
rheumatoid arthritis (n=3)	$+^{21}$, $-^{27}$, $-^{38}$	$-^{@}$, $-^{@}$, $-^{@}$
myofascial pain (n=3)	$+^{23}$, $+^{26}$, $-^{28}$	$+^{@}$, $+^{@}$, $-$
knee problems (n=4)	$+^{35}$, $+^{37}$, $+^{34}$, $-^{24}$	$+$, $+$, $-^{@}$, $-^{@}$
trigger points (n=1)	$+^{36}$	$-^{@}$
pressure ulcers (n=3)	$+^{22}$, $+^{24}$, $+^{32}$	$-$, $+^{@}$, $+^{@}$
tennis elbow (n=4)	$-^{33}$, $-^{39}$, $+^{40}$, $-^{41}$	$-$, $-$, $-$, $-$
tendonitis (n=1)	$+^{25}$	$+^{@}$
low back pain (n=2)	$+^{30}$, $-^{31}$	$-$, $-^{@}$

Pre-post comparisons are recalculated as between comparisons.
Superscript numbers identify the study, where; - = not effective, + = effective and ? = undecided.
@ identifies studies with a quality score of less than 40 points.

Studies reporting efficacy (according to the authors) had used on average dose of 1.3

Studies reporting efficacy (according to the authors) had used on average dose of 1.3 J/cm^2, whereas studies reporting no results had used an average dose of 2.1 J/cm^2. The use of different dosages per study could not be related to the year of publication of the study.
However, it is interesting to see that the methodological quality of the studies seems to be increasing over time (see Figure 1).

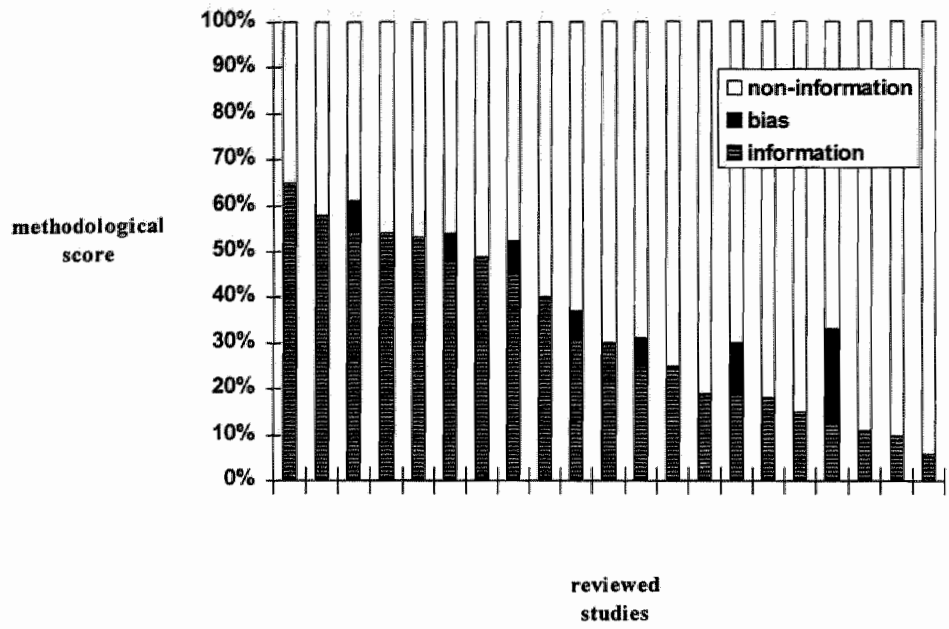
Figure 1: Methodological score versus publication year



It is also noteworthy that studies with a negative outcome (according to the authors) have on average a significant better methodological score (p=0.01). The average methodological score for positive studies is 25 (sd=13), and for negative studies 42 (sd=14). This phenomenon could be hinting at publication bias, showing that positive studies with low methodological quality get published more easily.

The methodological score of the studies is based on the items that are reported and well performed. Figure 2 shows that the missing points are mainly due to lack of information and only to a minor extent to bias.

Figure 2: Informativeness, non-informativeness and bias per study



Discussion

The value of a literature review depends on the success in obtaining the results of all trials (RCTs) which have been conducted on the issue of interest. It is possible that relevant studies reported in fora not accessible to us or in languages incomprehensible to us were omitted from this review. There are also indications that, especially, small clinical trials with negative results are not as easily published as small positive trials.[46] Thus, publication bias could form a threat to the validity of the results presented here.

There is a considerable number of randomised clinical trials that study the effects of LT. However, many of the reviewed studies showed serious methodological flaws, and much information was lacking in the publications. When assessing methodological quality the primary goal is to achieve an estimate of both the effects and the chance of bias in the results of the studies performed.[47,48] One method of assessing quality is by using a criteria list which tries to measure internal validity, precision of the study and relevance of the choices with respect to population, interventions and measures of effect. Assigning weights to these criteria anticipates the argument that some errors in trial design are more crucial than others. Although controversial, weighting does give some insight into the quality of the studies performed and provides an overview of the credibility of the results. It also enables the reviewed studies to be ranked to some extent,

according to their methodological quality. The fact that systematic reviews use reported material to judge the quality of the trials under consideration is a consequence of this type of research, but is also cause for concern. As seen in this review, the methodological score is more influenced by non-informativeness than by methodological flaws (see Figure 2). This is a pity, since non-informativeness could have been easily avoided by authors of studies or journal editors.

Of the 21 trials in our review 7 reported results that were not in concordance with a correct data-analysis procedure. When we corrected their positive outcomes by appropriate analysis, that is, analysis between groups instead of within groups, no effects of LT were found.

A study of the dosage in these trials did not reveal firm relationships between the dosage and the outcome of the study. In cases where no dosages were provided, but enough parameters were at hand to calculate the dose at skin level, this was done. Where necessary, specifications from the laser industry were obtained to be able to calculate the applied dosages as accurate as possible. The column "interventions" in Table 3 specifies which doses were calculated.

It should be noted that the actual laser dose is often lower than the one mentioned by the authors or the laser industry. We can think of five possible reasons for this. First, lasers used for medical purposes are allowed to deviate about 3% in output, thus delivering lower or higher output. Second, 904 nm lasers are notorious for cooling problems, since the output depends strongly on the rise in temperature of the laser resonator. The higher the temperature the lower the output. 904 nm lasers loose on average about 20% of their output in the first half hour.[49] A third factor which influences output negatively is the optical system of the laser apparatus. Mirrors, fibre-optics and lenses all take away about 25% of the dose each. For instance a three mirror system, often used in laser devices capable of scanning an area, lose 75% in output due to these mirrors. Fourth, divergence of the laser bundle, which can amount to up to 35^0 in 904 nm lasers, results in loss of energy.[50] Finally, reflection, refraction and absorption play an important role in diminishing output power, especially in laser scanning devices. Although these latter mechanisms are also claimed to be essential parts of the working mechanism, when output is lowered before reaching the target tissue, these phenomena work as barriers, preventing adequate dose delivery in the target tissue.

The 21 studied RCTs can be considered the best available evidence when studying the efficacy of 904 nm LT in musculoskeletal disorders. Because of their use of random allocation of the patients and the use of control treatments, their potential to supply valid answers is much larger than that of uncontrolled or non-randomised controlled studies. Nevertheless, the observed study quality ranged from very poor (6 points) to only reasonable (65 points). Many (avoidable) errors in design and data-analysis were noted. Therefore, we suggest that in the future more attention should be paid to larger sample sizes, improved prognostic comparability of the groups, and avoiding drop outs and co-interventions. Furthermore, mentioning side-effects and the use of between group comparisons could help answer the question of whether 904 nm LT has favourable effects in musculoskeletal disorders. Last but not least, better reporting of future studies is imperative.

We did not pool the results of the trials because patient characteristics, illnesses studied and treatments given were not similar enough to allow for pooling, neither as a total nor in subgroups. In addition, the methodological quality of the studies was low. Furthermore, sixteen out of 21 studies did not present data that allowed pooling.

In conclusion, the results clearly show that the efficacy of LT in musculoskeletal disorders is questionable. In none of the studied diseases in which LT is supposed to be effective could firm evidence be provided that LT was superior to placebo, sham or other treatment modalities. Also, outcome measures such as general improvement or change in range of movement, failed to show advantageous effects of LT.

We conclude that there is little evidence that 904 nm LT in musculoskeletal disorders is effective. Larger trials with better methodological quality could provide more definite and convincing answers.

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APPENDIX

Each criterion is applied independent of the other criteria.

A1 if the target population (with certain disease or complaints) is defined by means of criteria for selection of patients (in- and exclusion criteria) **2 points**

A2 if a homogenous study population is selected by means of restriction (to patients with or without certain characteristics or) **2 points**

B1 if the allocation procedure used is randomised, if the allocation of the selected patients to the treatment groups does not lead to bias **10 points**

B2 if the allocation procedure has been blinded **10 points**

C if the study groups are comparable for the relevant prognostic variables **6 points**

D1 if the smallest group immediately after randomisation is bigger than 25 patients **3 points**

D2 if the smallest group immediately after randomisation is bigger than 50 patients **3 points**

D3 if the smallest group immediately after randomisation is bigger than 75 patients **3 points**

E1 if there are no drop outs **7 points**, or

E2 if the number of patients that withdrew (drop outs) during treatment period after randomisation is given for each study group separately **2 points**

E3 if reason for withdrawal of patients (drop outs) during treatment period after randomisation is given for each study group separately **2 points**

E4 drop outs not leading to bias (less than 5% drop outs) **3 points**

F Loss to follow-up: all randomised patients minus the number of patients at the main moment of follow-up measurement for the main outcome measure (if not stated then judgement according to the opinion of the reviewers), divided by all randomised patients, times 100%

F1 if loss to follow-up is less than 20% in each group **1 point**

F2 if loss to follow-up is less than 10% in each group **1 point**

F3 if loss to follow-up does not lead to bias (according to reviewer) **1 point**

G1 type of the intervention, if control group: is it a placebo control group? **2 points**

G2 intensity/solution of the intervention **2 points**

G3 duration/site of each treatment session **2 points**

G4 frequency of treatment sessions **2 points**

G5 total number of treatment sessions **2 points**

G6 compliance described **2 points**

H if all co-interventions are avoided in the design of the study (until the most important moment of effect measurement) **2 points** or
if data about co-interventions are presented and comparable between the groups (until the most important moment of effect measurement) **2 points**

I1 if patients were blinded (unaware of the treatment given), or when patients were not familiar with the experimental intervention (fully naive) **3 points**

I2 when blinding is evaluated and successful (in more than 90% of the patients in every study group) **3 points**

J1 if the therapist who performs the

treatment is blinded (unaware of the treatment given) **3 points**

J2 if blinding of the therapist is evaluated and successful (in more than 90% of the patients in every study group) **3 points**

K1 if the observer who conducts outcome measurements is blinded (unaware of the treatment given) **3 points**

K2 if blinding of the observer is evaluated and successful (in more than 90% of the patients in every study group) **3 points**

L if the results are reported explicitly for the following outcome measures **maximum 5 points**

L1 pain

L2 global measure of improvement for the presented symptoms

L3 other outcome measures used (if relevant)

L4 other outcome measures used (if relevant)

L5 other outcome measures used (if relevant)

M1 if the timing of measurement is comparable **2 points**

M2 if the moment of effect measurement is immediately after the last treatment **1 point**

M3 if the moment of effect measurement is after 3 months or longer (after randomisation), or at an adequate time (according to reviewer) **2 points**

N if side effects were reported for each group separately **2 points**

O if frequencies or mean & standard deviation or median & quartiles are presented for most important outcome measure on the most important moment of effect measurement **1 point**

P intention-to-treat-analysis as well as an alternative analysis (worst-case-analysis which accounts for drop outs and missing values) is presented for most important outcome measure on the most important moment of effect measurement **3 points**

Q If adequate corrections for base-line differences or drop-outs on most important outcome measures are presented **3 points**

4 THE PROGNOSIS OF ANKLE SPRAINS

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ABSTRACT

We developed a new diagnostic tool for predicting the severity of ankle sprains just after injury. Since hard data obtained by diagnostic imaging techniques are still imperfect, we decided to use data from history taking and signs and symptoms that are part of the intake routine. During a three month period data were collected on thirty-five patients with lateral ankle sprains who visited the first aid department of the University Hospital of Maastricht. Assessments took place at intake and at two and four weeks after injury. Assessors were the first aid physician, a physiotherapist and the patient. Dependent variables were healed ankle in two and four weeks. Predicting variables were the data obtained at intake by the physician, the physiotherapist and the patient. The ability to predict outcome after two and four weeks was determined in a bivariate analysis, followed by logistic modelling.

Accurate prediction of recovery time at intake appeared to be possible. Best two weeks predictor was the modified function score, an accuracy of 97% was achieved. Four weeks prediction was most accurate when function score was used together with the report mark from the doctor and the palpation score (accuracy of 81%).

Keywords: ankle sprains, prognosis, functional recovery, diagnosis

Introduction

In the Netherlands one in four sports injuries concerns the ankle.[8] In hospitals four out of 1000 Dutch people are treated for ankle sprains every year. The costs involved are high. Moreover, expenses on sick leave and (semi)-permanent invalidity[4] are even higher, since about a quarter of all injured people are absent from school or work for more than seven days. Data from studies in other countries confirm these findings.[9,11,16,20]

Ankle sprains are quite common (in fact they are the most frequent form of ankle injury), yet there seems to be only consensus about initial treatment. Rest, Ice, Compression and Elevation (RICE) are considered to be appropriate and effective.[5,22] Rucinsky et al.[21] on the other hand question the effectivity of compression. Also there has been a shift from a static (plaster of Paris) to a more dynamic treatment approach (taping or brace) over the last decade.[7,12] Plaster of Paris evidently shows worse results than operation or taping, and the latter shows quicker functional recovery and re-uptake of work.[1,7,12] Efficacy of additional treatments like functional exercise therapy, laser therapy, ultrasound therapy or electro therapy show conflicting results.[1,3,7,13,14,23] Reasons for non-uniformity of treatment are, among other things, the difference in tradition and severity of trauma.

Being able to separate mild from severe cases has a major advantage; mild cases could receive less or modified treatment (and save costs), while more severe cases can be treated more suitably. Adequate treatment procedures could be initiated from the moment of diagnosis, if prediction of clinical outcome is possible. Probably early initiation of adequate treatment also reduces the reported 10-20 percent of chronic lateral ankle instabilities after treatment[6,11] to a major extent.

Lack of proper diagnostic criteria hampers discrimination between mild and severe sprain injuries. Yet, studies report a whole range of diagnostic tests for evaluating lateral ankle sprain injuries.[1,3,7,13,18,23] Severe injuries such as fractures and avulsion fractures can be adequately detected by X-ray examination. Van Moppes and Van den Hoogenband[18] found that the severity of the injury cannot be determined by means of stability and stress photography. Jongen[10] states that "the very limited value of X-ray photography in the diagnosis of ankle sprains, by means of stress tests or arthrography, is due to low reproducibility, low correlation with objective findings and complaints and investigator dependency." Other diagnostic imaging techniques such as CT-scan or ultrasound are difficult to interpret, so the extent of the damage is hard to determine. MRI (Magnetic Resonance Imaging) might be an adequate solution to determine the extent of tissue damage and indeed it might be used as a gold standard in studies to assess the validity of less expensive diagnostic instruments. However, costs of this technique are extremely high and go beyond everyday routine. In MRI diagnostics one assumes that tissue damage reflects the severity of the injury. It is questionable whether this is correct. It seems more appropriate to define the severity of injury in terms of prognosis. Injuries that heal in a short span of time are very likely to be mild injuries, where long-term recovery of ankle sprains suggests the presence of a severe injury. Of course, age and workload might prove factors modifying recovery rate.

We performed a study to elucidate diagnostic criteria for severity of ankle sprains. We decided to use data from history taking and signs and symptoms that are already part of the intake routine. Our primary study objective

was to examine whether it is possible to distinguish between mild and severe cases at intake (just after the injury has occurred), solely on the basis of these data. Outcome was defined on the basis of clinical course and functional recovery.

Material and Methods

During a three-month period (15 September - 15 December, 1992) data were collected from 35 consecutive patients with a lateral ankle sprain injury visiting the first aid department of the University Hospital of Maastricht. This is the only hospital in the area. The catchment area is rather large and about 50% of the population are known to report with an ankle sprain injury due to sports activities. After the patients had given informed consent, assessments of their ankles were made on three moments: at intake, at two weeks and at four weeks after injury. A routine follow-up was performed at six weeks. The three assessors, the first aid physician, a physiotherapist and the patient, were blinded for each other's data.

A standardized intake by the first-aid physician and an X-ray examination were carried out. Patients with fractures and/or severe injuries demanding operative interventions, as well as patients with open wounds were excluded from participation in this trial.

Hour and date of injury, time and hour of visit to the first aid department and activity during which the injury had occurred were recorded. Swelling, spontaneous pain, kissing pain (pain on the medial malleolus because the medial malleolus collides with the talus) and occurrence of previous ankle sprains in the last year, as well as ankle stability and function were judged.

The doctor asked which first aid measures had been taken immediately after injury and recorded data on sports participation and sports level. Most of these questions are part of the normal hospital routine, but were standardised for the purpose of the investigation. In addition, the doctor had to estimate the severity of the injury by means of a report mark at intake. The report mark ranged from 0 to 10 points, where 10 points represented the most severe injury. The doctor also predicted the chance of recovery at two and four weeks after initial injury. Finally the number of days after which the patient could go back to work or school and participate in sports activities had to be estimated. All these assessments were made at intake.

At intake, and at two and four weeks the physiotherapist carried out a palpation and stress test. This test consisted of detecting the most painful area by means of a pressure gauge and manual stress of the three lateral ligaments.

The severity of the ankle injury was assessed by means of a function score. The function score was derived from the Lysholm score[15] and adapted for ankle sprain injuries. Originally, the Lysholm score was developed for patients with knee problems. It measured the patients' capability of performing activities of daily life when assessing function in relation to level of complaints.

The function score consists of five categories (table 1) on which a number of points could be achieved. To reach 75 points or more, the patient had to score rather high in every category. This represents being able to maintain a normal gait pattern under almost all circumstances.

Table 1: Function score for assessment of lateral ankle sprains

Category	item	score
Pain	none	35
	during sports	30
	during running on non-level surface	25
	during running on level surface	20
	during walking on non-level surface	15
	during walking on level surface	10
	while carrying load	5
	constant pain	0
Instability	none	25
	sometimes during sports (less than once a day)	20
	frequently during sports (daily)	15
	sometimes during ADL* (less than once a day)	10
	frequently during ADL* (daily)	5
	every step	0
Weight bearing	jumping	20
	standing on toes of injured leg	15
	standing on injured leg	10
	standing on two legs	5
	none	0
Swelling	none	10
	light	6
	mild	3
	severe	0
Gait pattern	running	10
	normal gait	6
	mild limp	3
	severe limp	0

*ADL: activities of daily living

The patient filled out questionnaires at intake and at two and four weeks. Information was asked about severity of pain, ability to work (or go to school), ability to participate in sports activities and ADL handicap. At two and four weeks the patient was asked about the number of days he or she had already returned to work and/or performed sports activities. During the assessment period all patients received the same treatment regimen. Initial treatment consisted of a pressure bandage until swelling had been reduced or until the ankle could be dorsiflected to an angle of 90 degrees. Then a taping procedure according to the Coumans protocol[18] was applied. The taping was renewed every fortnight. After six weeks 27 of the 35 patients were cured. Five patients were still having difficulty in performing ADL activities and received further treatment (physiotherapy), while their ankle was supported

by a brace when necessary. Three patients were lost to follow up.

Statistical Analysis

The obtained data were first analysed bivariately and subsequently multivariately by means of logistic modelling[2,19] in order to be able to predict outcome. Dependent dichotomous variables were healed in two and four weeks respectively. A patient was considered healed when he or she obtained more than 75 points out of 100 on a function score, and received a score of less than two out of twelve points on the palpation and/or stress-test, measured at two and four weeks respectively. Predictor variables were all variables obtained at intake.

Results

From all thirty-five persons a complete intake form was obtained. Data on two and four weeks assessment was obtained in thirty-three and thirty-one of the initially enrolled patients respectively. The missing cases had no complete follow up, were missed by one of the assessors or had incomplete forms. Mean age of the patients was 28 years (sd 10; range 13-59). There were thirteen females and twenty-two males. Almost all patients had pain and swelling at intake; fourteen out of thirty-five patients had a swelling at intake that developed slowly, rather in days than hours. In about 50% of the cases the 'kissing' phenomena had occurred, and 43% could bear weight on the injured foot (and thus supporting full body weight).

Injuries had occurred during work (17%), during sports activities (57%) and at home or elsewhere (26%). Half of the sports injuries were due to playing soccer.

Of the cases 71% had some first aid measure taken; 66% had been treated with ice or water for cooling, 23% had been given a wrapping and about 20% had elevated the injured foot. Several variables were assessed by both the first aid physician and the physical therapist. These data were used as a cross-check instrument and were very similar. We chose to use the data obtained by the physician because he or she is the person who has to make a proper diagnosis in daily practice.

Table 2 presents two and four weeks outcome related to data from history taking and signs and symptoms. The table should be interpreted as follows: of the injured patients who where still injured after two weeks 93% had spontaneous pain at intake compared to 75% of the cured patients.

It appeared that the function score was an excellent predictor for healing within two weeks. This is no surprise since the function score is an index that combines the items pain, instability, weight bearing, swelling and gait pattern. Individually these items also relate rather well to outcome, especially weight bearing. The doctors' prediction of cure in four weeks is rather poor. Table 3 shows a sensitivity of 97% and a specificity of 100% for the function score as a diagnostic test, when discriminating between light and severe ankle sprain. Light and severe sprains are defined as being cured within two weeks or not.

Table 2: Prediction on two and four weeks outcome on data from history taking and signs and symptoms used by the first aid doctor

variables	two weeks outcome		four weeks outcome	
	injured (n=29)	cured (n=4)	injured (n=16)	cured (n=15)
spontaneous pain	93 %	75 %	93 %	80 %
kissing pain	55 %	25 %	50 %	47 %
instability* severe	15 %	0 %	21 %	7 %
moderate	54 %	50 %	71 %	43 %
not	31 %	50 %	7 %	50 %
weight bearing impossible	66 %	0 %	56 %	47 %
swelling	96 %	75 %	100 %	93 %
rather poor gait	100 %	75 %	100 %	93 %
function score ≤ 35	97 %	0 %	94 %	73 %
rather poor ankle function	62 %	50 %	71 %	50 %
> 2 painful points	66 %	25 %	64 %	47 %
> 2 ligaments painful on stress	62 %	0 %	62 %	47 %
recidive	27 %	25 %	13 %	47 %
prediction on:				
severity (report mark ≤ 5)	76 %	25 %	88 %	60 %
not cured within 2 weeks	88 %	50 %	93 %	79 %
not cured within 4 weeks	8 %	25 %	0 %	14 %
not at work within 7 days	15 %	0 %	29 %	0 %
not sports within 2 weeks	55 %	33 %	60 %	33 %

No data available of 2 patients at two weeks, and 4 patients at four weeks
* Instability was defined by the doctor on duty on a 3-point scale

Table 3: Prediction of two weeks outcome by function score

		Healed in two weeks (gold standard)		
		injured	cured	
Predicted by function score	injured (≤ 35 points)	28	0	Pred val +100%
	cured (> 35 points)	1	4	Pred val - 80%
		Sens 97%	Spec 100%	

Healing within four weeks was best predicted by the report mark for severity that the physician gave at intake together with the function score and palpation score. Yet, in six out of 31 patients the wrong prediction is made. Table 4 shows the results of prediction by these variables at the moment of intake, when compared with healing in four weeks. Sensitivity was 81% and specificity was 80%.

Table 4: Prediction of four weeks outcome by report mark, function score and palpation score

		Healed in four weeks (gold standard)		
		injured	cured	
Predicted by report mark from doctor, function and palpation score	injured	13	3	Pred val + 81%
	cured	3	12	Pred val - 80%
		Sens 81%	Spec 80%	

The probability function defining the odds to be cured within four weeks conditional on the intake criteria report mark, function score and palpation score reads as follows:

$$Prob = \frac{1}{1 + e^{(-0.81 + report\ mark \times 0.54 - function\ score \times 0.07 + palpation\ score \times 0.34)}}$$

We also developed an even more complex model, where interaction terms of the variables were considered. In that case sensitivity was 88% and specificity was 87%. Yet, adequate use of such a model might prove difficult in daily practice.

Discussion

Exploratory studies, such as this one, have their limitations. Although they can provide new insights in underinvestigated territories, the results from such studies should be confirmed to be good predictors in subsequent studies. It should be kept in mind that the designed test was developed on the basis of a small study population.

In this study we tried to solve a diagnostic problem by studying prognosis. We chose prognosis in terms of recovery time as a measure of severity. Taking prognosis as a gold standard for diagnosis requires proper discrimination between diagnostic indicators, prognostic determinants and adequate outcome parameters. Some variables in this trial are hardly sensitive to change at all (e.g., age) but are good predictors for prognosis. Other variables (e.g., pain) measure change very satisfactorily, but are of no value when predicting variables at the onset of the complaint. Every sprained ankle is painful, thus pain cannot discriminate between light and severe injuries (table 2).

It seems strange that the doctors' prediction of cure in four weeks performs rather poorly, while their report marks for severity performs rather well. Apparently doctors use different data for diagnosis and prognosis. It seems that in order to predict prognosis they use variables with poor predictive value.

It can be argued whether our operationalisation of being healed within two and four weeks is valid. Choosing cut-off points to declare a patient cured or not after two weeks

is very subjective. The cut-off point for being healed was defined as obtaining more than 75 points on a function score and scoring less than two out of 12 points on the palpation and/or stress test. This definition is arbitrary. As suggested in the prologue, accurate prediction on the basis of walking ability just after injury seems feasible. For being able to walk, minimal 35 points need to be obtained. If we look at the function score, combinations of the following items fulfill these conditions; the ability to walk on level surface (10 points), a rather low level of instability (10 points), being able to stand on one leg (10 points), allowing for gait (3 points) and another 3 points for not too much swelling.
The fact that it was possible to predict outcome in acute lateral ankle ligament injury is promising. Not only is the accuracy of the diagnostic instrument used here high, it also totally depends on non-imaging techniques. For two weeks prediction a standardised scale suffices, where for four weeks prediction, additional information from the doctor and the palpation score is necessary.
It is shown that although long-term prediction may require more elaborate models, accuracy of the prediction can be fairly high. As a tool for everyday practice we think that a rule of thumb might be feasible. When a given patient (i) scores more than 35 points on the function score and (ii) is assessed by the doctor as having a report mark of more than five out of ten (see table 2), the patient has a high probability of being cured within two weeks.

Conclusion

Through the use of history taking and signs and symptoms that are already part of the intake routine it seems possible to predict the severity of the injury fairly accurately. Prediction of two weeks recovery can be done based on one variable: function score, whereas four weeks prediction appears to involve more variables: function, opinion of the doctor and palpation score. Often used variables such as pain and swelling appear to be poor predictors on their own. Further investigation is necessary to confirm these findings.

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5 EFFICACY OF LASER THERAPY IN ANKLE SPRAINS
DESIGN OF A RANDOMISED CLINICAL TRIAL

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ABSTRACT

Studies on low intensity 904 nm laser therapy in the treatment of musculoskeletal disorders show conflicting results. Yet, on the basis of an earkly systematic review we concluded that 904 nm laser therapy for musculoskeletal disorders seems to be promising, when compared to placebo laser therapy. Quick pain relief and fast functional recovery are reported to be the most prominent claims of laser therapy.

This paper presents a rationale of choices regarding the patients and type of treatment when designing a randomised, double blind, clinical trial on 904 nm laser therapy, as well as safeguards concerning optimum dose, constancy of dose and double blinding the actual laser therapy.

Keywords: RCT, 904 nm laser, lateral ankle sprain

Introduction

Since the early nineteen eighties the biological and medical effects of low level laser therapy (LLLT) have been studied. During this time, many articles have appeared in North American and European journals. Nevertheless, the subject remains controversial, with many medical scientists doubting the validity of the claims attributed to LLLT.[1,2]

Two aspects have attributed to this controversy. Firstly, many of the reports on low level laser therapy show serious methodological flaws and, therefore, the validity of the reported effects is questionable.[3] Secondly, the lack of convincing elucidation of biological mechanisms explaining the clinical effects induced by LLLT, also hampers acceptance. Moreover, arguments and specu-lation about proper dosages and treatment indications arise from this lack of know-ledge.[4]

On the basis of a systematic review of 35 randomised clinical trials it was concluded that LLLT for musculoskeletal disorders seemed to be promising, when compared to placebo laser therapy.[3] Randomised clinical trials in rheumatic diseases and post traumatic injuries showed quick pain relief and a quicker functional recovery; yet, in the treatment of soft tissue injuries conflicting results were reported. Owing to the poor methodological quality of the studies, conclusions about the effectivity of LLLT should be drawn with caution.

In this paper we present the proposed study design of our randomised clinical trial (RCT) on the efficacy of LLLT for the treatment of acute lateral ankle sprains. Several arguments can be given to publish a trial design before publishing the data generated from the actual trial. First, it prevents publication bias. It is known that only part of the studies which have been performed are actually published, and unpublished studies sometimes show different results from the published ones.[5] Second, critical assessment of the study method independent of study outcome is possible, thus allowing the reader to check for explicit choices regarding design, dosimetry and study population. Third, the publication of choices made in measures of effect and analysis strategies prohibits selective data reporting, and prevent data dredging or skewing.

This paper discusses choices regarding the selection of patients and the selection of the appropriate LLLT wavelength and dosage. In addition, the most important outcome measures and preferred data analysis strategies are presented.

Selection of eligible patients

When selecting patients for an RCT on the efficacy of LLLT, four guiding principles apply. Firstly, the patients need to present with a lesion that appears frequently, for reasons of trial efficiency and relevancy. Secondly, to be effective, the lesion has to be located just under the skin surface and should allow a clear localisation of the region. The rays from a laser apparatus as used in physiotherapy only permit superficial and small area irradiation. Thirdly, the laser therapy is intended to serve as an additional therapy and, therefore, the basic treatment protocol should allow for standardisation to prevent differences in co-interventions among the contrasted groups in the trial. Fourthly, to test the claim that LLLT gives quick pain relief and fast functional recovery, a type of injury has to be chosen which presents initially with a fair amount of pain and loss of function.

A type of disorder that meets all these criteria

is a lateral ankle sprain. Lateral ankle sprains occur frequently. In the Netherlands alone, 4 out of 1000 people are treated for ankle sprains every year.[6] In our intended research location, the University Hospital of Maastricht, about 600 patients per year seek medical aid after a lateral ankle sprain. Ankle sprains are superficial injuries and can be localised easily. In addition, it seems possible to standardise the treatment regime. Lastly, ankle sprains typically present initially with quite a lot of pain and functional impairment.

SELECTION OF INTERVENTION

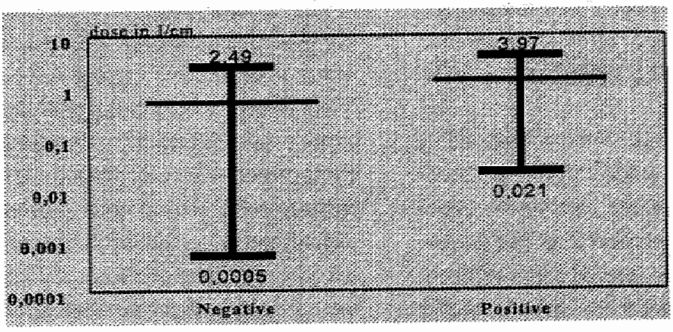
Although laser therapy has been investigated and used clinically for about twenty years,[7] biological mechanisms and clinical effects are hardly understood. Until now it remains unclear which wavelength and what dosage, if any, should be used to obtain optimal results.[4,7] Based on theoretical arguments and previous research we tried to determine the most optimal wavelength for treating soft tissue injuries.[8]

Laser light with a wavelength between 790 and 950 nm penetrates the skin most easily. Comparison with wavelengths of 600 to 790 nm shows considerable differences in penetration depth. Wavelengths of 600 to 790 nm penetrate the tissue up to about 4 nm, whereas wavelengths between 790 and 950 nm penetrate the tissue up to 5 cm or more.[8] The highest intensities for the latter are reached just below the skin. Recent research shows that not only the depth which laser light reaches, but also the intensity of laser light at that particular depth determines whether laser therapy can be successful or not.[9] A certain amount of incident photon energy (threshold dose) is needed to trigger biochemical reactions in the target tissue, in order to be effective. Results from randomised clinical trials about the efficacy of LLLT laser[3] show that trials with positive findings report an average dose at skin level of 1.3 J/cm^2 (SD 1.31),[10-18] whereas negative trials report an average dose of 0.49 J/cm^2 (SD 0.72).[19-27]

The therapeutic dose of LLLT varies enormously. Reported doses at tissue level range from 0.0005 J/cm^2 [27] to 3.97 J/cm^2.[15] No adverse reactions from 904 nm LLLT have been reported in the normal therapeutic range. Go et al.,[28] reported adverse skin reactions in doses above 450 J/cm^2. These doses lie far above the therapeutic maximum that is used in physiotherapy.

Figure 1 shows the dose, range and outcome of the reported trials. Positive trials appear to have used higher doses throughout the entire range than have the negative trials.

Figure 1: Trial outcome related to average dose and 95% CI's



As discussed previously, not only the total dose but also the intensity seems relevant. One can imagine that reaching a threshold in a shorter time might be economical, yet too high an intensity might show adverse effects. No one knows yet whether there might not be a rebound effect when applying high doses and/or high intensities to biological tissue.[7]
In addition, the inconstancy of the laser output has proved to be problematic in previous trials. True pulsed infrared lasers are notorious for loss of output power when they heat up after some time. Therefore, the manufacturer of the system for use in the present proposed trial constructed a very heavy duty probe incorporating an adequate and efficient internal cooling system. In tests the output remained constant within a 1% margin for over half an hour.[9] Since the actual irradiation takes 200 seconds only, this seems quite satisfactory.
To err on the safe side and hopefully not to miss the effect of laser therapy we have opted for two doses: a low dose of 0.5 J/cm^2 and a high dose of 5 J/cm^2; both to be reached in 200 seconds.
Before, during and after the trial the laser output will be checked by an independent party using a calibrated power meter.

Patient recruitment

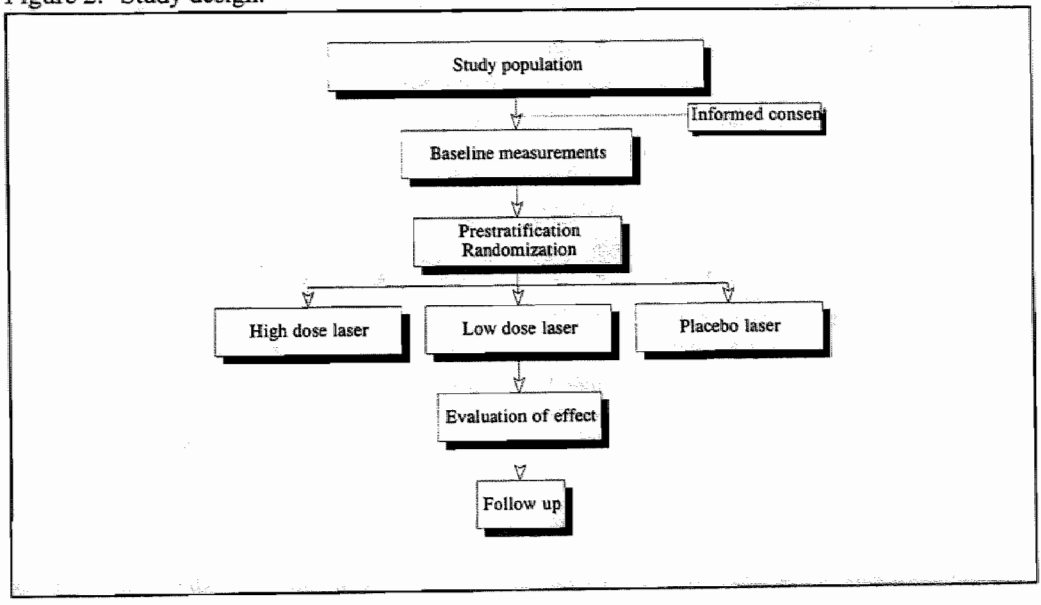
Patients with an acute lateral ankle sprains who report to the Accident and Emergency department of the Department of Surgery of the University Hospital of Maastricht are considered potential candidates to enter the trial.
Exclusion criteria are based on the following arguments. Patients for whom effect modification is likely to influence outcome are excluded. Therefore, patients who have been treated with LLLT previously are excluded. Also excluded are patients with an ankle sprain that occurred less than a year ago, patients with previous ankle sprains that were surgically treated, multiple trauma patients, patients who are not able to walk properly because of inadequate lower limb function, and patients with congenital laxity of the joints. Patients over 65 years of age are also excluded because of possible degenerative processes in the joints and therefore possible delayed recovery compared to other participants in the trial. Finally, patients are excluded if they present with an ankle injury older than 48 hours, since laser is believed to be most effective in fresh injuries and also for the sake of a comparable timing of the beginning of the intervention.
A second argument for exclusion are contra-indications. Patients who present with fractures or open skin lesions or who are suspected of having tumours or systemic diseases are excluded. Patients are also excluded if they are younger than 18 years of age, because of non-closed growth discs. Exclusion on ethical grounds is applicable if no informed consent is obtained or if the injury is considered to be too mild. In addition, in very mild injuries laser is thought not to be able to prove its potential effects.
Practical reasons for exclusion apply to patients who live too far away from the hospital, or who are suspected of being unable to attend all therapy sessions (e.g., going on holiday, working abroad).

Informed consent and randomisation

When a patient meets the entry criteria, the informed consent procedure will be completed. The patient will sign a letter that provides all the relevant information on the study including the 33% chance of receiving a placebo laser treatment. The outcome of interviews and physical examination will be

recorded, and the patient will fill out a questionnaire to provide baseline data. After that, randomisation will take place, using a computer generated random sampling set obtained from a blinded statistician.
Prestratification by severity of injury (mild versus severe) and sports participation (does or does not participate in sports activities) will be performed to prevent unequal distributions by chance for these important prognostic factors between the treatment groups. The random permuted block size is three. The patients are then randomly allocated to three groups receiving either laser treatment with a high laser dose, laser treatment with a low laser dose or placebo laser treatment. All groups will receive a basic standardised treatment regimen. The study design is presented in figure 2.

Figure 2: Study design.



SAMPLE SIZE

The study aims at enrolling 225 patients, divided over three treatment groups of 75 persons. Group size was determined on the results of a pilot study.[29] In this pilot study, after five days the laser group showed 20% more pain relief than the placebo group, and 33% more pain relief than the control group. To be able to reproduce a 20% pain relieving effect, with a power of 80% (1-β) and a two tailed level of significance (α) of 5% (p=0.025), between the laser group and the placebo group, group size was calculated at 50 persons. In view of what we perceived to be clinically relevant effects, we have opted for a large trial with 75 persons per group.

STUDY TREATMENTS

The standardised treatment consists of four days elastic wrapping followed by three and a half weeks of bracing with a Push® ankle brace. We will also provides standardised patient information and standardised home exercises. The home exercises consist of

simple mobility exercises for the ankle, re-learning to take weight on the injured foot, and later on to regain balance and ensure a proper gait pattern.

The additional 904 nm laser therapy will be similar in all three groups except for the dose. The laser apparatus to be used is a Uniphy Phyaction 796®, with a peak power of 25 Watts, a pulse duration of 200 nsec and a circular beam profile with an effective irradiated area of 6.4 mm^2. The laser dose in group one will be 0.5 J/cm^2, the laser dose in group two will be 5 J/cm^2 and group three will be treated with a nonexistent laser beam (placebo).

The target tissue is considered to lie maximally 1 cm under the surface of the skin. Energy density at tissue level is calculated to be 0.07 J/cm^2, 0.7 J/cm^2 and 0 J/cm^2 for each dose, respectively. Laser output will be validated before the start of the trial and will be checked at three monthly intervals during the trial.[9]

The three output levels will be randomised over 21 settings of the apparatus. Each patient will receive a treatment code ranging from 1 to 21, which he or she will keep throughout the intervention period. We will randomise the settings on the apparatus in order to minimise speculation on effectiveness, as well as not having to stop the trial in case of unexpected unmasking of one of the settings. In the unfortunate event of unmasking there will still be 20 settings left to complete the trial.

The target location will be considered to be the most painful area on the lateral side of the ankle as indicated by the patient and checked by means of a pressure gauge. This will be circled with a water proof marker during the first visit. Before applying laser therapy, the area will be cleaned with alcohol (96%) to minimise backscatter and reflection from fatty skin. Then the probe will be placed in the centre of the circumscribed area, directly on the skin, thereby preventing energy loss due to divergence and minimising reflectance loss from the stratum corneum. All groups will be following the same treatment schedule: 5 treatment sessions in the first week, 3 treatment sessions in the second week and 2 treatment sessions per week in the third and fourth week. Thus, twelve treatment sessions in total will be followed.

At each treatment session every patient will receive 200 seconds of laser therapy. Both patient and therapist will be fully blinded. In all three groups the laser apparatus will produce a soft sound and a display will read "warning: laser beam active!". Both patient and therapists will also wear protective glasses. After therapy the patient will replace his or her brace or elastic wrapping.

Outcome measures

In this trial we consider the most important outcome measures those that are capable of reflecting the actual state of the complaint from the patients' point of view. Therefore we have opted for subjective measurements as the primary measure of effect. Quick pain relief and hastened functional recovery are most prominently reported as the major effects of LLLT in soft tissue injuries.[1,3] Therefore, primary measures of effect are (i) change in perceived pain measured on a visual analog scale (VAS)[30,31] and (ii) speed of functional recovery measured on a function scale.[32] Both measures of effect are validated and have already proven their eligibility.[31,32]

As secondary measures of effect the following items will be measured;

- subjective recovery on a 11 point scale (range 0 - 10, where 0 represents no recovery and 10 total recovery),[29]
- limitation in Activities of Daily Living (ADL) on a 11 point scale (range 0 - 10, where 0 represents totally limited in ADL and 10 no limitation in ADL,[29]
- validated measurement of swelling of the ankle by means of volumetric difference at intake and at several points in time during the intervention,[33]
- validated pressure threshold test (in kg/cm^2) by means of an algometer,
- clinical evaluation by a blinded doctor on the basis of a standardised interview and a physical examination,[32]
- moment of re-uptake of sports (measured in days since the onset of trauma),
- total days of sick leave from work, school or housekeeping due to ankle trauma (measured in days since the onset of trauma),
- measurement of satisfaction about recovery rate and received treatment on a 11 point scale (range 0 - 10, where 0 represents not satisfied and 10 totally satisfied),
- measurement of number of relapses during the one year follow-up.

Table 1: Timing of the measures of effect

	Days									Weeks			Months			Y
Instrument	intake	2	3	4	5	6	7	10	14	3	4	6	3	6	9	1
Standard Therapy & intervention	#	#	l/@	l/@	l/@	l/@	l/@	l/@	l/@	l/@	l/@					
Patient information, interview data & X-ray	x															
Check for blinding											x					
Pain (VAS)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Modified Lysholm	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Subjective recovery	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ADL (VAS)	x		x	x	x	x	x	x	x	x	x	x				
Swelling	x			x			x	x	x	x	x					
Pressure threshold	x			x			x	x	x	x	x	x				
Judgement of doctor	x											x				
Amount of instability	x											x				
Function of ankle	x											x				
Sports participation		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Sick leave		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Satisfaction recovery											x	x				x
Satisfaction treatment											x	x				x
Relapses												x	x	x	x	x

standard treatment; l laser therapy; @ brace

Data management and statistical analysis

Data will be stored on a personal computer in dBASE IV™.[34] The data entry routine has already been tested and used for storing data from a diagnostic trial on ankle sprains.[32] Data will be checked for completeness, inconsistencies and for the range of possible values. Subsequently, the data will be further analysed with SPSSWIN/PC™.[35] Analysis will be performed in a blinded manner; the identity of the three treatment groups will only be revealed after the final analysis has been carried out.

Prognostic comparability of baseline characteristics among the three study groups will be assessed critically for age, first-aid measures taken, level of sports participation and work setting by an independent team of experts in a blinded fashion. In addition, outcome and relevancy of the effects will be assessed before blinding is broken.

Two data sets will be prepared; an intention to treat set and a per protocol set. For the intention to treat set missing data will be substituted with the last known data per patient.

Primary analysis will be done by means of analysis of variance. In case of significant differences between groups, secondary analysis will be performed by means of Student t-tests.

Short term and long term analyses will be performed. For the short term the outcomes of interest are change in perceived pain and functional recovery. The differences between groups at five, ten and fourteen days will be regarded as the primary endpoints. Additionally, resumption of work and sports activities, as well as swelling and pressure threshold tests and patient satisfaction will be analysed for the short term results. Finally, a check for blinding will be carried out.

For the long term follow up (one year) the emphasis will be placed upon functional recovery, re-uptake of work and sports activities. Also the number of relapses will be analysed. The onset of the first relapses will be used to compare groups by means of a survival analysis model.

In the event of a positive outcome a cost-effectiveness calculation will also be made. Change in perceived health status, change in medical consumption and change in work absenteeism are regarded as important outcome measures. They will be related to direct medical costs such as personal and material costs. It will be interesting to relate effects in laser and placebo treatment groups separately to the cost of treatment.

Discussion

There have been a number of trials on the efficacy of LLLT and soft tissue injuries. However, these studies have been criticised for methodologic and dosimetric flaws, as mentioned in the introduction. The lack of power from previous studies is to be tackled by having a large sample size. Here we aim at having three groups, each containing 75 patients. If reported effects from the pilot study[29] prove to be consistent, the results should be reproducible with a two-sided alpha of 0.05 and a power of 80% in groups of 50 patients each.

If the results of the pilot do not hold, we feel that the credibility and clinical relevance of LLLT will be questionable, and think that larger trials than this one will not be a logical next step.

The only reason for large groups is the necessity of being able to detect relapses. In the literature[36,37,38] the number of relapses is estimated at about 30% within one year. Should laser prove effective, a reduction of 50% in the number of relapses is thought to be clinically interesting. If these effects exist, it can be shown with a one-sided alpha of 0.05 and a power of 80% with 75 patients per group. Consequently, if we expect improvement, one-sided testing seems feasible.

From another point of view it is also concievable that if low level laser therapy indeed provides quick pain relief, it does not automatically imply that recovery will follow at the same pace. People who feel free of pain will possibly undertake activities which might be unwise from the perspective of ligamentous repair processes. Therefore, relapses can also be regarded as a measure of effect in the negative direction.

The comparison of low and high doses will hopefully show which is the most effective. If it turns out that neither dose is more effective than a placebo, we will conclude that (1) LLLT is not effective in the treatment of ankle sprains and (2) there seems to be little reason to apply LLLT on soft tissue injuries, since we expect the assumed working mechanisms to be the same for all soft tissue injuries.

Another problem in previous studies was the lack of adequate dosimetric descriptions.[8] In this study we state an explicit dose at skin level and at tissue level. We will control for adequate output of the laser device throughout the trial.

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6 EFFICACY OF LOW LEVEL LASER THERAPY IN ANKLE SPRAINS: SHORT TERM RESULTS OF A RANDOMISED CLINICAL TRIAL

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ABSTRACT

Objective: To test the efficacy of laser therapy on lateral ankle sprains as an addition to a standardised treatment regimen, we conducted a trial in which high dose laser, low dose laser and placebo laser therapy were compared with each other.
Design: A randomised, double blind controlled clinical trial with a total follow up time of one year. Patients, therapists, assessors and analysts were blinded for the assigned treatment.
Setting: The trial was performed in an ambulatory care setting.
Patients: After informed consent and verification of exclusion criteria 217 patients with acute lateral ankle sprains were randomised to three groups.
Interventions: 12 Treatments of laser therapy in four weeks as an adjunct to a standardised treatment regimen of four weeks of brace therapy.
Primary outcome measure: pain as reported by the patient.
Results: Intention to treat analysis of the short term results showed no statistical significant difference on the primary outcome measures pain (p=0.41) and function (p=0.50), although the placebo group was slightly in favour. The placebo group performed significantly better on days of sick leave (p=0.02), and at some points in time for hindrance in activities in daily life and pressure pain, as well as subjective recovery (p=0.05). Subgroup analysis did not alter these findings.
Conclusion: Neither high nor low dose laser therapy is effective in the treatment of lateral ankle sprains.

Keywords: laser therapy, ankle sprains, RCT

Introduction

Each year 4% of the population in western countries sprain their ankle, about half of them during sports activities. Some 20% of these patients need medical care.[1]

Treatment cost and absenteeism from work form not a negligible part of direct and indirect costs. About 21% of all people who have had ankle sprain injuries are absent from school or work for about 7 days.[2] In addition, sports absenteeism and the emotional burden of sudden incapacitation influence a relatively simple injury negatively.

One of the new treatment modalities for ankle sprain injuries is low level laser therapy (LT), which is either used as an additional therapy, combined with taping or bracing, or as a stand-alone therapy.[3,4]

Working mechanism

During the past 20 years, several authors have postulated biostimulative effects of LT. Biostimulation refers to the application of electromagnetic energy by LT to body tissues, which is supposed to influence all kinds of cell functions.[5,6,7] The effects are thought to consist of stimulation or inhibition of biochemical, physiological and proliferative activities. Since both stimulation and inhibition seem possible, one also refers to bio-effects of LT. The magnitude of the effect is reported to be dependent on wavelength, dosage and dose-intensity of LT.[8]

One theory which attempts to explain bio-effectivity of LT claims that, in the event of an impairment or disorder, the energy state of a cell is changed, consequently altering the electromagnetic communication between cells. Laser therapy is thought to influence this communication favourably.[9,10]

Photochemical theory offers an alternative explanation. The absorption of laser light takes place in tissue chromophores (photo acceptors). These chromophores may either be enzymes, membrane molecules or any other cellular or extracellular substances. Activation of these chromophores by LT is considered responsible for the postulated bio-effects.[11]

Neither theory has been thoroughly confirmed in research; the supposed working mechanism remains therefore unclear. Moreover, recent research on tissue samples, using various dosages, have failed to show any effects on cell metabolism, and hence has not provided corroborative evidence.[12]

The lack of a convincing biological background explaining the clinical effects induced by LT not only hampers further explanation, but also generates uncertainties about proper dosage and treatment indications.

In a preliminary trial[13] with 38 patients, LT was found to have substantial pain relieving qualities. After five days the laser group showed 20% more pain relief than the placebo group. To reproduce these results, with a power of 80% (1-β) and a two tailed level of significance (α) of 5%, we would need 50 persons per group. In view of what we perceived to be clinically relevant effects, we opted for a larger trial with 75 persons per group.

Study design

We compared the effects of high dose LT and low dose LT with that of a placebo in patients with an acute lateral ankle sprain. LT acted as an additional therapy, applied upon a standardised treatment regimen which consisted of four days elastic wrapping followed by three and a half weeks of bracing

with a Push® ankle brace. Efficacy was evaluated on the basis of four and six week results and three, six, nine and twelve month results. The four week follow up period was intended to reflect the actual healing process, and to provide preliminary information about resumption of work and sports participation. Follow up to one year was carried out to detect long term effects and possible relapses. In this article we present results up to four weeks as short term results.

The study was approved by the medical ethics committee of Maastricht University and the University Hospital of Maastricht (the Netherlands). A detailed description of the protocol can be found in chapter 5 of this thesis.

Selection of patients

Patients who reported to the Accident and Emergency department of the University Hospital with an acute lateral ankle sprain, who were between 18 and 65 years of age and whose injury was not older than 48 hours, were selected by the doctor on call. Patients who had had an ankle injury in the preceding year, or those patients who had received previous ankle surgery were excluded. In addition, patients with fractures (confirmed by obligatory radiography), direct open trauma and underlying abnormalities of the foot and/or legs were excluded. Finally, those with systemic diseases (e.g. rheumatoid arthritis or diabetes) and mental handicap were excluded, as well as people with difficulties with the Dutch language. Patients could also be excluded for practical reasons, for instance if they lived too far away or if they could be expected not to attend all therapy sessions (e.g., going on holiday, work abroad).

Eligible patients were given a detailed description of the intended treatment procedure, and were informed about the chance of receiving a placebo therapy as well as having a right to withdraw from the trial at any time. After receiving this information in writing, the patients gave their informed consent to participate. The following morning they were seen by a trained research assistant who checked inclusion and exclusion criteria. The research assistant also kept a record of the baseline interview and physical examination and the patient filled out a questionnaire to provide baseline data.

Randomisation

Patients were stratified by severity of injury (mild versus severe) and sports participation (does or does not participate in sports activities) to prevent unequal distributions by chance for these prognostic factors between treatment groups.[14] After informed consent, 217 consecutive patients were randomly allocated to one of three groups by means of a computer generated table, with a random permuted block size of three. The first group (n=74) received laser therapy with a low dose, the second group (n=72) received laser therapy with a high dose and the third group (n=71) received placebo laser therapy. Patients, therapists, outcome assessors and analysts were blinded for the treatments given.

Interventions

All patients received a standardised treatment regimen, which consisted of four days elastic wrapping followed by three and a half weeks of bracing with a Push® ankle brace. We also provided standardised patient information and standardised home exercises. The home exercises consisted of simple mobility exercises for the ankle, learning to bear weight on the injured foot, and later on to

regain balance and ensure a proper gait pattern.

The additional 904 nm laser therapy was similar in all three groups except for the dose. The laser apparatus delivered a peak power of 25 Watts, a pulse duration of 200 nsec and a circular beam profile with an effective irradiated area of 6.4 mm^2. Laser dose at skin level in the low dose group was 0.5 J/cm^2, in the high dose group 5 J/cm^2 and 0 J/cm^2 in the placebo group.

The target tissue was considered to lie at a maximum of 1 cm under the surface of the skin. Energy density at tissue level was calculated to be 0.07 J/cm^2, 0.7 J/cm^2 and 0 J/cm^2 for each dose, respectively. Laser output was validated before the start and at the end of the trial and was checked at regular intervals during the trial.

The most painful area on the lateral side of the ankle was chosen as target location. The patient indicated the painful area. This was consequently checked by means of an algometer. The target area was circumscribed with a water proof marker during the first visit. Before applying laser therapy, the area was cleaned with alcohol (96%) to minimise backscatter and reflection from fatty skin. Then the probe was placed perpendicularly in the centre of the circumscribed area, directly on the skin, thereby preventing energy loss due to divergence. All three groups followed the same treatment schedule: 5 treatment sessions in the first week, 3 treatment sessions in the second week and 2 treatment sessions per week in the third and fourth week. Thus adding up to twelve treatment sessions, during a four weeks intervention period.

At each treatment session every patient received 200 seconds of laser therapy. Both patient and therapist were fully blinded. In all three groups the laser apparatus produced a soft sound and the display read "warning: laser beam active!". Both patient and therapists also wore protective glasses. After therapy the patient replaced his or her brace or elastic wrapping.

We allowed patients to take standardised pain medication (Paracetamol, 500 mg, maximum dosage one tablet every four hours). These drugs were provided at intake, and the patients kept a record of the amount they took.

Outcome measures

In this trial we considered the most important outcome measures those that were capable of reflecting the actual state of the complaint from the patients point of view. Therefore, the primary measures of effect were perceived pain measured on a 0 to 10 point scale and function. For measuring pain we specifically chose a 0 to 10 point scale because this way of grading pain is familiar and easy to use by patients and other assessors. Moreover it is quite similar to the Dutch report-mark system. Numerical rating scales, with a range from 0-10 points, provide reliable and consistent measures of clinical pain intensity when compared to VAS, both in acute as well as chronic pain measurements.[14, 15, 16]

The idea for a function scale was derived from the Lysholm score and adapted to ankle sprain injuries. Originally, the Lysholm score was developed for patients with knee problems. It measured the patients capability of performing activities of daily life when assessing function in relation to level of complaints. When considering the functions of the lower limb, items such as weight bearing, pain on function and instability are quite similar for the ankle as for the knee. Therefore we decided to use these items for the original Lysholm scale and added swelling and gait pattern. The thus developed contruct has been developed further with the

use of Guttman scaling techniques to give proper weights to the various items. After that it was validated by clinical experts (content validity). Consequently, it was tested in a pilot sample of 35 patients and the present study provided the material for further validation on 217 patients.

Secondary outcome measures were total days of sick leave from work, school or house-keeping due to trauma and moment of re-uptake of sports (measured in days since the onset of trauma). We also measured hindrance in limitation in Activities of Daily Living (ADL) on a 0 to 10 point scale, swelling of the ankle by means of the volumetric difference between swelling at intake and at several points in time during the intervention, pressure threshold test (in kg/cm^2) by means of an algometer,[17,18] subjective recovery on a 0 to 10 point scale and satisfaction about recovery rate and received treatment on a 0 to 10 point scale.

Success of blinding, side effects and relapses were evaluated at the end of the intervention period. All measurements were carried out in a blinded fashion by means of a standardised protocol.

Data management and statistical analysis

Data were stored on a personal computer in dBASE IV™[19] and were checked for completeness, inconsistencies, for the range of possible values and for protocol deviations. Subsequently, the data were analysed with SPSSWIN/PC™ statistical software.[20] Analysis was performed in a blinded manner and according to the intention to treat principle: all participants, including those with poor compliance and those who had withdrawn from therapy, remained in the group to which they were assigned by randomisation. Subsequently, a per-protocol analysis was performed to see whether protocol deviations influenced the results.

The primary and secondary outcome measures were compared between the three treatment groups. Differences between the means of groups at 5, 10, 14 and 28 days, respectively, were compared by using a two-tailed ANOVA model. The decrease in the primary outcome measure pain was compared between the groups by regression analysis. For each patient the individual curve was estimated, where after mean group scores of the estimated regression coefficients were compared by using ANOVA.

Subgroup analyses were carried out to determine whether particular subgroups showed other outcomes than the treatment groups as a total. Dichotomised subgroups were formed according to age (cut-off: 35 years), sports-participation (yes/no), gender (female/male), job (sitting/standing work).

The coding was broken after final analyses had been carried out.

Results

From September 1, 1993 till December 31, 1995, 217 consecutive patients were included and randomised. All patients were present for baseline measurements; yet, 2.1% of all treatment sessions were missed and thus formed gaps in the data set (43 out of 2064 treatment sessions; 0.4% from the low dose group, 0.7% from the high dose group and 1% from the placebo group). Three categories of missings were detected.

Seven patients missed only one treatment session due to illness or work. These missings were substituted by the mean value of preceding and following measurements in the data-set in both intention to treat as well as per-protocol analyses.

Eight patients missed 21 treatment sessions because (they felt) they were cured. For these

patients the last known entry was substituted for the intention to treat analysis. Two of these patients belonged to the low dose group, one patient to the high dose group and 5 patients belonged to the placebo group. Three patients withdrew from the trial without being cured. These were two patients from the low dose group: one patient missed two treatment sessions in a row and the other stayed away 10 days after trauma; one patient from the high dose group stayed away 8 days after initial trauma. For these patients the last known value was substituted for the intention to treat analysis.

The three treatment groups were similar with respect to demographic characteristics and baseline measures, although age and gender differed slightly in the high dose group, compared to the other two groups (Table 1).

Table 1: Comparison of treatment groups with respect to demographic and prognostic variables

	Low laser	High laser	Placebo
No of patients	74	72	71
Mean age in years (sd)	30.2 (9.6)	33.2 (10.4)	30.9 (10.3)
Sex (female/male)	30/44	17/55	22/49
Baseline measurements			
mean pain score (sd)*			
during the day	3.7 (2.7)	3.8 (2.5)	3.6 (2.8)
in the morning	4.8 (2.9)	4.4 (2.9)	4.2 (3.0)
mean number of pain tablets (sd)	0.5 (1.0)	0.8 (1.4)	0.7 (1.4)
mean pressure pain in kg/cm^2 (sd)			
calcaneo fibular ligament	3.2 (1.9)	3.3 (1.9)	3.5 (1.9)
anterior talofibular ligament	1.7 (1.3)	1.8 (1.4)	1.6 (1.0)
posterior talofibular ligament	3.6 (2.0)	3.1 (2.0)	3.3 (1.8)
mean sports category (sd)†	2.2 (0.8)	2.1 (0.8)	2.1 (0.8)
mean prognosis on recovery (sd)‡			
2 weeks	7.2 (1.2)	6.9 (1.2)	7.4 (1.2)
4 weeks	9.4 (0.8)	9.2 (0.8)	9.4 (0.9)
blue/white collar ratio#	37/35 (2)	37/35 (5)	35/32 (4)
work load			
light	21	17	20
normal	19	18	19
heavy	28	30	27
very heavy	6	7	5

* measured on a 0 to 10 point scale (0 no pain, 10 extremely painful)
† measured on a 4-point scale (0 no sports participation, 1 recreational, 2 competition sports, 3 professional)
‡ measured as a report mark (0 not recovered at all, 10 fully recovered)
# numbers between brackets indicate unemployed persons

Figure 1 shows scores of the groups for 'pain during the day'. All treatment groups improved, and, the placebo group showed consistently more improvement from day 8 onward compared to the other groups. However, comparison of the entire curves using regression analysis showed no significant differences between the three groups (p=0.41).

Figure 1: Daily pain score of the treatment groups for four weeks; (0=no pain, 10=extremely painful)

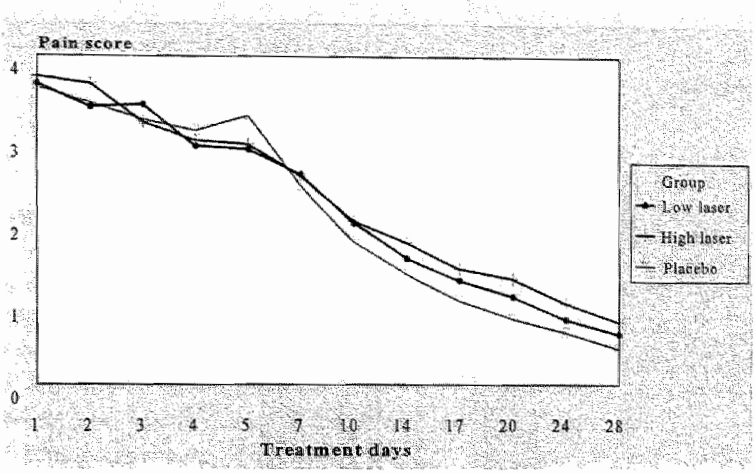

Table 2 provides information about recovery on primary and secondary measures of effect.

As can be seen from the table the outcomes on function score on day 10 and 14, days of sick leave, hindrance in ADL on day 10, pressure pain on anterior talofibular ligament on day 14 and subjective recovery reach statistical significance. In all these cases the placebo group performs better than the laser groups.

No side-effects of laser therapy were reported or observed during or after treatment.
The per-protocol analysis showed similar results. Analysis for success of blinding showed that placebo laser therapy was not unmasked by the patients (see Table 3).
Subgroup analyses revealed no difference in outcome for age (cut-off: 35 years), sports-participation (yes/no), gender (female/male), job (light/heavy work).

DISCUSSION

In this study we tried to overcome flaws encountered in a systematic review of 36 randomised trials of LT.[21] Attention was paid to prognostic comparability at baseline level, group size and blinding of the entire procedure. Furthermore, explicit details were given about dose and intensity of LT. An independent party checked for adequate dosimetric output of the laser device before, during and after the trial.

In this trial we compared a low dose, a high dose and placebo group. To determine whether the claimed effects of LT were present we incorporated a placebo group, as new technologies are known to be surrounded by novelty effects, and thus have the potential of enhancing placebo responses. We opted for a low dose and a high dose group because of the ongoing debate on adequacy of the dose. The low dose represented a dose and intensity

Table 2: Measures of effect (mean and standard deviation) on several days during treatment and P-values of differnces in means using ANOVA.

		Lower laser	High laser	Placebo	P-value (two sided)
Perceived pain (mean, sd)@	day 5	2.8 (2.2)	2.9 (2.1)	3.3 (2.4)	0.60
	day 10	2.0 (2.0)	2.1 (1.9)	1.7 (1.9)	0.48
	day 14	1.6 (1.9)	1,7 (1.7)	1.4 (1.7)	0.42
	day 28	0.6 (1.0)	0.8 (1.2)	0.4 (1.0)	0.14
Function score*	day 5	25.1 (15)	24.7 (15.1)	25.7 (14.8)	0.92
	day 10	42.2 (16.1)	44.1 (14.9)	49.9 (15.9)	0.01
	day 14	56.3 (16.1)	56.0 (15.7)	60.0 (17.1)	0.03
	day 28	73.6 (14.7)	74.3 (17.5)	76.4 (14.9)	0.5
Days of sick leave (mean, sd)		12.5 (11.1)	11.2 (10.0)	7.8 (9.2)	0.02
Re-uptake of sports in mean days (sd)		27.3 (7.9)	27.4 (7.5)	25.3 (9.8)	0.26
Hindrance in ADL (mean, sd)@	day 5	4.4 (2.6)	4.9 (2.8)	4.8 (2.7)	0.42
	day 10	3.7 (2.7)	3.3 (2.4)	2.6 (2.2)	0.03
	day 14	2.8 (2.6)	2.7 (2.1)	2.0 (2.1)	0.08
	day 28	0.9 (1.5)	1.0 (1.5)	0.8 (1.6)	0.83
Decrease in swelling of the ankle in % of total foot volume (mean, sd)	day 5	1.6 (2.6)	2.1 (2.5)	2.0 (2.6)	0.44
	day 10	3.5 (2.8)	4.3 (3.2)	4.1 (2.6)	0.20
	day 14	4.4 (2.9)	4.8 (3.3)	4.9 (3.0)	0.55
	day 28	5.2 (3.8)	4.5 (3.5)	5.2 (3.2)	0.39
Pressure pain in kg/cm^2 (mean, sd)	day 5				
on calcaneo fibular ligament		4.0 (1.8)	4.0 (1.8)	4.0 (1.8)	1.00
on anterior talofibular ligament		2.3 (1.7)	2.4 (1.4)	2.2 (1.4)	0.71
on posterior talofibular ligament		3.9 (1.8)	3.9 (1.8)	4.2 (1.8)	0.71
	day 10				
on calcaneo fibular ligament		5.0 (1.4)	4.8 (1.5)	5.0 (1.4)	0.81
on anterior talofibular ligament		3.4 (1.7)	3.6 (1.6)	3.5 (1.5)	0.68
on posterior talofibular ligament		4.9 (1.5)	5.1 (1.3)	5.0 (1.4)	0.56
	day 14				
on calcaneo fibular ligament		5.3 (1.3)	5.5 (1.2)	5.5 (1.1)	0.69
on anterior talofibular ligament		3.9 (1.7)	4.6 (1.4)	4.5 (1.6)	0.01
on posterior talofibular ligament		5.3 (1.2)	5.4 (1.2)	5.4 (1.1)	0.65
	day 28				
on calcaneo fibular ligament		5.7 (0.8)	5.8 (0.7)	5.7 (0.7)	0.91
on anterior talofibular ligament		5.3 (1.0)	4.9 (1.2)	5.1 (1.2)	0.09
on posterior talofibular ligament		5.7 (0.9)	5.4 (1.2)	5.7 (0.8)	0.32
Subjective recovery (mean, sd)@		8.6 (0.9)	8.7 (0.9	8.9 (0.8)	0.05

@ Measures on a 0 to 10 points scale (not limited 0, severely limited 10)

Table 3: Succes of blinding per group

Which treatment did you get?	Low laser	High laser	Placebo
Do not know	61%	60%	69 %
Low dose	21%	19%	13 %
High dose	12%	14%	13 %
Placebo	6%	7%	3 %
	100%	100%	100 %

used in current physiotherapy practice. Since there are claims that this dose is too low to be effective, we also incorporated a high dose group in the trial. In this fashion we would be able to determine a dose-response relationship in case of cumulative effects, an inadequate dose-response relationship in case of too low a dose, or perhaps a rebound effect in case of too high a dose. Although no adverse effects of LT were reported by the patients themselves, the outcome measures clearly showed a delayed recovery in the LT groups.

The chosen wavelength was derived from the results of previous trials. It seemed that trials on musculoskeletal diseases and sports injuries which used 632 nm laser showed, on average, less positive results than trials using 904 nm laser.[21] Possibly the relative lack of penetration depth of 632 nm laser may have played a part in these findings, although other factors such as inadequate dosimetry may also have influenced these results.[22]

In a pilot study (n=38) with a dose setting that was comparable to our low dose group we found LT to have beneficial effects.[13] After five days of treatment the pain score appeared to have decreased significantly more in the laser group than in the placebo group. In the present investigation a slight effect of LT on decreasing pain score was also found at 5 days (see Figure 1). However, this difference was only 4%, whereas in the pilot trial a difference of 33% was noted. In the present investigation, both laser groups performed less than the placebo group.

All patients were allowed to take standardised pain medication provided by us at intake. Pain medication was registered throughout the trial. It turned out that after two days of intervention almost everybody had stopped the use of medication. Moreover, drug intake was comparable between the groups. Since the differences in effect described here started to take place after five days of treatment, drug intake could not have influenced the outcome.

When considering secondary measures of effect, days of sick leave shows a worrying difference between the placebo and the laser groups. Compared to placebo a mean difference of 3.4 days for high dose laser and 4.7 days for low dose laser may be regarded highly cost-ineffective, especially when taking into account the extra medical costs of laser treatment. For the total trial it meant for the laser groups a loss of 593 working days when compared to the placebo group.

We conclude that LT is not effective in the treatment of ankle sprains. On the basis of this trial, therapists should reconsider the use of LT as an additional treatment of ankle sprains.

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7 EFFICACY OF LOW LEVEL LASER THERAPY IN ANKLE SPRAINS: ONE YEAR RESULTS OF A RANDOMISED CLINICAL TRIAL

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ABSTRACT

Absenteeism from work due to lateral ankle sprains is high. In the literature absenteeism from work is estimated at 7.3 days, while the one year prevalence of chronicity of these injuries ranges from 10 - 50%. Since laser therapy is thought to be an effective means in the management of lateral ankle sprains on both the short and long term, we present the long term results of a double blind, randomised, clinical trial.

217 Patients with acute lateral ankle sprains were randomised in three groups and received high or low dose or placebo laser therapy as an addition to a standardised treatment regimen. Twelve treatments in four weeks were given, followed by long term measurements at 3, 6, 9, and 12 months. Patients, therapists, assessors and analysts were blinded for the assigned treatments.

Intention to treat analysis showed that total days of absenteeism from work and sports were remarkably lower in the placebo group when compared to the laser groups; ranging from 3.7 to 5.3 and 6 to 8 days, respectively. The total number of relapses in the low dose laser group (n=22) was significantly higher than in the other two groups (high laser n=13 and placebo n=13).

We conclude that laser therapy in ankle sprains is not an effective therapy in the reduction of absenteeism from work or sports and the prevention of relapses.

Keywords: laser therapy, ankle sprains, RCT, one year follow up

Introduction

Each year 4% of the population in western countries sprain their ankle, about half of them during sports activities. Some 20% of these patients need medical care.[1] In people with a sedentary lifestyle such injuries can be painful but relatively non-disruptive. However, in people with a more demanding or athletic work setting or hobby, such injuries might have important, sometimes life-long effects.
The prevalence of chronic ankle damage after inversion trauma varies between 10-20%,[2,3] and 30-40%[4-7] and even 50%.[8] It is likely that each author defines chronic instability in his own way, and therefore obscures these findings. However, these figures are worrisome.
Absenteeism from work and school is estimated at 7.3 days per sprain[9,10] while sprains are responsible for 10-15% of total absenteeism from work in the Netherlands.[1]
Traditionally, ankle ligament injuries are graded from I (stretch), II (partial tear) to III (complete tear). However, research shows that both partial as well as complete tears reach the same level of recovery after one year.[11]

In the Netherlands laser therapy (LT) is claimed to be an effective therapy in the treatment of inversion injuries of the ankle.[12] On the short term it is supposed to linder pain and hasten functional recovery and therewith reduce absenteeism from work. In the long term it is expected to reduce the number of relapses and the number of chronic ankle injuries after inversion trauma. Also, one holds the opinion that high dose laser is more effective than low dose laser.[13-15]

To shed light on the above stated claims we conducted a randomised clinical trial to assess the efficacy of high dose LT versus low dose LT versus placebo LT in the treatment of patients with an acute lateral ankle sprain. LT served as an additional therapy, and was applied upon a standardised treatment regimen. Efficacy was evaluated on the basis of 4 and 6 week results and 3, 6, 9 and 12 month results. The four week follow up period was intended to reflect the actual healing process, and to provide preliminary information about resumption of work and sports participation. One year follow up was carried out to detect long-term effects and possible relapses. In this article we present the 3, 6, 9 and 12 month results.
The study was approved by the medical ethics committee of Maastricht University and the University Hospital of Maastricht (the Netherlands). A detailed description of the protocol can be found chapter 5 of this thesis.

Method

Patient selection

Patients who reported to the Accident and Emergency department of the University Hospital of Maastricht with an acute lateral ankle sprain, who were between 18 and 65 years of age and whose injury was not older than 48 hours, were selected by the doctor on call.
We excluded patients who had had an ankle injury in the preceding year, and patients who had received previous ankle surgery. Also, patients with radiographically confirmed fractures, direct open trauma or underlying abnormalities of the foot and/or legs were excluded, as well as those with systemic diseases or mental handicap. Patients could also be excluded for practical reasons, for instance if they had difficulties with the Dutch language, lived too far away or if they could be expected not to attend all therapy sessions (e.g., going on holiday, work abroad).
Eligible patients received a detailed descrip-

tion of the intended treatment procedure, and were informed about the chance of receiving placebo therapy as well as having the right to withdraw from the trial at any time. After receiving this information, the patients had to give their written informed consent. The next morning a trained research assistant checked inclusion and exclusion criteria and performed the baseline interview and physical examination. The patient filled out a questionnaire to provide baseline data.

Randomisation

Patients were stratified by severity of injury (mild versus severe) on the basis of a function score[16] and sports participation (does or does not participate in sports activities) to prevent unequal distributions by chance for these prognostic factors between treatment groups. After they had given informed consent patients were allocated at random to one of three groups by means of a computer generated table, with a random permuted block size of three. The first group received laser therapy with a low dose (LD), the second group received laser therapy with a high dose (HD) and the third group received placebo laser therapy (PD). Patients, therapists, outcome assessors and data analysts were blinded for the treatments given.

Interventions

All patients received a standardised treatment regimen, which consisted of four days elastic wrapping followed by three and a half weeks of bracing with a Push® ankle brace. We also provided standardised patient information and standardised home exercises. The patient information held advice and regulation of ADL activities during the first few days after injury, while the home exercises consisted of simple mobility exercises for the ankle, learning the patient to bear weight on the injured foot, and later on to regain balance and ensure a proper gait pattern.

The additional 904 nm LT was similar in all three groups except for the dose. The laser apparatus delivered a peak power of 25 Watts, with a pulse duration of 200 nsec and had a circular beam profile with an effective irradiated area of 6.4 mm^2. Laser dose at skin level in the low dose group was 0.5 J/cm^2, in the high dose group 5 J/cm^2, and 0 J/cm^2 in the placebo group.

The target tissue was considered to lie at a maximum of 1 cm under the surface of the skin. Energy density at tissue level was calculated to be 0.07 J/cm^2, 0.7 J/cm^2 and 0 J/cm^2 for each dose, respectively. Laser output was validated before the start and at the end of the trial and was checked at regular intervals during the trial by an independent party.

The patient indicated the most painful area on the lateral side of the ankle, which was consequently checked by means of an algometer. The thus identified and verified target area was circumscribed with a water proof marker during the first visit. Next, the area was cleaned with alcohol (96%) to minimise backscatter and reflection from fatty skin. Then the probe was placed perpendicularly in the centre of the circumscribed area, directly on the skin, in order to prevent energy loss due to divergence. All three groups received 12 treatments in four weeks; 5 treatments in the first week, 3 treatments in the second week and 2 treatments per week in the third and fourth week.

During each treatment session every patient received 200 seconds of laser therapy. Both patient and therapist were fully blinded. In all three groups the laser apparatus produced a soft sound and the display read "warning: laser beam active!". Both patient and therapist wore protective glasses. After therapy the elastic wrapping or brace was replaced.

We allowed patients to take standardised pain medication (Paracetamol 500 mg, maximum dose one tablet every four hours). The drugs were provided at intake, and the patients kept a record of the amount they took during the treatment period.

Outcome measures

To assess the long term efficacy of LT we were interested in the total number of days of absenteeism from work, school or housekeeping due to trauma and in the moment of re-uptake of sports (measured in days since the onset of trauma). We also measured level of activity on a 0 to 10 point scale, level of complaints on a 0 to 10 point scale, function on a 0 to 100 point scale and the use of a brace during ADL and sports activities. The 0 to 10 point scales are quite similar to the Dutch schoolreport mark system, and therefore easy to use by the assessors. They also provide reliable and consistent measures when compared to VAS.[16] The function score was validated in previous research.[17]

Also the number of relapses per group were measured. All long term measurements were performed by telephone by a trained research assistant. Non responders received letters which urged them to reply. Serious relapses were checked at the University Hospital by the doctor on call.

Data management and statistical analysis

Data were stored on a personal computer in dBASE IV™ [18] and were checked for completeness, inconsistencies, for the range of possible values and for protocol deviations.

Subsequently, the data were analysed with SPSSWIN/PC™ statistical software.[19] Analyses were performed in a blinded manner and according to the intention to treat principle: all participants, including those with poor compliance and those who had withdrawn from therapy, remained in the group to which they had been assigned by randomisation. Subsequently, a per protocol analysis was performed to see whether protocol deviations influenced the results.

The outcome measures were compared between the three treatment groups. Differences between the means of groups at 3, 6, 9 and 12 months, respectively, were compared by using a two-tailed ANOVA model for continuous data or a Chi-square test for dichotomous data. The number of relapses was compared between the groups by a Cox-regression model. Differences in days of absenteeism from sports was calculated by a Kruskal-Wallis test for non-normal distributed data.

Subgroup analyses were carried out to determine whether particular subgroups showed other outcomes than the treatment groups as a total. Dichotomised subgroups were formed according to age (cut-off: 35 years), sports-participation (yes/no), gender (female/male), and job (heavy/light work) and job setting (blue/white collar).

Results

From September 1, 1993 until December 31, 1995, 217 patients were included and randomised.

The three treatment groups were similar with respect to baseline measures, although age and gender differed slightly in the high dose group, compared to the other two groups (Table 1).

Table 1: Comparison of treatment groups with respect to demographic and prognostic variables at baseline level

	Low Dose (LD)	High Dose (HD)	Placebo Dose (PD)
No patients	74	72	71
Mean age in years (sd)	30.2 (9.6)	33.2 (10.4)	30.9 (10.3)
Sex (female/male)	30/44	17/55	22/49
Baseline measurements			
mean pain score (sd)*			
during the day	3.7 (2.7)	3.8 (2.5)	3.6 (2.8)
in the morning	4.8 (2.9)	4.4 (2.9)	4.2 (3.0)
mean number of pain tablets per day (sd)	0.5 (1.0)	0.8 (1.4)	0.7 (1.4)
mean sports category (sd)†	2.2 (0.8)	2.1 (0.8)	2.1 (0.8)
mean function score (sd)‡	13.1 (10.6)	12.1 (10.8)	13.4 (11.8)
blue/white collar ratio#	37/35 (2.0)	37/35 (5.0)	35/32 (4.0)
work load			
light	21	17	20
normal	19	18	19
heavy	28	30	27
very heavy	6	7	5

* measured on a 0 to 10 point scale (0 no pain, 10 extremely painful)
† measured on a 4- point scale (0 no sports participation, 1 recreational, 2 competition, 3 professional)
‡ measured on a 0-100 point scale (0 no function, 100 perfect function)
\# numbers between brackets indicate unemployed

All patients were present for baseline measurements; yet, in the follow up 3.6 to 8.3% of the patients were lost to follow up as time passed by. Table 2 shows the numbers per group as compared to the baseline attendance, as well as outcome measures at 3, 6, 9 and 12 months of follow up.

The low dose group showed 6 losses to follow up after one year; 4 patients had moved, 1 patient did not respond to either written or telephonic requests and one patient's phone was disconnected.
In the high dose group 2 patients had moved and one patient had left an erratic phone number; thus 3 patients in total were missed.
The placebo group showed 8 losses to follow up after one year; 6 patients had moved, one patient's phone was disconnected and one patient had no telephone and did not react to written requests.

As can be seen from table 2 there is a striking difference between the two laser groups and the placebo group when we compare absenteeism from work and sports. Other outcome measures do not show large differences. Also correction for baseline differences on sex and age with ANOVA did not alter the results. The per-protocol analysis showed similar results.

Table 3 shows the amount of relapses per 3 months in the three groups. No patient had more than one relapse. The total number of relapses was 45 (20.7 - 22.6%, depending on comparison with number of patients at baseline attendance or at the end of follow up) of which 22 occurred in the low dose group.

Table 2: Outcome measures at 3,6,9 and 12 months of follow up

	Low Dosis		High Dosis		Placebo		Anova, Chi-square[#2], or Kruskall-Wallis[KW] (all 2-tailed)
number of patients	74		72		71		
Total days of sick leave due to ankle sprain (mean, sd) at one year follow up	13.1	(12.3)	11.5	(10.7)	7.8	(9.3)	0.013
Days until re-uptake of sports (median, range)°°							
number of patients	51		54		48		
at nine months follow up	41	(7-274)	40	(10-272)	33.5	(3-275)	0.36[KW]
at one year follow up	42	(7-365)	40	(10-272)	34	(3-365)	0.26[KW]
3 months results							
number of patients	72		72		66		
activity level*	5.6	(2.3)	5.7	(2.3)	5.4	(2.6)	0.82
free of complaints†	8.7	(1.7)	8.8	(1.8)	8.6	(2.2)	0.80
function score‡	85.3	(15.7)	85.5	(15.9)	84.5	(21.5)	0.94
use of brace in ADL (yes/no)	7/65		6/66		6/60		0.96[#2]
use of brace during sports (yes/no)°°	28/17		27/21		18/21		0.33[#2]
6 months results							
number of patients	69		70		63		
activity level	5.7	(2.2)	6.0	(2.2)	6.1	(2.3)	0.54
free of complaints	9.2	(1.2)	8.9	(1.7)	9.3	(1.1)	0.38
function score	88.5	(13.5)	88.4	(13.6)	89.8	(15.1)	0.83
use of brace in ADL (yes/no)	3/66		3/67		5/57		0.49[#2]
use of brace during sports (yes/no)°°	23/21		24/24		15/27		0.25[#2]
9 months results							
number of patients	68		69		63		
activity level	5.8	(2.3)	5.9	(2.2)	5.9	(2.3)	0.93
free of complaints	9.4	(1.3)	9.4	(1.1)	9.5	(1.1)	0.91
function score	89.16	(13.9)	89.8	(13.5)	88.8	(15.2)	0.92
use of brace in ADL (yes/no)	2/66		2/67		2/60		0.99[#2]
use of brace during sports (yes/no)°°	14/31		18/30		10/31		0.41[#2]
12 months results							
number of patients	68		69		63		
activity level	5.8	(2.3)	6.2	(2.2)	5.9	(2.2)	0.61
free of complaints	9.5	(1.2)	9.5	(1.0)	9.7	(0.8)	0.59
function score	89.6	(14.8)	91.5	(13.0)	88.9	(14.5)	0.53
use of brace in ADL (yes/no)	0/68		0/69		2/59		0.51[#2]
use of brace during sports (yes/no)°°	15/29		8/31		11/37		0.31[#2]

* measured on a 0 - 10 point scale
† measured on a 0 - 10 point report mark scale (10 is free of complaints)
‡ measured on a 0 - 100 point scale (0 is no function, 100 perfect function)
°° only applicable in patients who participate in sports

From a Cox-regression model a significant trend (p=0.04) towards a greater relapse ratio in the LD laser group compared to the HD laser group or placebo group was found.

Discussion

Efficacy of laser therapy is mostly studied on a short term basis, even in musculoskeletal disorders.

Table 3: Number of relapses in the three groups at 3, 6, 9, and 12 months

	LD	cum	HD	cum	PD	cum	Total	Chi²
relapses per period								
at 3 months	11/72		6/72		5/66		22/210	0.26
at 6 months	7/69	18	2/70	8	4/63	9	13/202	0.22
at 9 months	4/68	22	2/69	10	1/62	10	7/199	0.39
at 12 months	0/68	22	3/69	13	0/62	10	3/199	0.04

In trials studying 904 nm laser therapy the longest follow up periods are one year[20] and 9 months[21], but most study its efficacy on a rather short term basis (e.g., during and immediately after the treatment period). This is because most authors are interested in short term effects such as pain reduction and lindering of swelling.[22,23]

However, also long term effects are of importance. In this trial the findings on differences in absenteeism from work and sports between the laser groups and the placebo group are quite substantial, favouring the placebo treatment. Axelsen et al.[24] also reported that 'patients treated with active laser had a significantly longer sick leave', although they used a laser with a wavelength of 830 nm.

Other studies[9,10] reported an average absenteeism from work due to ankle sprains of 7.3 days. The average absenteeism found in the placebo group of 7.8 days is quite comparable. This makes it more likely that the remaining difference in absenteeism is largely attributable to laser therapy. Or, to put it in another way, of the total number of days of absenteeism in this trial (2283 days), 590 days (about 25%) could have been avoided if we had not given laser to two-thirds of the study population. The number of relapses in this trial is substantial, but to be expected. Other trials report corresponding figures.[5,7] No reason can be thought of why the low dose group is responsible for half the number of relapses.

Apart from the number of relapses and days of absenteeism, we found no other differences between the three therapy groups, hinting at biological rationales. An answer in the ongoing debate on the adequacy of proper dose can therefore not be given. One could argue that the laser doses used here were suboptimal. They could be either too low, too high or both on opposite sides of the optimum dose. However, in our opinion this is unlikely. The low dose was chosen as an adequate reflection of the dosimetric principles that were known in 1994.[25] To create a therapeutic contrast we chose a high dose which was ten times higher than the low dose. This dose is nowadays used in physiotherapeutic practice as the optimal dose. The use of even higher doses in laser therapy is therefore not recommended; there is still no biological rationale for this.

The noted effects are most likely not attributable to incomparability of the study population: baseline measures, prognostic variables, work setting and workload were comparable between groups. Moreover, additional correction for baseline differences did not alter the results. Since blinding of this trial was only broken after the final data were collected, and also because during follow up the research assistant who was responsible for follow up measurements was unaware of group the allocation, it is unlikely that our findings have been biased by foreknowledge.

Hence, we conclude that these results show that laser therapy is not effective. It prolongs

absenteeism from work and sports participation substantially, and also increases the number of relapses in the LD group. We therefore state that laser therapy has no beneficial effects in the treatment of sprained ankles.

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8 GENERAL DISCUSSION

This chapter discusses the findings of this thesis. Firstly, it reflects on the evidence derived from the two systematic reviews that have been described in chapters 2 and 3. Secondly, the feasibility of our prognostic study, described in chapter 4, will be discussed. Finally, we will address the internal and external validity of our clinical trial, as reported upon in chapters 5 to 7. This chapter concludes with my personal view on the efficacy of laser therapy.

Reviews

In summarising the evidence of physiotherapy trials we have encountered several problems. The quality of the studies varies widely from low to rather high. If there is no apparent relationship between methodological quality of the studies and the effect sizes,[1] all studies might be included for the purposes of drawing the final conclusion. If, however, there is a relationship, it makes sense to allow only the best quality studies to have the greatest influence on final outcome. However, choices about cut-off points and the justification of omitting lower quality evidence are always arbitrary and difficult.

Physiotherapy trials often harbour a multitude of measures of effect which are hardly comparable between studies. Decisions about combining the results must ultimately rely on good sense and clinical judgement. In such cases it is important to consider whether the participants, interventions and outcomes in each of the trials included are sufficiently similar to allow for meaningful combination of outcomes.[2] To date, combining measures of effect does not often apply to physiotherapy trials. That is why we placed the accent on qualitative rather than quantitative analyses of studies under review.

We performed two systematic reviews. Both used the same criteria list for assessing methodological quality. The criteria list tries to measure the internal validity, precision and relevance of the choices with respect to population, intervention and measures of effect[3] and thus gives an impression of the adequacy of the performed research. The list was originally designed by Ter Riet et al.,[4] and modified over the years by Koes et al.,[5] and van der Heijden et al.[6] It is based on generally accepted principles of intervention research[7] and has been adapted for each review with respect to the intervention and relevant outcome measures.[3]

In the review of conservative interventions in the treatment of acute lateral ankle sprains (chapter 2) we found the overall methodological quality to be low. Only two studies scored above 60 points, implying the methodological inadequacy of the remaining 42 trials. Of course we are aware of the fact that the quality of the reported material does not necessarily reflect the quality of the primary research. Yet these publications are the best available evidence and are our best source for answers regarding the efficacy of conservative interventions in acute lateral ankle sprains. It is especially disappointing to see that many easily avoidable errors in design, reporting and data-analyses were made. One striking finding is the reluctance (or sloppiness) to assure proper blinding. This is

worrisome, since recent research shows that unblinded trials are bound to deliver more biased answers. Reporting is often further flawed on description of drop outs, prognostic comparability, co-interventions and side effects. In the data-analysis many trials report outcomes that are not based on between group comparisons.
Apart from the quality issue, there is the problem of adequately summarising the available evidence. The reviewed studies use different instruments to assess identical outcome measures. We therefore assessed the outcomes of all studies qualitatively. However, since pooling of effect sizes seems to be the fashion nowadays[9] and reviewers are urged to do so, we also tried to pool the reviewed studies. Because of the different measurement instruments in the various studies, we used effect size calculations[10] to allow for pooling of the material. However, only half of the studies allowed for effect size calculations, and were poolable in the end. Moreover, differences were found when comparing the outcomes between the qualitative and quantitative methods, still leaving uncertainty about the efficacy of the interventions studied. Although small differences between interventions were observed, no firm conclusions on the efficacy of conservative interventions in the treatment of acute lateral ankle sprains can be drawn.

For the review on 904 nm laser therapy (chapter 3) we found the methodological quality of these studies to be poor as well. Grosso modo the same flaws were detected as in the other review. To complicate things, laser was used on multiple indications, thus inferring a large heterogeneity in study population and measures of outcome. For these reasons, pooling of the data was impossible and we therefore used a qualitative manner of describing the results. No positive effects of laser therapy were found, although some areas seem promising. Furter in vivo and in vitro research is needed.

Both reviews showed another shortcoming of the performed research. Most studies lacked an adequate sample size, therewith introducing imprecise answers. It is possible that small positive studies were more easily published than small negative ones, thus creating publication bias. Therefore larger trials with sound methodology are called for.

Prognosis

Our research on the prognosis of ankle sprains (chapter 4) showed that despite the lack of hard diagnostic criteria it is feasible to establish a proper model for predicting the outcome on recovery in acute lateral ankle sprains just after the moment of injury. For two weeks prediction a standardised scale which measures function suffices. Not only was the accuracy of the diagnostic instrument high, it was also totally independent from imaging techniques.
We also found that pain and swelling as such are bad predictors for recovery, but related to functioning of the patient they can predict outcome rather well. Therefore, we suggest that in the future doctors only look at complaints like pain and swelling in relation to function.
We planned to validate the model in our clinical trial. However, the amount of light cases turned out to be too small to confirm our previously established model. Proper validation of the piloted model is still called for.

Trial of laser therapy in ankle sprains

In our laser trial we tried to avoid errors in trial design as they were encountered in the reviews. In the following paragraphs we will discuss items bearing on the internal validity and the external validity of our trial.

The internal validity of a trial is ascertained by the use of proper randomisation proce-dures, blinding, avoidance of withdrawals and sufficient power

The external validity of a trial depends on the proper choice of patients, interventions and measures of outcome. In the next paragraphs these choices will be discussed.

Randomisation procedure

Randomisation is meant to assure comparability of the study groups for baseline characteristics.[11] An important feature of a proper randomisation method is the masking of the assignment procedure, therewith effectively assuring unpredictability of future assignments and the preclusion of cheating.

In our trial we used a fairly elaborate assignment method. Patients were stratified by severity of their injury and their sports participation to prevent unequal distributions by chance for these important prognostic factors. We further used a random permuted block size of three, assuring that every triplet of patients was distributed evenly over each treatment arm. The randomisation scheme was prepared before the start of the trial by an independent party and the assignment codes were kept in a safe vault in a sealed envelope, only to be opened after the short term data had been analysed.

After finishing the trial we checked the distribution and agreed that randomisation was successful. In a subsequent analysis we checked for work setting and work load. They were quite com-parable (see chapter 7). Fortunately, these factors were equally divided over the intervention groups. Furthermore, the randomisation procedure should have eliminated systematic differences in patients psychological characteristics

Blinding

Most physiotherapy trials are inadequately blinded (see chapters 2 and 3). The common excuse is that it is impossible to blind physiotherapy manoeuvres. Of course, some interventions are hard or impossible to blind at the patient and therapist level (e.g., massage or exercise therapy). However, recently performed trials[12-14] show that many physiotherapy interventions can effectively be blinded if one invests some time and ingenuity in the concept of blinding. Also blinding of the observer is easily achieved in almost all trials, unless the intervention leaves traceable marks on the patient.

In our trial we used a laser device that was blinded for both the patient and the therapist. The blinding procedure consisted of masking the optic properties of the laser beam and of manipulating the laser device. The patient and therapists both wore safety goggles with dark green glass in a clearly illuminated room. When the apparatus was turned on, it produced the same output on the screen irrespective whether the laser output was placebo, low or high dose laser. It additionally produced a soft whining noise during operation and an alarm sounded after completion of a 200 second treatment cycle. The 904 nm wavelength is invisible to the human eye.

As an extra precaution we randomised the three output levels over 21 settings on the laser apparatus, since in the unfortunate event

of de-masking a treatment code the entire trial becomes unblinded when only one code for each arm of the trial exists. We further blinded the observers and the data analysis procedure, thus hoping to avoid biases on all foreseeable levels. After completion of the individuals' treatment series we checked for success of blinding the patients. Our blinding procedure appeared to have been successful.

Withdrawals

A major threat to the validity of a trial is the amount of drop outs and losses to follow up. In the reviews we noted that some trials managed to loose over half of their participants. In our trial we monitored each patient carefully and used treatment calendars and small gifts to enhance compliance. All patients were present for baseline measurements. During the treatment period only 3 patients among 217 participants dropped out of the trial (1.4%).
Long term measurements (3 months to 1 year follow up) were performed by telephone interviews. At one year follow-up we had lost 7.8% of the patients. In total 12 patients had moved to an unknown address, 2 patients had their phones disconnected, one patient had no telephone, one patient had left an erratic phone number and one patient did not respond to either written or telephonic requests. All missing data were accounted for in an intention to treat analysis. There was no difference in outcome between the intention-to-treat analysis and the per protocol analysis. Therefore we think that the results of our trial are not biased by selective withdrawal rates.

Power of the study

Sample size calculations are part of the design of each clinical trial and have practical and ethical consequences.[15] A sufficient sample size also guards against biases inferred by unequal distribution of prognostic variables. At the onset of this project there was uncertainty about the efficacy of laser therapy in musculoskeletal disorders. Subsequent meta-analyses did not shed light on our research question. Therefore we formulated a hypothesis which aimed at researching the possible beneficial effect of laser therapy (see chapter 4). Although initially a one-sided cause-effect relationship was suspected, given the amount of uncertainty it was determined right from the start of the project that two-sided testing was called for. Our power calculations therefore demanded a sample size of at least 75 persons per group (α=0.05/two-tailed; 1-β=80%) when we assume a difference of interest of at least 20%. But we also felt that if we needed more than 75 persons per group, although statistically significant differences could occur, clinical relevant differences would not be of interest any more. To our surprise laser therapy performed worse than the placebo therapy, which justified our decision for two-sided testing. As can be learned from the results, the outcome of power calculations varies per outcome measure. For instance, the difference in sick leave at one year would already have become significant with a sample size of 22 patients per group (α=0.05/two-tailed; 1-β=80%). The difference in pain after 28 days (α=0.05/two-tailed; 1-β=80%) however would need at least 97 patients per group to become significant. The achieved power in this trial was 67% for pain as a measure of outcome.

Patients

One often worries about the homogeneity of a study population with respect to the maximal sensitivity to the intervention under

study.
In this study we studied patients with sprained ankles. Patients with fractures were excluded. As is described in chapter 5 (selection of patients) we used strict entry criteria to assure a homogeneous study population with an optimal chance for responding to the interventions of the study.
We stratified successfully for severity of injury and sports participation. Also work load appeared to be equally distributed over the study groups.

Intervention

Preceding and during the conduct of our trial there was much debate on which dose is the most adequate when one applies laser therapy in musculoskeletal injuries.[16,17] In our trial we compared a low dose laser with a high dose laser and a placebo laser treatment. To determine whether the claimed effects of LT were present we incorporated a placebo group, as new technologies are known to be surrounded by novelty effects, and thus have the potential of enhancing placebo responses. We were interested in the specific effects of laser therapy. The low dose represented a dose and intensity used in current physiotherapy practice. Since there are claims that this dose is too low to be effective, we also incorporated a high dose group in the trial. In this way we would be able to determine a dose-response relationship in case of cumulative effects, an inadequate dose-response relationship in case of too low a dose, or perhaps a rebound effect in case of too high a dose. None of the above relations were found. Both laser groups performed worse than the placebo group. However, there seems to be an influence of laser on the irradiated tissue. The deceleration of the healing process in treated (laser) compared to non-treated (placebo) patients is remarkable.

Effect measurements

In our trial we used several outcome measures. Our primary measures of effect were pain and function, while our secondary outcome measures were subjective recovery, limitation in ADL, swelling, pain pressure testing, clinical evaluation, re-uptake of work and sports, satisfaction with the recovery rate and received treatment and the number of relapses. Pain was measured on a 11 point scale and very similar to the Dutch report mark system. Numerical rating scales, with a range from 0-10 points, provide reliable and consistent measures of clinical pain intensity when compared to VAS, both in acute as well as chronic pain measurements.[18-20]
Patients were allowed to take standardised pain medication in this trial. Pain medication was provided by us at intake and the use of it has been registered throughout the trial. It turned out that already two days after the intake almost everybody had stopped the use of medication. Moreover, the intake of pain medication during the first days was comparable between the groups. Since our primary measure of effect was measured at 5 days and onward, drug intake will probably not have influenced the outcome.
The other primary measure of effect, function, was measured on a 100 point scale, where 0 stands for no function and 100 for perfect function. Because a validated instrument for ankle function was lacking, we adapted the Lysholm scale[21] which was originally intended to measure knee function. It is described in more detail in chapters 4 and 5, where the prognosis and the design of the trial are discussed. Although it has not been validated in the traditional sense, since there is no gold standard to compare with, we think that it has high face and content validity.
As for the other measures of outcome we opted for many, mostly validated measures of

outcome. This is quite easy to do, both from a practical as well as a theoretical perspective and it assures detailed information about the trial, but also enhances the possibility of chance findings. We guarded against chance findings by blinding the analysis procedure, and having a team of blinded experts declare whether the observed effects were meaningful. Most measures of effect pointed in the same direction, and the power of the significant findings was high.

Personal view

One can wonder whether the trial as described in this thesis adds to the evidence. A lot of trials become more or less obsolete because of the time lapse between the initiation of the trial and the presentation of the final results. In this case it also took 4 years from the beginning to the end. Yet, when we look at the results of the 904 nm laser review, it is apparent that no one else has studied 904 nm laser therapy in ankle sprains before. Therefore the present study fills a gap in our knowledge. The outcome shows that laser therapy performs worse than placebo therapy and therewith reinforces our initial doubt whether 904 nm laser therapy would be effective in ankle sprains. Since the working mechanism of laser in musculoskeletal disorders such as tennis elbow, low back pain and strains and sprains in general is thought to be the same as in ankle sprains, we also suspect non-effectiveness of laser therapy in these disorders.

Recent research with 904 nm laser on tissue samples, using various dosages, has failed to show any effects on cell metabolism, and hence has not provided corroborative evidence.[12]

However, it does not rule out the possibility that other wavelengths or other dosing regimens can deliver positive results.

The claim that laser therapy has no effect in biological tissues can be refuted. For, laser therapy does show capabilities of decelerating the healing process, and thus interferes with the metabolism of the tissue. Although a good model does not exist to clarify this mechanism, it could be possible that LT decelerates the inflammation process. Further in vivo and in vitro research is needed to shed light on this hypothesis and is being initiated right now.

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SUMMARY

CHAPTER 1 provides an introduction to this thesis by posing questions about effective therapies and prognosis that every patient likes to ask when spraining an ankle. Additionally, the thesis gives answers on the research question concerning the efficacy of laser therapy, which is advocated as a successful means in the treatment of acute lateral ankle sprains.

CHAPTER 2 reports on a systematic review that summarises the efficacy of conservative interventions in acute lateral ankle sprains. By means of computer aided searches of databases and of bibliographic indexes we retrieved trials on the efficacy of conservative interventions in acute lateral ankle sprains. Furthermore, we checked congress reports, reviews and relevant citations. Subsequently, all retrieved studies were scored on these methodological quality. Effect sizes were calculated for days of sick leave, pain and swelling.
We investigated the effects of physiotherapy interventions versus other interventions or placebo interventions, in subjects with acute lateral ankle sprains. Of all studies, 44 fulfilled our entry criteria. Study quality ranged from poor (9 points) to rather good (70 points), of which only two studies scored more than 60 points. Both studies (on pulsed shortwave therapy) showed no effect. Tape was found to be superior over other types of treatment, in effect shortening the duration of sick leave, while plaster of Paris treatment seemed to prolong sick leave.

CHAPTER 3 presents a systematic review on the efficacy of 904 nm low level laser therapy (LT) in musculoskeletal disorders.
In order to retrieve randomised trials computer aided searches of databases and of bibliographic indexes were performed. Furthermore, congress reports, reviews and handbooks were all checked for relevant citations. Subsequently, all retrieved studies were scored on methodological quality.
We looked especially at the effects of 904 nm LT versus placebo or any other intervention, in subjects with a condition for which LT was thought a feasible intervention. Of all studies, 21 fulfilled our entry criteria, and were assessed in a blinded manner on methodological criteria. Overall, study quality ranged from poor to reasonable. No convincing evidence was found for the efficacy of LT, except perhaps for knee problems and myofascial pain, where the results were inconsistent. We conclude that 904 nm LT has not yet proven to be effective in the treatment of musculoskeletal disorders, but that further and improved research is needed to shed more light on its efficacy.

CHAPTER 4 shows the development of a diagnostic tool for predicting the severity of ankle sprains just after injury. Since data obtained by diagnostic imaging techniques are still imperfect, we decided to use data from history taking, and signs and symptoms that are part of the intake routine. During a three month period data were collected on 35 patients with lateral ankle sprains who visited the Accident and Emergency department of the University Hospital of Maastricht. Assessments took place at intake and at two and four weeks after injury. Dependent variables were 'healed ankle after two and four weeks.' Predicting variables were the data obtained at intake by the physician, the

physiotherapist and the patient. The ability to predict outcome after two and four weeks was determined in a bivariate logistic analysis, followed by multivariate logistic modelling.
Accurate prediction of recovery time at intake appeared to be possible. Best two weeks predictor was the modified function score, with which an accuracy of 97% was achieved. Four weeks prediction was most accurate when function score was used together with the report mark from the doctor and the palpation score (accuracy of 81%).
Since it was a pilot study, a larger study is called for to confirm these results.

CHAPTERS 5 TO 7 report on the design, the short term and the long term results of a randomised clinical trial of the efficacy of LT on lateral ankle sprains. 217 Patients with acute lateral ankle sprains were randomised into three groups and received high or low dose or placebo laser therapy as an addition to a standardised treatment regimen, which consisted of four weeks of brace therapy, together with standardised home exercises. Twelve treatments in four weeks were given. Short term assessment took place every treatment day, followed by long term measurements at 3, 6, 9, and 12 months. Patients, therapists, assessors and analysts were blinded for the assigned treatment. Intention to treat analysis of the short term results showed no significant difference on the primary outcome measure pain, although the placebo group was slightly in favour. The placebo group performed significantly better on the other primary outcome and function measure days of sick leave, and at some points in time for hindrance in activities in daily life and pressure pain, as well as subjective recovery .
Long term analyses showed that total days of absenteeism from work and sports were remarkably lower in the placebo group when compared to the laser groups: on average 4.5 (work) and 7 (sports) days. The total number of relapses in the low dose laser group was much higher than in the other two groups.
We conclude that laser therapy in ankle sprains is not an effective therapy. On the short term it fails to alleviate pain or to speed up ADL recovery. On the long term it does not reduce absenteeism from work or sports, nor does it prevent relapses.

CHAPTER 8 presents a general discussion on various aspects of the research of in this thesis. The chapter is divided in four parts. The first part evaluates the value and outcomes of the systematic reviews, while the second part addresses the prognostic study. In the third part the clinical trial is discussed. Special attention is paid to factors influencing internal and external validity. The discussion concludes with a personal view on the efficacy of laser therapy.

NEDERLANDSE SAMENVATTING

Dit proefschrift is geschreven in het Engels, en meestal in een taalgebruik dat voor de niet vakinhoudelijk geschoolde lezer moeilijk te doorgronden is. Vandaar deze uitgebreide samenvatting in het Nederlands voor diegenen die meer willen weten omtrent de effectiviteit van (laag vermogen) lasertherapie bij laterale enkelbandletsels (verstuikte enkels). In het eerste deel worden in het kort de twee literatuuroverzichten uit dit proefschrift besproken. Het tweede deel behandelt onderzoek naar het klinisch verloop van enkelbandletsels en het ontwikkelen van voorspellingsmodellen. In het derde deel worden de achtergrond van het eigen onderzoek, alsmede de opzet, resultaten, discussie en de conclusies beschreven.

DEEL 1

META-ANALYSES

In het kader van dit proefschrift zijn twee systematische literatuuroverzichten geschreven. Eén gaat over de effectiviteit van 904 nm laag vermogen lasertherapie bij aandoeningen van het bewegingsapparaat, terwijl de andere gaat over conservatieve therapieën die gebruikt worden ter behandeling van patiënten met een enkelbandletsel.
Het gaat te ver om in deze samenvatting de gehele methode van literatuuronderzoek uit te leggen, maar toch wil ik u een korte samenvatting van beide literatuuroverzichten niet onthouden.

CONSERVATIEVE THERAPIEËN TER BEHANDELING VAN PATIËNTEN MET EEN ENKELBANDLETSEL

Met behulp van de geautomatiseerde literatuurbestanden MEDLINE en EMBASE zijn

studies opgespoord die conservatieve (niet-operatieve) behandelingen bij laterale enkelbandletsels bestudeerden. Daarnaast is de Cochrane Database voor Randomised Trials en de database van het Rehabilitation and Related Therapies Field geraadpleegd. Van alle gevonden artikelen zijn de referenties nagelopen en tevens zijn congresverslagen, literatuuroverzichten en handboeken geraadpleegd. In totaal zijn 81 studies opgespoord, waarvan er uiteindelijk 44 aan de inclusiecriteria voldeden. Deze 44 studies werden vervolgens op methodologische kwaliteit beoordeeld en effect-sizes (gestandaarde verschillen in effect tussen de bestudeerde interventies) werden berekend voor ziekteverzuim, pijn en zwelling. Opvallend was het grote aantal verschillende behandelwijzen dat werd bestudeerd.
De methodologische kwaliteit op een 100 punts-schaal varieerde van slecht (9 punten) tot goed (70 punten). Slechts twee studies scoorden meer dan 60 punten.
Tabel 1 laat de effecten zien zoals deze te berekenen waren voor de uitkomstmaten ziekteverzuim, pijn en zwelling.
Wanneer we kijken naar dagen ziekteverzuim dan lijkt taping of bandage de beste (meest economische) therapievorm, terwijl gips het slechtst presteert. Op de andere effectmaten is het moeilijker een oordeel te geven daar er weinig gegevens bekend zijn.

Tabel 1: Effect van behandelingen bij acute enkelbandletsels

Behandeling	Kwalitatieve analyse	
	studies	*conclusie*
Brace vs ander		
pijn	$+^{27}$, 0^{29}, 0^{36}, $+^{54}$, $-^{57}$, $+^{57}$	pijn vermindering
zwelling (in ml)	$+^{27}$, 0^{29}, $-^{57}$, $+^{57}$	reductie
ziekte verzuim	$+^{27}$, 0^{37}, $+^{39}$, 0^{54}, $-^{57}$	onbeslist
Tape vs ander		
pijn	$-^{16}$, $-^{19}$, $-^{48}$, $-^{57}$	geen pijn vermindering
zwelling (in ml)	$+^{57}$	reductie
ziekte verzuim	0^{14}, 0^{48}, $+^{52}$, $+^{57}$	reductie
Bandage vs ander		
pijn	$-^{15}$, $+^{27}$, $-^{33}$, $+^{34}$, $-^{46}$, $+^{47}$	onbeslist
zwelling (in ml)	$+^{27}$, $+^{46}$, $-^{57}$, $-^{51}$	onbeslist
ziekte verzuim	$+^{21}$, $-^{23}$, $+^{27}$, $+^{34}$, $-^{39}$, $-^{46}$, $+^{59}$	onbeslist
Gips vs ander		
pijn	$-^{27}$, 0^{29}, $+^{33}$, 0^{36}, $-^{54}$	onbeslist
zwelling (in ml)	0^{21}, $-^{27}$, 0^{29}, $+^{33}$	onbeslist
ziekte verzuim	$-^{21}$, $-^{23}$, $-^{27}$, $-^{29}$, 0^{37}, $-^{52}$, $-^{54}$	toename
Placebo vs ander		
pijn	$-^{17}$, 0^{18}, $-^{19}$, 0^{25}, 0^{40}, 0^{42}, $-^{50}$, 0^{53}	geen pijn vermindering
zwelling (in ml)	0^{17}, 0^{18}, 0^{21}, 0^{40}, $-^{42}$, $-^{49}$, $-^{50}$	geen reductie
ziekte verzuim	$-^{17}$	geen reductie

\+ reductie vergeleken met andere behandeling(en);
0 geen verschil
– toename

EFFECTIVITEIT VAN 904 NM LAAG VERMOGEN LASERTHERAPIE BIJ AANDOENINGEN VAN HET BEWEGINGSAPPARAAT

Ook voor dit literatuuroverzicht zijn met behulp van de geautomatiseerde literatuurbestanden MEDLINE en EMBASE alle gerandomiseerde effectonderzoeken op gebied van 904 nm laser therapie opgespoord die gedurende de periode 1966 tot 1996 waren verschenen. Van alle gevonden artikelen zijn de referenties nagelopen en tevens zijn congresverslagen, literatuuroverzichten en handboeken geraadpleegd.

In totaal werden 25 studies gevonden die het effect van 904 nm laser therapie onderzochten en waarin deze therapie gecontrasteerd werd met een placebobehandeling of een andere behandeling. Hiervan voldeden er 21 aan onze inclusiecriteria; deze werden vervolgens op hun methodologische kwaliteit beoordeeld.

Drie studies rapporteerden het effect van laser (LT) bij patiënten met reuma; twee studies vonden geen effect. Eén studie rapporteerde positieve bevindingen. Deze waren echter gebaseerd op een voor-na vergelijking; tussen de groepen waren er geen verschillen. Twee van de drie studies bij patiënten met aangezichtspijn vonden positieve resultaten.

Drie van de vier studies die knie aandoeningen bestudeerden vonden positieve trends; de resultaten van één van deze studies waren echter gebaseerd op een voor-na vergelijking; tussen de groepen waren er geen verschillen. Slechts één studie naar het effect van laserbehandeling bij trigger points en liet positieve resultaten zien.

Drie studies onderzochten de effectiviteit van LT bij patiënten met decubitus. Alhoewel alle

Kwantitatieve analyse		
verschillen (99% BI)	*conclusie*	*gecombineerde conclusie*
1,03 (-0.40 / 2,26)[27, 29, 54]	geen pijn vermindering	onbeslist
	geen data	zwellingsreductie
0,55 (-0.64 / 1,74)[39, 54]	geen reductie	onbeslist
	geen data	geen pijn vermindering
	geen data	zwellingsreductie
2,97 (1,63 / 4,31)[48, 52]	reductie	reductie
0,72 (-2,95 / 4,38)[15, 27, 33, 34]	geen pijn vermindering	onbeslist
-14,8 (-20 / -9,58)[51]	geen reductie	onbeslist
0,38 (0,17 / 0,59)[21, 23, 34, 39]	reductie	reductie
-0,29 (-1,64 / 1.06)[27, 33, 36, 54]	geen pijn vermindering	onbeslist
0,17 (-0,06 / 0,27)[33]	geen reductie	onbeslist
-4,52 (-5,10 / -3,94)[21, 23, 54]	toename	toename
-3,59 (-1,16 / 6,00)[17, 42]	geen pijn vermindering	geen pijn vermindering
-3,38 ml (-3,68 / -3,08)[17, 50]	geen reductie	geen reductie
	geen data	onbeslist

drie positieve resultaten lieten zien zijn er ernstige fouten in de opzet en uitvoering van het onderzoek gemaakt.
Vier studies bestudeerden patiënten met een tenniselleboog; deze waren alle negatief. Eén studie onderzocht tendinitis en liet positieve resultaten zien. Tenslotte bestudeerden 2 onderzoeken het effect van LT bij lage rug klachten. Bij beide waren er echter methodologische problemen in opzet en uitvoering van het onderzoek.
Tabel 2 laat samengevat nog eens de resultaten zien.

Samenvattend kunnen we zeggen dat de methodologische kwaliteit varieerde van slecht tot redelijk. Slechts op het gebied van knie aandoeningen en aangezichtspijn lijken er voorzichtige aanwijzingen te zijn die duiden op effectiviteit van lasertherapie.

Tabel 2: Effect van 904 NM laser therapie bij aandoeningen van het bewegingsapparaat

Aandoening (aantal studies)	Resultaten volgens de auteurs	Resultaten volgens de reviewers*
reuma (n=3)	$+^{21}$, $-^{27}$, $-^{38}$,	$-^{@}$, $-^{@}$, $-^{@}$
aangezichtspijn (n=3)	$+^{23}$, $+^{26}$, $-^{28}$	$+^{@}$, $+^{@}$, -
knie aandoeningen (n=4)	$+^{35}$, $+^{37}$, $+^{34}$, $-^{24}$	+, +, $-^{@}$, $-^{@}$
trigger points (n=1)	$+^{36}$	$-^{@}$
decubitus (n=3)	$+^{22}$, $+^{24}$, $+^{32}$	-, $+^{@}$, $+^{@}$
tennis elleboog (n=4)	$-^{33}$, $-^{39}$, $-^{40}$, $-^{41}$	-, -, -, -
tendinitis (n=1)	$+^{25}$	$+^{@}$
lage rug klachten (n=2)	$+^{30}$, $-^{31}$	-, $-^{@}$

Voor- na vergelijken zijn herberekend als tussengroeps vergelijking. Nummers in superscript verwijzen naar de studies (terug te vinden in hoofstuk 6 van dit proefschrift), terwijl ; - = niet effectief, + = effectief en ? = onbeslist.
@ studies met een methodologische score lager dan 40 punten (uit maximaal 100)

Discussie

Beide systematische reviews in dit proefschrift maken gebruik van dezelfde criteriumlijst om de interne validiteit, de precisie en de relevantie van de onderzochte studies te meten. Alhoewel de lijst is gebaseerd op algemeen geaccepteerde principes van klinisch wetenschappelijk onderzoek, blijft het moeilijk om de kwaliteit van de onderzoeken adequaat in te schatten. Dit komt mede door dat veel studies weinig informatie bevatten, of omdat een aantal voor de hand liggende middelen om de kwaliteit van de studies te verbeteren niet zijn toegepast.
Het meest opvallend is het gebrek aan blindering. Zeker op nivo van effectmeting en analyse is dit goed mogelijk. Daarnaast had in een aantal studies ook op patiënt- en behandelaarsnivo geblindeerd kunnen worden.
Adequate beschrijving van uitvallers, prognostische vergelijkbaarheid van de patiëntengroepen en beschrijving van neveneffecten en nevenbehandelingen ontbreekt eveneens in vele gevallen. Interpretatie van de gegevens wordt hierdoor ernstig bemoeilijkt.

DEEL 2

Prognosebepaling van enkelbandletsels

Om een goede behandeling van enkelbandletsels te kunnen garanderen is een goede inschatting van de ernst van het letsel en de prognose van het te verwachten herstel belangrijk. Zoals al uit de inleiding in deel 1 bleek, is het moeilijk de ernst van het letsel goed vast te stellen, mede omdat harde diagnostische criteria ontbreken of onbetrouwbaar zijn.

We hebben geprobeerd om met behulp van anamnestische gegevens en eenvoudig lichamelijk onderzoek lichte van ernstige letsels te kunnen onderscheiden op basis van de prognose.

Methode

35 patiënten die zich bij de eerste hulp afdeling van het academisch ziekenhuis Maastricht (azM) meldden met een acuut lateraal enkelbandletsel zijn anamnestisch en lichamelijk uitgebreid onderzocht.
De bevindingen van de dienstdoende arts, de fysiotherapeut en de patiënt zelf werden systematisch verzameld. Daarbij waren de arts en de fysiotherapeut geblindeerd voor elkaars waarnemingen.
Na de intake kregen alle patiënten de standaard behandeling, bestaande uit 5 dagen een drukverband en daarna een Coumans bandage gedurende maximaal zes weken.
Omdat de patiënten iedere twee weken terugkeren voor het verwisselen van de Coumans bandage zijn zij op 2 en 4 weken na het trauma opnieuw door ons onderzocht.
Bij de uiteindelijke analyse zijn herstel na twee en vier weken als afhankelijke variabele meegenomen en als voorspellende variabelen alle data die verzameld zijn uit de anamnese en het lichamelijk onderzoek bij de intake. Met behulp van een bivariaat model zijn de uitkomsten op 2 en 4 weken bepaald. Om als beter (hersteld) te kunnen worden aangemerkt, diende de patiënt zelfstandig te zijn wat betreft de activiteiten van het dagelijkse leven (dit komt overeen met een functiescore van meer dan 76 punten), en op minder dan twee van de twaalf vooraf gedefinieerde punten op de enkel pijn aan te geven.

RESULTATEN

In tabel 3 staan de uitkomsten met betrekking tot de twee en vier weken voorspellingen gerelateerd aan de data zoals die verzameld zijn tijdens de intake.

Tabel 3 dient als volgt geïnterpreteerd te worden: van de patiënten die nog ziek zijn na twee weken had 93% spontane pijn aan de enkel bij intake, vergeleken met 75% spontane pijn bij de patiënten die na twee weken beter waren.

Tabel 3: Twee en vier weken voorspellingen in relatie tot bevindingen uit anamnese en lichamelijk onderzoek bij intake

	2 weken resultaten		4 weken resultaten	
variabelen	ziek (n=29)	beter (n=4)	ziek (n=16)	beter (n=15)
spontane pijn	93%	75%	93%	80%
kissing pijn	55%	25%	50%	47%
instabiliteit: ernstig	15%	0%	21%	7%
matig	54%	50%	71%	43%
geen	31%	50%	7%	50%
gewicht nemen op aangedane voet onmogelijk	66%	0%	56%	47%
zwelling	96%	75%	100%	93%
slecht looppatroon	100%	75%	100%	93%
functie score ≤ 35 *	97%	0%	94%	73%
slecht functie enkel	62%	50%	71%	50%
> 2 pijnpunten	66%	25%	64%	47%
recidief	27%	25%	13%	47%
ernst letsel (rapport cijfer ≥ 5)	76%	25%	88%	60%
niet beter in 2 weken	88%	50%	93%	79%
niet beter in 4 weken	8%	25%	0%	14%
niet aan het werk in 7 dagen	15%	0%	29%	0%
niet aan het sporten in 2 weken	55%	33%	60%	33%

- De functie score is een 100 punten schaal die pijn, zwelling, instabiliteit, gewicht nemen op de aangedane voet en looppatroon combineert.

In tabel 4 wordt de functie score uitgezet tegen de gouden standaard "beter of ziek". Uit onze data bleek dat een bij een afkappunt van 35 punten op de functieschaal het kleinste aantal patiënten verkeerd werd geclassificeerd.

Tabel 4: Twee weken voorspelling op genezing met behulp van de functie score

		Beter in 2 weken (gouden standaard)		
		ziek	beter	
Voorspeller: functie score	ziek (≤ 35 punten)	28	0	+ Pred val 100%
	beter (> 35 punten)	1	4	- Pred val 80%
		Sens 97%	Spec 100%	

Genezing na vier weken werd het best voorspeld door een combinatie van het rapportcijfer voor ernst van het letsel, samen met de functie score en de pijnpunten score (zie Tabel 5). Toch wordt in dit model bij 6 van de 31 patiënten een foute voorspelling gemaakt.

Tabel 5: Vier weken voorspelling op genezing door een combinatie van rapport cijfer ernst, functie score en pijnpunten score

		Beter in 4 weken (gouden standaard)		
		ziek	beter	
Voorspellers: rapport cijfer ernst, functie score, pijnpunten	ziek	13	3	+ Pred val 81%
	beter	3	12	- Pred val 80%
		Sens 81%	Spec 80%	

Discussie

Met dit onderzoek hebben we geprobeerd een diagnostisch probleem op te lossen door de prognose van het herstel na enkelbandletsel te bestuderen. Sommige variabelen in dit onderzoek bleken nauwelijks gevoelig voor verandering, bijvoorbeeld leeftijd, maar zijn vaak uitstekende voorspellers voor prognose. Andere variabelen, zoals pijn, zijn weliswaar zeer gevoelig voor verandering, maar zijn juist slechte prognostische factoren. Immers, iedereen heeft pijn na een inversietrauma, en dus kan pijn slecht discrimineren tussen lichte en zwaardere letsels.

Uit het onderzoek blijkt dat het tamelijk goed mogelijk is een voorspellend model te ontwikkelen omtrent de korte termijn genezing van enkelbandletsels met behulp van een eenvoudige schaal: de functie score. Als vuistregel kan hieruit worden afgeleid dat indien de pa-tiënt wandelend binnenkomt, hij of zij een grote kans heeft dat het een licht letsel is en binnen twee weken genezen. Zwelling en pijn zijn slechte voorspellers voor herstel.

DEEL 3

ACHTERGROND VAN HET ONDERZOEK

In Nederland zijn bijna 5 miljoen sporters actief, waarvan er meer dan de helft jaarlijks een letsel of blessure oplopen tijdens de sportbeoefening. Hiervan worden er 1,2 miljoen jaarlijks medisch behandeld. Een kwart van deze letsels betreft het kapselbandapparaat van de enkel. Nog afgezien van de medische kosten die dit met zich meebrengt, zijn ook de kosten in verband met ziekteverzuim alsmede tijdelijke of blijvende arbeidson- geschiktheid aanzienlijk. Circa 20% van alle geblesseerden inzake enkelbandletsels kent als gevolg hiervan een arbeids- of schoolverzuim van 7,3 dagen, en zorgt voor zo'n 10-15% van alle werkverzuim in Nederland.

Ten aanzien van de behandeling van laterale enkelbandletsels bestaat er in de literatuur geen uniformiteit. Dit wordt ten dele veroorzaakt door de gebrekkige diagnostiek. Laterale enkelbandletsels laten zich met de huidige mogelijkheden in de beeldvormende diagnos-tiek (röntgen) moeilijk vaststellen. Ook met andere beeldvormende

diagnostische technieken, zoals echografie, CT-scan is de aanwezigheid en ernst van het letsel niet goed te bepalen. Daarnaast blijkt dat, omdat de behandelresultaten van operatie of bandagetherapie, één jaar na letsel vergelijkbaar zijn en omdat in feite alle laterale enkelbandletsels zich lenen voor bandagetherapie de ernst van het letsel niet of nauwelijks van invloed is op het herstel op lange termijn.
Herstel van de functie op de korte termijn (weken) wordt behalve door mogelijke instabiliteit mede bepaald door de mate van zwelling rondom het enkelgewricht. Deze zwelling wordt veroorzaakt door hematoom- en oedeemvorming rondom het verscheurde kapselbandapparaat. De zwelling kan worden tegengegaan door middel van ijs, drukverbanden, rust en elevatie in de eerste uren na letsel.
In de literatuur wordt (laag vermogen) laser therapie in een aantal publikaties vermeld als een effectieve aanvullende therapievorm bij de behandeling van weke delen letsels. In een aantal gerandomiseerde effectonderzoeken is een versnelde pijnvermindering en een sneller functioneel herstel gerapporteerd. Alhoewel het hier gerandomiseerde onderzoeken betreft, was de onderzoeksmethode niet optimaal en zijn er tevens vragen over de toegepaste dosering van lasertherapie, zowel in vaststelling van de gehanteerde dosis als in het gebruik van de optimale dosis. Toch wordt lasertherapie in de dagelijkse (sport- en fysiotherapeutische) praktijk veel gebruikt ter behandeling van laterale enkelbandletsels.

Werkingsmechanisme van laser

Er zijn twee theorieën die het werkingsmechanisme van lasertherapie proberen te verklaren. Eén theorie stelt dat in het geval van een letsel of trauma de weefseltoestand verandert, waar-door de elektromagnetische communicatie tussen cellen verslechtert. Lasertherapie zou deze disbalans kunnen herstellen. De andere theorie stelt dat laserlicht aangrijpt op membraaneiwitten van de cel en zodoende de stofwisseling in de cel beïnvloedt. De biologische effecten die aan laser worden toegeschreven zijn: pijndemping, ontstekingsremming en herstel van bot-, spier- en bindweefsel.
Ten aanzien van de gebruikte doseringen bestaat er geen overeenstemming. Het is vooralsnog onduidelijk met welke dosering en met welke golflengte laag vermogen lasers het meest effectief zijn. Laag vermogen lasers zijn in tegenstelling tot chirurgische lasers, bij applicatie via de huid onschadelijk en laten een grote variatie in doseringen toe. Een bovengrens in de dosering voor softlaser therapie wordt pas gevonden vanaf 450 J/cm^2; dan treden weefseleffecten in de vorm van oedeem en eerstegraads verbranding op. Ten tijde van het begin van het onderzoek (1993) onderscheidde men binnen de softlaser therapie twee dosimetrische opvattingen; de opvatting dat er laag gedoseerd dient te worden versus de opvatting dat er hoog gedoseerd dient te worden. Lage doseringen bevinden zich voor softlaser tussen 0,01 en 0,5 J/cm^2 terwijl hoge doseringen zich tussen 0,5 en 5 J/cm^2 bevinden.

Onderzoeksopzet

Onderzoeksvraag

Uit het bovenstaande kunnen twee vraagstellingen worden gedestilleerd.
Wat is de toegevoegde waarde van lasertherapie als aanvulling op de gebruikelijke functionele behandeling van

laterale enkelbandletsels, en welke dosering is het meest effectief?
Bij de beantwoording van deze onderzoeksvragen wordt gelet op zowel korte als lange termijn effecten. Voor de korte termijn zijn pijn- en zwellingsvermindering alsmede functieherstel van belang, terwijl op de middellange en lange termijn werk- en sporthervatting en het verminderen van het aantal recidieven (herletsels) op de voorgrond staan.

Design

In dit onderzoek hebben we het effect van lasertherapie in twee doseringen vergeleken met een placebo laserbehandeling door middel van een geblindeerd en gerandomiseerd experiment, waarbij de laserbehandelingen als extra therapie gegeven worden op een gestandaardiseerde en geaccepteerde behandeling.

Selectie van patiënten

In dit onderzoek zijn in totaal 217 patiënten over 3 groepen gerandomiseerd, waarbij er voor gezorgd is dat in alle drie de groepen evenveel personen met een licht of ernstig letsel zitten, terwijl ook het aantal sporters per onderzoeksgroep vergelijkbaar is. Alle patienten mogen aan het onderzoek meedoen indien zij zich binnen 48 uur na trauma op de eerste hulp melden met een lateraal enkelbandletsel, tussen de 18 en 65 jaar oud zijn en het informed consent ondertekenen.
Patiënten die in het voorafgaande jaar al eerder een lateraal enkelbandletsel hebben gehad of die al eens aan de enkel zijn geopereerd worden voor het onderzoek uitgesloten. Ook patiënten met fracturen, open wonden of afwijkingen aan de onderste ledemaat of voet worden uitgesloten. Patiënten met congenitale afwijkingen, systeemziekten en verstandelijke handicap alsmede personen die de Nederlandse taal niet machtig zijn worden eveneens uitgesloten. Ook patiënten die gedurende de behandelperiode van het onderzoek van plan zijn op vakantie te gaan, of buiten de regio te gaan wonen c.q. werken worden van deelname uitgesloten.
Patiënten die geschikt zijn om mee te doen krijgen een gedetailleerde beschrijving van het onderzoek, waarin ook staat dat men door het lot aan een behandelgroep werd toegewezen. Na deze intake procedure door de arts op de eerste hulp, worden zij de volgende ochtend op de afdeling fysiotherapie verwacht voor de eerste behandeling en meting.

Keuze van de behandelingen

In ieder onderzoek streeft men naar een voldoende groot contrast tussen de diverse onderzochte groepen om klinisch relevante verschillen te kunnen ontdekken. In dit onderzoek is uitgegaan van een standaard behandeling bij enkelbandletsels, waarbij de lasertherapie als extra moest dienen. Om een zuivere schatting van het effect van lasertherapie te krijgen is één groep behandeld met een placebo-laser, terwijl beide andere groepen echte laserbehandelingen krijgen, maar met verschillende doseringen. In de onderstaande paragrafen worden de keuzen voor de behandelingen uitgelegd.

Aangezien er in de literatuur geen duidelijkheid bestaat over de juiste dosering of intensiteit hebben we gekozen voor drie doses, namelijk hoog (5 J/cm^2), laag (0,5 J/cm^2) en placebo (0 J/cm^2), waarbij de intensiteit in het weefsel op respectievelijk 0.7, 0.07 en 0 Joule per cm^2 ligt.
De standaardbehandeling die iedere deelnemer krijgt bestaat uit vier dagen een drukverband met vette watten gevolgd door 3½ week een Push® brace. Patiënten krijgen tevens ge-

standaardiseerde huiswerkoefeningen en informatie over het te verwachten herstel.
De laserbehandeling is in de drie groepen gelijk, met uitzondering van de dosis. De meest pijnlijke plek aan de buitenkant van de enkel (door de patiënt en therapeut bepaald) wordt met de laser gedurende 200 seconden behandeld. Hierbij wordt de te bestralen plek eerst met alcohol schoongemaakt. Alle groepen volgen hetzelfde behandelschema. In de eerste week krijgt men 5 behandelingen, in de tweede week 3 en in week drie en vier telkens 2 behandelingen per week. Zowel de patiënt als de therapeut zijn geblindeerd voor de behandeling; dat wil zeggen dat ze geen idee hebben in welke behandelgroep de patiënt zit. Na afloop van de behandeling wordt de voet steeds weer ingezwachteld of weer voorzien van de brace.

Effectmeting

In dit onderzoek hebben we gekozen voor effectmaten die de vanuit het perspectief van de patiënt de klacht het beste weergeven. Gekozen zijn voor de mate van pijn als een rapportcijfer (0 tot 10) en een functiescore (van 0 tot 100). De functiescore is een 100 punten schaal die pijn, zwelling, instabiliteit, gewicht op de aangedane voet nemen en looppatroon combineert. Als secundaire effectmaten is gekozen voor het aantal dagen werk- en sportverzuim, functioneren in activiteiten van het dagelijks leven (ADL), drukpijn, enkelzwelling, recidieven, subjectief ervaren herstel en tevredenheid over de behandeling en herstel.
Er wordt gedurende alle behandeldagen gemeten, en daarna na zes weken, en 3, 6, 9 en 12 maanden na randomisatie. Daarnaast wordt door de arts aan het begin van de behandelingen en na zes weken bepaald hoe de stabiliteit en functionaliteit van de enkel is.

Gegevensopslag en statistische bewerking

Alle uit het onderzoek verkregen gegevens worden anoniem verwerkt en opgeslagen in dBASE IV. De data zijn gecontroleerd op volledigheid, inconsistenties en protocolafwijkingen. Vervolgens worden de data geanalyseerd met het statistische pakket SPSSWIN/PC. De analyse geschiedt door middel van het intention-to-treat principe: alle deelnemers, inclusief diegenen met slechte compliance en uitvallers, blijven tijdens de analyse in de groep waartoe zij gerandomiseerd zijn. De data analist was gedurende de analyses niet op de hoogte van de doseringen die de drie onderzoeksgroepen hebben gehad. De verschillen in primaire en secundaire uitkomstmaten tussen de drie groepen worden met ANOVA (tweezijdig) geanalyseerd. Een nadere analyse in subgroepen (leeftijd, sportdeelname, soort werk) wordt uitgevoerd om te kijken of deze factoren van invloed zijn op het herstel. Pas na volledige analyse wordt de blindering doorbroken.
Verschillen tussen de groepen op de lange termijn worden eveneens met ANOVA (tweezijdig) geanalyseerd, of in geval van dichotome variabelen wordt met behulp van een Cox regressiemodel gerekend, terwijl verschillen in sporthervatting tussen de groepen met een Kruskal-Wallis test voor niet normaal verdeelde data wordt berekend.

Resultaten

Beschrijving van de patiëntenpopulatie

Van 1 September 1993 tot 31 December 1995 zijn 217 patiënten gerandomiseerd. Van alle patiënten zijn baseline gegevens verkregen.

Van de 2064 behandelingen (217 x 12) zijn er slechts 43 gemist. De uitval kwam voor 0.4% voor rekening van de groep met de lage laser dosering, 0.7% van de groep met de hoge laser dosering en 1% van de placebo groep.

De 1 jaars follow-up is uiteindelijk door 18 patiënten gemist; 6 in de groep met de lage laser dosering (L) groep, 4 van de groep met de hoge laser dosering (H) groep en 8 van de placebo groep (P). Deze waren telefonisch of schriftelijk onbereikbaar, verhuisd of reageerden niet. In tabel 6 staan de baseline gegevens van de drie groepen.

Tabel 6: Baseline gegevens van de onderzoekspopulatie

	lage laser dosis	hoge laser dosis	placebo
aantal patiënten	74	72	71
gemiddelde leeftijd (sd)	30,2 (9,6)	33,2 (10,4)	30,9 (10,3)
geslacht (vrouw/man)	30/44	17/55	22/49
baseline metingen			
gemiddelde functie score (sd)#	13,1 (10,6)	12,1 (10,8)	13,4 (11,8)
gemiddelde pijn overdag (sd)*	3,7 (2,7)	3,8 (2,5)	3,6 (2,8)
gemiddelde pijn 's ochtends (sd)*	4,8 (2,9)	4,4 (2,9)	4,2 (3,0)
gemiddeld aantal pijnstillers (sd)	0,5 (1,0)	0,8 (1,4)	0,7 (1,4)
gemiddelde drukpijn in kg/cm² (sd)			
lig calcaneo fibulare	3,2 (1,9)	3,3 (1,9)	3,5 (1,9)
lig talofibulare anterius	1,7 (1,3)	1,8 (1,4)	1,6 (1,0)
lig talofibulare posterius	3,6 (2,0)	3,1 (2,0)	3,3 (1,8)
gemiddelde sport categorie°	2,2 (0,8)	2,1 (0,8)	2,1 (0,8)
gemiddelde prognose omtrent herstel (sd)¿			
na twee weken	7,2 (1,2)	6,9 (1,2)	7,4 (1,2)
na vier weken	9,4 (0,8)	9,2 (0,8)	9,4 (0,9)

gemeten op een 100 punts functie schaal
* gemeten op een rapportcijfer schaal (0 is geen pijn, 10 is uiterst pijnlijk)
° gemeten op een 4-punts schaal (0 is geen sport, 1 recreatief, 2 competitie, 3 professioneel)
¿ gemeten op een rapportcijfer schaal (0 is niet hersteld, 10 is volledig hersteld)

De groepen zijn op baseline niveau goed vergelijkbaar. Alleen de gemiddelde leeftijd van de hoge laser dosering groep is iets hoger dan van de andere twee groepen en de verhouding tussen mannen en vrouwen verschilt.

Bij verdere verdeling van de groepen naar type werkzaamheden of zwaarte van de verrichte arbeid zijn geen opmerkelijke verschillen te constateren (zie tabel 7).

Tabel 7: Indeling naar type en zwaarte van de arbeid

		hoge laser dosis	lage laser dosis	placebo
blue/white collar		37/30 (5)*	37/35 (2)	35/32 (4)
arbeid	licht	17	21	20
	normaal	18	19	19
	zwaar	30	28	27
	erg zwaar	7	6	5

* tussen haakjes staan de aantallen personen die aangeven niet te werken; huisvrouwen en studerenden zijn als respectievelijk blue en white collar werkenden aangemerkt

KORTE TERMIJN RESULTATEN

Tabel 8 laat de resultaten zien van de primaire en secundaire effectmaten, gedurende de behandelperiode en de afsluiting daarvan (eerste vier weken).

Op 10 en 14 dagen na het trauma treden de grootste verschillen op tussen de groepen. Er zijn geen significante verschillen waarneembaar in ervaren pijn, drukpijn en zwellingsafname. De uitkomstmaten functie en ADL beperking laten de grootste verschillen tussen de groepen zien op 10 en 14 dagen: met de placebogroep gaat het hier significant beter. Ook qua werkhervatting presteert de placebogroep significant het best: vergeleken met de lasergroepen zijn patiënten in de placebogroep 3,4 tot 4,7 dagen eerder aan het werk. Het verschil in dagen tot sporthervatting is gering. Het subjectief ervaren herstel, een samenvattende waarderingsmaat van de patiënt, laat een klein voordeel zien voor de placebogroep ten opzichte van de twee lasergroepen.

Tabel 8: Uitkomsten (gemiddelden en sd) gedurende de eerste vier weken van het onderzoek en p-waarden van de verschillen (geanalyseerd m.b.v. ANOVA)

Primaire effectmaten		Lage laser dosis n = 74	Hoge laser dosis n = 72	Placebo n = 71	P-waarde (twee-zijdig)
Ervaren pijn (gem, sd)@	dag 5	2,8 (2,2)	2,9 (2,1)	3,3 (2,4)	0,6
	dag 10	2,0 (2,0)	2,1 (1,9)	1,7 (1,9)	0,48
	dag 14	1,6 (1,9)	1,7 (1,7)	1,4 (1,7)	0,42
	dag 28	0,6 (1,0)	0,8 (1,2)	0,4 (1,0)	0,14
Functie score (gem, sd)*	dag 5	25,1 (15,0)	24,7 (15,1)	25,7 (14,8)	0,92
	dag 10	42,2 (16,1)	44,1 (14,9)	49,9 (15,9)	0,01
	dag 14	56,3 (16,1)	56,0 (15,7)	60,0 (17,1)	0,03
	dag 28	73,6 (14,7)	74,3 (17,5)	76,4 (14,9)	0,5
Secundaire effectmaten					
Werkhervatting in dagen (gem, sd)		12,5 (11,1)	11,2 (10,0)	7,8 (9,2)	0,02
Sporthervatting in dagen (gem, sd)		27,3 (7,9)	27,4 (7,5)	25,3 (9,8)	0,26
		(2,6)	(2,8)	(2,7)	
ADL beperking (gem, sd)@	dag 5	4,4 (2,7)	4,9 (2,4)	4,8 (2,2)	0,42
	dag 10	3,7 (2,6)	3,3 (2,1)	2,6 (2,1)	0,03
	dag 14	2,8 (1,5)	2,7 (1,5)	2,0 (1,6)	0,08
	dag 28	0,9	1,0	0,8	0,83
Subjectief ervaren herstel aan het einde van de behandeling (gem, sd)@		(0,9) 8,6	(0,9) 8,7	(0,8) 8,9	0,05

@ Gemeten op een rapportcijfer schaal (niet beperkt 0, uiterst beperkt 10)
* Gemeten op een 100 punts schaal (0 is uiterst beperkt, 100 uitstekende functie)

Lange termijn resultaten

In tabel 9 staan de resultaten zoals gemeten gedurende de lange termijn follow-up. Ook na zes weken blijft het opmerkelijke verschil in werkhervatting bestaan: het verschil is zelfs iets groter dan bij 4 weken.

Kortom, de placebogroep vertoont het meeste herstel. Bij sportverzuim is een verschil van ongeveer 7 dagen te zien, waarbij de placebogroep het snelst weer aan het sporten is.
De andere uitkomstmaten laten geen significante verschillen zien op 3, 6, 9 en 12 maanden na letsel.

Tabel 9: Lange termijn resultaten

	Lage laser dosis	Hoge laser dosis	Placebo dosis	Anova, Chi-square, of Kruskall-Wallis (2-zijdig)
Werkhervatting (gem, sd)				
aantal patiënten	74	72	71	
op 4 weken	12,5 (11,1)	11,2 (10,0)	7,8 (9,2)	0,02
op 6 weken	13,1 (12,3)	11,5 (10,7)	7,8 (9,3)	0,013
Sportverzuim (mediaan, range)				
aantal patiënten	68	69	63	
na 9 maanden follow-up	41 (7-274)	40 (10-272)	33,5 (3-275)	0,36[KW]
na 1 jaar follow-up	42 (7-365)	40 (10-272)	34 (3-365)	0,26[KW]
3 maanden				
aantal patiënten	72	72	66	
activiteiten niveau*	5,6 (2,3)	5,7 (2,3)	5,4 (2,6)	0,82
klachtenvrij†	8,7 (1,7)	8,8 (1,8)	8,6 (2,2)	0,80
functie score‡	85,3 (15,7)	85,5 (15,9)	84,5 (21,5)	0,94
gebruik brace in ADL (ja/nee)	7/65	6/66	6/60	0,96[f2]
gebruik brace tijdens sport (ja/nee)°°	28/17	27/21	18/21	0,33[f2]
6 maanden				
aantal patiënten	69	70	63	
activiteiten niveau*	5,7 (2,2)	6,0 (2,2)	6,1 (2,3)	0,54
klachtenvrij†	9,2 (1,2)	8,9 (1,7)	9,3 (1,1)	0,38
functie score‡	88,5 (13,5)	88,4 (13,6)	89,8 (15,1)	0,83
gebruik brace in ADL (ja/nee)	3/66	3/67	5/57	0,49[f2]
gebruik brace tijdens sport (ja/nee)°°	23/21	24/24	15/27	0,25[f2]
9 maanden				
aantal patiënten	68	69	63	
activiteiten niveau*	5,8 (2,3)	5,9 (2,2)	5,9 (2,3)	0,93
klachtenvrij†	9,4 (1,3)	9,4 (1,1)	9,5 (1,1)	0,91
functie score‡	89,2 (13,9)	89,8 (13,5)	88,8 (15,2)	0,92
gebruik brace in ADL (ja/nee)	2/66	2/67	2/60	0,99[f2]
gebruik brace tijdens sport (ja/nee)°°	14/31	18/30	10/31	0,41[f2]
12 maanden				
aantal patiënten	68	69	63	
activiteiten niveau*	5,8 (2,3)	6,2 (2,2)	5,9 (2,2)	0,61
klachtenvrij†	9,5 (1,2)	9,5 (1,0)	9,7 (0,8)	0,59
functie score‡	89,6 (14,8)	91,5 (13,0)	88,9 (14,5)	0,53
gebruik brace in ADL (ja/nee)	0/68	0/69	2/59	0,15[f2]
gebruik brace tijdens sport (ja/nee)°°	15/29	8/31	11/37	0,31[f2]

* gemeten op een 0 - 10 punten schaal
† gemeten op een 0 - 10 punten schaal (10 is klachtenvrij)
‡ gemeten op een 0 - 100 punten schaal (0 is geen functie, 100 perfecte functie)
°° alleen van toepassing op sporters

Tabel 10 tenslotte laat het aantal recidieven per drie maanden zien. Het cumulatieve aantal recidieven na 1 jaar verschilt significant tussen de drie groepen. De groep met een lage dosis laser laat de meeste recidieven zien.

Tabel 10: Aantallen recidieven per drie maanden

recidieven per periode (maanden)	lage laser dosis	cum	hoge laser dosis	cum	placebo	cum	totaal	Chi²	Trend analyse
3 maands recidieven / N	11/72		6/72		5/66		22/210	0,26	0,18
6 maands recidieven / N	7/69	18	2/70	8	4/63	9	13/202	0,22	0,08
9 maands recidieven / N	4/68	22	2/69	10	1/62	10	7/199	0,39	0,346
12 maands recidieven / N	0/68	22	3/69	13	0/62	10	3/199	0,04	0,037

DISCUSSIE

De effectiviteit van laser therapie wordt meestal bestudeerd op basis van korte termijn resultaten. Dit komt mede omdat de meeste auteurs geïnteresseerd zijn in de korte termijn effecten zoals pijn- en zwellingsvermindering. Dit onderzoek laat zien dat lasertherapie ook op de middellange en lange termijn (1 jaar) interessante bevindingen oplevert. Het is opvallend dat zowel op de korte als de lange termijn de placebogroep beter presteert qua werkverzuim en sporthervatting. Op de korte termijn zijn ook functiescore en ADL beperking op bepaalde momenten significant in het voordeel van de placebogroep, terwijl de lange termijn laat zien dat het aantal recidieven bij de placebogroep significant het geringst is. Hierbij dient aangetekend te worden dat het aantal recidieven in de lage doseringsgroep het grootst is en daarmee verantwoordelijk is voor het significante verschil tussen de groepen. Het aantal recidieven in dit onderzoek is vergelijkbaar met dat van andere onderzoeken. Toch is niet te verklaren waarom de groep met de laagste dosering de meeste recidieven laat zien.
Als we het gemiddelde werkverzuim veroorzaakt door enkelbandletsels in Nederland (7.3 dagen) vergelijken met dat van de placebogroep (7.8) dagen, dan zijn deze redelijk tot goed vergelijkbaar.

Het werkverzuim van de lasergroepen is gemiddeld 4 dagen langer; deze zijn waarschijnlijk grotendeels toe te schrijven aan het negatieve effect van laser. Subgroepanalyses op type werkzaamheden en zwaarte van het werk lieten tussen de drie groepen geen verschillen zien (zie ook tabel 3b). Van de 2283 dagen werkverzuim in dit onderzoek, zijn er 590 toe te schrijven aan lasertherapie. De gevonden effecten zijn ook niet toe te schrijven aan verschillen in de onderzoeksgroepen. Immers, baseline variabelen, prognostische variabelen, type werkzaamheden, zwaarte van het werk, niveau van sportbeoefening waren vergelijkbaar.

De blindering van dit onderzoek was volledig en succesvol. Patiënten, behandelaars, effectbeoordelaars en data-analisten waren geblindeerd voor de groepsindeling, en bleven dat ook tot na de hoofdanalyses waren uitgevoerd. Bij controle voor blindering bleek deze geslaagd te noemen.

Helaas moeten we, gezien het bovenstaande concluderen, dat lasertherapie niet de gewenste of verwachte effecten sorteert bij de behandeling van enkelbandletsels, die men in het algemeen verwacht had. Op basis van deze bevindingen lijkt het dan ook verstandig 904 nm laser niet meer te gebruiken bij de behandeling van enkelbandletsels.

EIGEN MENING

Tenslotte kan de lezer zich afvragen of de vragen die gesteld werden aan het begin van dit proefschrift afdoende beantwoord zijn. De verrichte reviews laten zien dat er nog veel onzekerheid bestaat over effectieve interventies bij acute enkelbandletsels. Tevens is de effectiviteit van 904 nm lasertherapie niet aan te tonen bij aandoeningen van het bewegingsapparaat.

Dit proefschrift laat zien dat een goede inschatting van het beloop van een acuut enkelbandletsel direct na trauma goed mogelijk is, maar dat nader onderzoek het ontwikkelde instrument moet bekrachtigen.

Aangaande de effectiviteit van 904 nm laser therapie kan gesteld worden dat het hier verrichte onderzoek duidelijk aangeeft dat toepassing ervan bij laterale enkelbandletsels geen zin heeft. In hoeverre dit ook voor andere, vergelijkbare aandoeningen van het bewegingsapparaat geldt dient nader uitgezocht te worden. Het is mogelijk dat bij andere indicatiegebieden laser wel effectief is, temeer daar ons experiment laat zien dat er een interactie bestaat tussen bestraald weefsel en laser. Het gevonden vertraagde herstel gedurende de acute ontstekingsfase zou voor patiënten met een chronische ontsteking (bijv. reuma) gunstig kunnen zijn; immers demping van de ontsteking zou in die gevallen een vermindering van gewrichtsbeschadiging en vermindering van klachten kunnen impliceren. Nader onderzoek dient hierover uitsluitsel te geven.

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In het najaar van 1991 kwam ik op uitnodiging van Frans van den Wildenberg eens praten bij de vakgroep algemene heelkunde van het azM over het opzetten van een grote studie naar de effectiviteit van laag vermogen lasertherapie bij laterale enkelbandletsels. We konden elkaar al snel vinden en onder het genot van sloten koffie en met veel plezier werd al snel een eerste voorstel gelanceerd. Lex Bouter hielp in die fase letterlijk van onder de kerstboom mee met schrijven. Na enige traumatische ervaringen in subsidieland werd het laser-project alsnog in 1993 gefinancierd. Het profileringsfonds, Uniphy bv, NEA international en de vakgroep epidemiologie van de UM stonden garant voor de financiering van het project. In de herfst van dat jaar kon er worden gestart. Nu, ruim vier jaar later, ligt het eindproduct voor u.
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Frans van den Wildenberg is begeleider van het eerste uur. Van achter zijn onafscheidelijke pijp kijken je altijd twee pretogen tegemoet, en voor een inhoudelijke en gezellige discussie gaat hij nooit uit de weg. Ik wil hem bedanken voor zijn geweldige inzet tijdens de praktische periode van het onderzoek, en zijn onstuitbare optimisme en enthousiasme in de begeleiding. Samen met Frans huldig ik het standpunt dat de smakelijkste discussies in het restaurant plaats vinden.

Ton Lenssen is als onderzoeksassistent de spil in het laseronderzoek geweest. Zonder zijn inzet en motivatie, maar ook zijn relativerende opmerkingen en actieve meedenken, was dit onderzoek nooit zo goed uit de verf gekomen. Ook denk ik met veel plezier terug aan alle 'randverschijnselen' die we samen hebben beleefd, en de vele autoritten van en naar bijeenkomsten in den lande, waar we over het wel en wee van de fysiotherapie hebben gefilosofeerd. Ik ben dan ook heel blij dat je mijn paranimf wil zijn.

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Arianne Verhagen is mijn andere paranimf, één van de eerste studenten van eigen kweek en mijn eerste AIO die ik samen met Riekie begeleid. Arianne, al jaren ben je met jouw no-nonsense benadering een mooie sparringspartner op onderzoeksgebied, en ik hoop dat we samen nog vele 'stukjes over de fysiotherapie' produceren. Bovendien weet je de weg in Amsterdam, wat voor een jongen uit de provincie mooi meegenomen is.

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Rob de Bie, Januari 1998

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ARTICLES EMANATING FROM THIS THESIS

Bie RA de, Verhagen AP, Lenssen AF, Vet HCW de, Wildenberg FAJM, Kootstra G, Knipschild PG. Efficacy of conservative interventions in the treatment of acute lateral ankle sprains: a systematic review. (submitted)

Bie RA de, Verhagen AP, Lenssen AF, Vet HCW de, Wildenberg FAJM, Kootstra G, Knipschild PG. Efficacy of 904 nm laser therapy in musculoskeletal disorders: a systematic review. Physical Therapy Reviews (accepted).

Bie RA de, Vet HCW de, Wildenberg FAJM, Lenssen AF, Knipschild PG. The prognosis of ankle sprains. International Journal of Sports Medicine 1997; 18(4): 285-9.

Bie RA de, Vet HCW de, Wildenberg FAJM, Lenssen AF, Bouter LM, Knipschild PG. Efficacy of laser therapy in ankle sprains: design of a randomised clinical trial. Laser therapy 1997; 9: 165-72.

Bie RA de, Vet HCW de, Lenssen AF, Wildenberg FAJM, Kootstra G, Knipschild PG. Efficacy of low level laser therapy in ankle sprains: short term results of a randomised clinical trial. Archives of Physical Medicine and Rehabilitation (accepted).

Bie RA de, Vet HCW de, Lenssen AF, Wildenberg FAJM, Kootstra G, Knipschild PG. Efficacy of low level laser therapy in ankle sprains: one year results of a randomised clinical trial. Archives of Physical Medicine and Rehabilitation (accepted).

Curriculum vitae

Rob de Bie werd geboren op 27 augustus 1963 te Onstwedde, Groningen. Na het behalen van het Atheneum-B diploma aan de Thorbecke Scholengemeenschap te Zwolle in juni 1983, studeerde hij fysiotherapie aan de Deventer Academie voor Fysiotherapie. Na het behalen van het diploma fysiotherapie in juli 1987, studeerde hij tot juni 1991 Bewegingswetenschappen aan de Rijksuniversiteit Limburg, met als keuzevakken epidemiologie en docententraining. Hij studeerde af op de effectiviteit van laag frequent magneetveldtherapie.

Daarna werd hij als toegevoegd docent bij de vakgroep epidemiologie aangesteld met als taakopdracht het ontwikkelen van een onderzoekersopleiding voor fysiotherapeuten. In februari 1992 kreeg hij bij de vakgroep Epidemiologie een vaste aanstelling als universitair docent, met als taakopdracht het verzorgen van epidemiologie onderwijs binnen de Faculteit der Gezondheidswetenschappen en het verrichten van onderzoek binnen het onderzoeksinstituut Extra, op het terrein van het bewegingsapparaat. Van 1987 tot 1992 is hij tevens werkzaam geweest als fysiotherapeut in praktijk voor fysiotherapie Mays te Maastricht.

Rob volgde cursussen bij Bouter, Kleinbaum, Miettinen, Rothman en Sackett.

Tevens is Rob editor voor de Cochane Back Group, de Cochrane Musculoskeletal Group en het tijdschrift Physical Therapy Reviews. Samen met Riekie de Vet coördineert hij het Cochrane Rehabilitation and Related Therapies Field.