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Low-intensity pulsed ultrasound (LIPUS) in fresh clavicle fractures: A multi-centre double blind randomised controlled trial

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Summary

Background: Several randomised trials have been published on the effect of low-intensity pulsed ultrasound (LIPUS) on fracture healing in both distal radius and tibia fractures. Most studies showed a positive effect on time to clinical and radiological healing. We hypothesised that LIPUS has a beneficial effect on the healing of fresh clavicle fractures as well and studied its effect in non-operatively treated shaft fractures.
Methods: We conducted a randomised double blind, placebo-controlled multi-centre trial in 101 adult patients with a non-operatively treated fresh clavicle shaft fracture. Of these patients, 49 used a placebo transducer and 52 patients had an active transducer with ultrasound stimulation (Exogen 2000®). Data were analysed on intention to treat basis. Baseline parameters of both groups were not significantly different.
Results: There were no differences in time to subjective clinical fracture healing, resumption of daily activities, sports or professional work, Visual Analogue pain Scores (VAS) and use of pain medication.
Conclusion: Our findings did not confirm that LIPUS accelerates clinical healing time of fresh clavicle shaft fractures.
Level of evidence: Level 1 evidence that low-intensity pulsed ultrasound does not accelerate clinical fracture healing in non-operatively treated fresh midshaft clavicle fractures.
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Introduction

Ultrasound is sound at an ultrahigh, inaudible frequency. In healthcare these acoustic waves are used for both diagnostic and therapeutic modalities. Diagnostic ultrasound has become standard practice in several disciplines, i.e. general surgery, trauma, urology and vascular surgery, at intensities between 0.5 and 50 mW/cm^2 with a frequency of 1–10 MHz.[14] Therapeutic ultrasound can be divided into two categories: high-intensity ultrasound with peak intensities from 5000 to 15 000 W/cm^2 and low-intensity ultrasound with intensities of 0.5–3000 mW/cm^2.[6] This low-intensity ultrasound is used in physical therapy (pain reduction, heating, increasing blood flow, etc.), while the high intensity seems to have potential for treating tumours by selectively heating tissue and causing necrosis.[6,25] One study published on an experimental device in the 1950s showed no positive effects of ultrasound on bone healing, and sometimes it even had disastrous effects.[2] It was not before the early 1980s that Duarte presented his first report on accelerated bone healing in animals using a different device at a very low intensity of 30 mW/cm^2 with a pulsed signal, while at the same time Dyson reported his first results of ultrasound stimulation of bone healing in animals.[7,8] A few years later Duarte's first results of clinical activities in humans were presented at the Annual Meeting of Latin American Orthopaedic Association. These studies showed stimulating effects on bone growth and inspired a number of studies in animals and humans. The first randomised, placebo-controlled study in humans on the effect of healing time of tibia shaft fractures was performed by Heckman et al. and showed acceleration in fracture healing, from 114 days in the control group to 86 days in the active ultrasound group.[11] Patients were treated with ultrasound stimulation daily during 20 min at an intensity of 30 mW/cm^2 SATA (spatial average, temporal average), with a burst width of 200 μs in 1.5 MHz sine waves, pulsed at 1 kHz. Another double blind, randomised controlled study was performed by Kristiansen et al. to study the effects of ultrasound on distal radius fractures and had comparable results.[13]

The clinical relevance of this accelerated radiological healing however has not been described. Maybe this explains why the routine use of ultrasound in the treatment of fresh fractures has not yet become common practice. In the Netherlands pulsed ultrasound is an accepted method of treatment for non-unions, but every treatment must be paid for by the hospital itself and therefore it is not propagated. In order to further examine the effect of low-intensity pulsed ultrasound (LIPUS) on clinically relevant fracture healing issues like pain, function and resumption of professional and personal activities, we conducted a trial on non-operatively treated closed midshaft clavicle fractures in adults. The choice to study clavicle fractures was decided by the large potential number of study participants in a country with ten million cyclists and approximately 8000–12 000 clavicle fractures per year.[24,20] Furthermore, fractures of this nature are easily accessible for both treatment by LIPUS and determination of clinical healing by the patient and the doctor and fractures of the clavicle do not need specific immobilisation or stabilisation.

Materials and methods

We performed a multi-centre, double blind randomised placebo-controlled trial. In this study, patients seen at the Emergency Departments of the participating hospitals between 1 March 2001 and 31 December 2003 who presented with an isolated, closed midshaft fracture of the clavicle, were examined. Six hospitals participated in the study (throughout the centre of the Netherlands, see acknowledgements). Approval of the local Medical Ethical Committee (METC) was obtained in all participating hospitals and all patients provided written informed consent.

In- and exclusion criteria

Inclusion criteria were: age 18 years and older; diaphyseal fracture (group I fracture according to Allman's classification)[1]; start of treatment within 5 days after trauma; sufficient understanding of Dutch language and signed informed consent (Table 1).

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Age $\geq$ 18 years
Monotrauma
Shaft fracture
Fresh fracture (<5 days)
Understanding of Dutch language
Written informed consent
Exclusion criteria
Age < 18 years
Multiple trauma
Re-fracture
Pathological fracture
Open fracture, or imminent skin perforation
Fracture in metaphysis
No possibilities for follow up

Multi-trauma patients, patients with an open or pathological (re-)fracture and patients with fractures in the medial or lateral metaphyseal area of the clavicle were excluded.

Total numbers of eligible patients were estimated from the national injury database (Stichting Consument en Veiligheid) and added up to a total of 1050 patients in the six participating hospitals during the study period.[24] Enrolment for this study took place at the first visit of the patient to one of the participating hospitals. Individual participation in the study started on the first successful out-patient clinic visit (on the first business day after trauma) and depended on the availability of a study transducer. It appeared that, especially in the first months of the study, study-equipment (transducers) was not in stock and consented patients could not be included in the trial. This de-motivated staff in the Emergency Department to continue recruiting participants in the study. In spite of that problem, with the thousands of non-operatively treated clavicle fractures per year in the Netherlands, we anticipated the patient recruitment to go much faster. In contrast to our plan, it took two years before sufficient numbers of people for each arm (>50 per arm) were included. In the Netherlands, clavicle fractures routinely are treated non-operatively (except for accompanying neurovascular damage or broken skin) and even sometimes are treated outside the hospital without X-rays. This could mean that any extra treatment and out-patient clinic units are regarded as overdone, and did not help to recruit patients for the study. Thus Emergency Departments may not be the ideal place to include people for randomised controlled trials, because it takes a considerable amount of time to inform patients and get all the paperwork done.

For each participating hospital consecutive numbered transducers were delivered in packs of four. Each hospital supply contained two randomly assigned active transducers and two placebo transducers (block randomisation) to ensure equal partitioning of both treatment regimens in all hospitals. Randomisation took place at the site of the manufacturer (Smith and Nephew Inc., Memphis, USA). The placebo transducers looked identical to the active ones and could only be identified by a unique serial number that was exclusively known by the manufacturer and was needed for decoding at the completion of the entire study (1 August 2004). At the end of the treatment period, the transducers were analysed with the help of a personal computer and appropriate software (Excom, PCM2000, Smith and Nephew Inc., Memphis, USA). From this analysis treatment compliance and number of successful treatments per transducer could be calculated.

Baseline data were collected concerning: age, gender, side of fracture, type of fracture (according to AO classification, Fig. 1a–c), type of accident, sports activities and professional activities.[17]

All patients were given a diary with a unique identifier (hospital/trial number) in which they had to record a daily update on their (subjective) feeling if the fracture had healed or not. They were also asked to write down a Visual Analogue Score (VAS) of pain and the level of daily activities (at home, at work and at sports) once a day. Daily activities were noted according to patients own judgement; i.e. how many hours of daily household work were performed (vacuum cleaning, dishwashing, etc.). This was also applicable for sport and professional activities, which were expressed as hours of activity per day. VAS was expressed as a cross in a bar with 10 equal sized boxes numbered 1–10. Standard non-steroidal painkillers were pre-

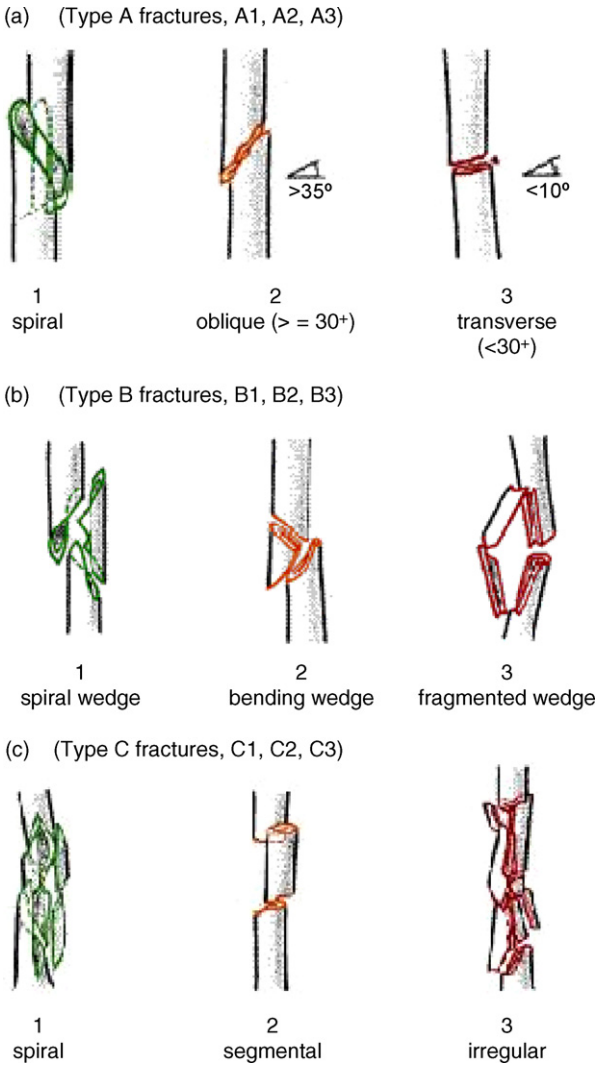


Figure 1 (a) Type A fractures, A1, A2, A3; (b) type B fractures, B1, B2, B3; (c) type C fractures, C1, C2, C3.

scribed (Paracetamol 6 × 500 mg daily, Naproxen 3 × 250 mg daily); patients were asked to record their daily use of painkillers in the first 28 days of the study.

The standard treatment of clavicle fractures in all hospitals was non-operative, consisting of passive support with a collar and cuff for patients' convenience as long as needed. Free arm movements within pain range were allowed from day 1. Patients were taught the use of the transducer and conductive gel and the proper placement and manual fixation of the transducer. They were instructed to apply the transducer daily for one treatment (treatment module automatically switches off after 20 min) during 28 days. Ultrasound treatment was ended after 28 days, because we expected that the majority of fractures would have been healed by that time. All participants were asked to record time of day and actual duration of each transducer application. The experimental group was given an active ultrasound transducer, while the placebo group received a transducer that seemed to the patients to be identical, but that did not produce ultrasound waves.

Outcome measures

We deliberately chose the clavicle fracture because it is easy for both doctor and patient to judge clinical symptoms and the moment of clinical healing is easily defined. We refrained from the use of radiological evidence of fracture healing because the development of visible callus on X-rays is not always related to clinical signs of fracture healing. Moreover, Kristiansen et al. state that in their randomised controlled study with LIPUS all radius fractures had clinically healed before radiological bridging of the fracture was confirmed. In their study clinical examination data were not reliably noted and not reported, but may well have shown no differences between treatment groups.[13] Therefore, our primary outcome measure was subjective fracture consolidation according to the patient. Secondary outcome measures were possible operation, painkiller use, pain (Visual Analogue Scale), adverse events, and resumption of sport and professional or household activities (Table 2). Painkiller use was analysed as the total number of tablets used from the standard medication prescription. Adverse events and failure of fracture healing were all noted according to patients' complaints. For this, every remark that was made in either diary or medical record and that might signal an abnormal (reaction to) fracture consolidation was taken along in the final analysis as potential adverse event or failure of fracture healing.

Table 2 Outcome measures

Primary outcome measure
Fracture consolidation according to the patient
Secondary outcome measures
Operation
Painkiller use
VAS score
Adverse events
Non-union
Resumption of sport, professional or household activities

Technical data

The active ultrasound treatment unit was an Exogen 2000® battery powered Main Operating Unit and a Treatment Head Module transducer (Smith and Nephew Inc., Memphis, USA) that delivers an ultrasound signal intensity of 30 mW/cm^2 SATA (spatial average, temporal average), with a burst width of 200 μs in 1.5 MHz sine waves, pulsed at 1 kHz. Dummy (placebo) transducers produced no signal, but showed similar messages on the display screen and could not be distinguished from active transducers.

Follow up

All patients were seen in the out-patient clinic approximately 1 week after start of treatment and again roughly 2, 4, 6 and 8 weeks after trauma. During each visit fracture consolidation was clinically assessed by the physician and, apart from the information in the diary, any special remarks about pain and about resumption of professional, household and sports activities were noted in the medical files. Fracture healing was deduced from clinical symptoms: pain, range of motion and local instability at the fracture area. Patients were specifically asked to record after how many days they felt that the fracture had healed (clinically stable). X-rays were taken on the day of trauma to confirm the diagnosis midshaft clavicle fracture. During follow up X-rays were only taken when indicated by the treating physician and not for monitoring fracture healing in the study.

All medical records and X-rays, were reviewed by the first author one year after completion of the study to check for late complications, related operations or false inclusion criteria.

Statistical methods

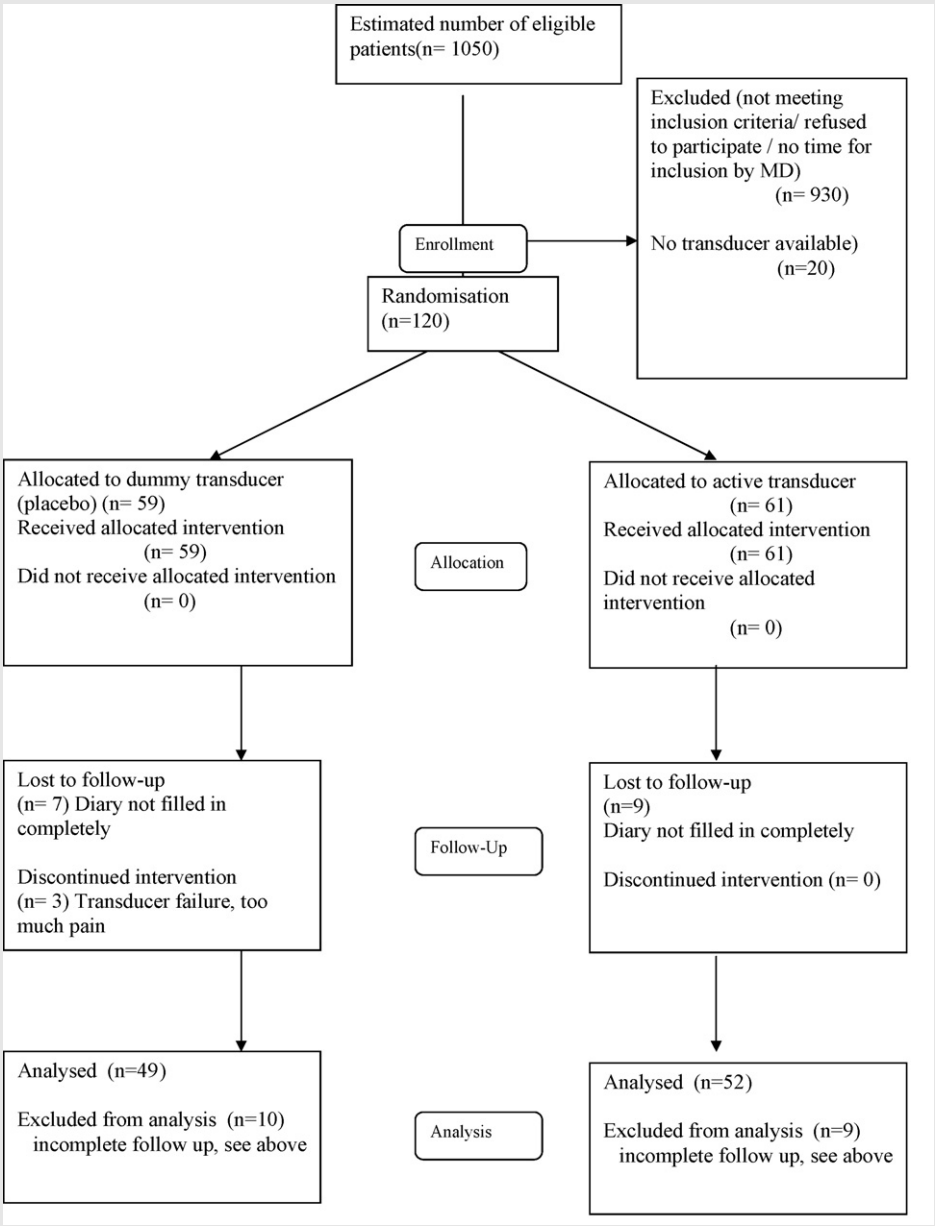
The sample size for this study was calculated based on a minimal clinical relevant reduction

in time to clinical healing of the fracture (according to the patient) by 20% with a power of 90% and a confidence interval of 95%. To detect this reduction 50 patients were needed in each group (active and placebo). All data was collected and saved in a Microsoft Excel database. For calculations, data were transferred to a database in SPSS (Statistical Package for Social Sciences, version 14.0, Chicago, IL, USA). Differences between groups were analysed using the Student's *t*-test and the Pearson Chi-square test where appropriate. Results were considered statistically significant when $p < 0.05$.

Results

A total of 120 patients (placebo group 59 patients, active group 61 patients) signed an informed consent for this study and effectively started study treatment. After revision of all medical records and X-rays in December 2004, 19 patients were excluded because they had incomplete follow up or ended the study preliminary (10 from the placebo group and 9 patients in the active group). The remaining 101 patients were analysed for baseline criteria and for the primary and secondary outcome criteria (Table 3).

Table 3 Consort flow chart



Demographic characteristics

From the 101 patients who were suitable for analysis, 49 patients were allocated to the placebo group and 52 patients received an active transducer unit. Demographic baseline characteristics are shown in Table 4. No differences were found in distribution of age, gender, side of fracture, AO type of fracture, type of accident and type of sports patients participated in before or after the accident. Small differences were found for professional activities (for example more craftsman in active ($n = 15$) than in placebo group ($n = 5$), $p = 0.002$). Differences in professional activities might influence resumption of these activities, but this was not conformed during further analysis. Transducers were used for an mean of 24.43 days in the placebo group and 25.38 days in the active group (mean difference 0.95, 95% CI −3.72, +1.81, $p = 0.49$).

Clinical fracture consolidation

The day that the fracture had clinically healed according to patients perception was determined in 92 patients (45 placebo, 47 active). Mean duration of time to clinical fracture healing was 27.09 days (placebo) and 26.77 days (active) (mean difference 0.33, 95% CI −5.27, +5.92, $p = 0.91$, Table 5).

Operation

Ten patients (placebo five, active five) did not note fracture healing at all. In all but one of these

Table 4 Baseline characteristics

	Placebo ($n = 49$)	Active ($n = 52$)	Total ($n = 101$)	p-Value
Gender				
Male	39	46	85	0.23
Female	10	6	16	
Trauma type				
Fall	13	15	28	0.92
Bike	23	16	39	
Motorbike	5	10	15	
Other	8	11	19	
AO classification fracture				
A1	4	8	12	0.57
A2	16	19	35	
A3	3	5	8	
B1	8	4	12	
B2	11	2	13	
B3	5	10	15	
C1	0	1	1	
C2	1	3	4	
C3	1	0	1	
Side of fracture				
Left	22	32	54	0.10
Right	27	20	47	
Sports activities				
No sport	13	14	27	0.21
Bike	6	9	15	
Fitness/jogging	6	7	13	
Ball	4	6	10	
Fieldhockey	5	2	7	
Other	7	3	10	
Missing	8	11	19	
Professional work				
Administrative	31	14	45	0.002
Craftsman	5	15	20	
Other	2	7	9	
Nowork	2	2	4	
Missing	9	14	23	

Table 5 Primary and secondary outcome measures (mean)

	Placebo	Active	Mean difference	95% CI		*p*
				Lower	Upper	
Fracture healing (days)	27.09	26.77	0.33	−5.27	5.92	0.91
Surgical procedures (number/group)	0.10	0.12	0.02	−0.14	0.11	0.83
Surgical procedures (days after trauma)	228	112	116	−44	276	0.13
Number of painkiller (tablets/28 days)	32.88	37.21	4.34	−23.53	14.86	0.66
Visual Analogue Score (VAS)	3.55	3.51	0.04	−0.54	0.63	0.90
Adverse events (number)	0.02	0.02	0.00	−0.05	0.06	0.97
Resumption of household activities (days)	12.24	9.38	2.86	−1.14	6.87	0.16
Resumption of professional work (days)	15.05	17.0	1.95	−6.33	2.42	0.38
Resumption of sport (days)	26.44	24.17	2.27	−0.19	4.72	0.07

patients surgical intervention with open reduction and internal fixation was performed. Time to operation was 228 days for the placebo group and 112 days for the active group (mean difference 116 days, CI −44, +276, $p = 0.13$). The remaining patient (placebo) underwent a surgical exploration of the fracture area in general anaesthesia for the suspicion of non-union on computer tomography, which was not confirmed during the operation. Another patient (active) underwent surgical removal of a painful bone spike in local anaesthesia.

Painkiller use

Painkiller use was measured as the total number of tablets of the prescribed drugs (both Paracetamol and Naproxen) in the first 28 days. For patients in the placebo group this was a mean of 32.88 tablets, in the active group 37.21 tablets were used (mean difference 4.34, 95% CI −23.53, +14.86, $p = 0.66$).

VAS

Painscore measured by daily VAS was not different between groups. Mean VAS in the 28-day treatment period for patients in the placebo group was 3.55 and in the active group 3.51 (mean difference 0.04, 95% CI −0.54, +0.63, $p = 0.90$).

Adverse events

Minor adverse side effects included skin irritation (placebo one, active one, NS). There were no allergic reactions to either the transducer gel or the transducer itself.

One patient from each group died more than 1 year after conclusion of the study, from reasons not related to the ultrasound treatment (car accident and motorcycle accident).

Resumption of activities

Resumption of activities was defined as the number of days between inclusion in the study and first day of activity. Household activities (vacuum cleaning, dishwashing, etc.) were resumed on average after 12 days (placebo) vs. 9 days (active) (mean difference 2.86, 95% CI −1.14, +6.87, $p = 0.16$).

Patients in the placebo and active groups went back to professional work after a mean of 15 and 17 days, respectively (mean difference 1.95, 95% CI −6.33, +2.42, $p = 0.38$). Sports activities were resumed after 26 days (placebo) and 24 days (active) (mean difference 2.27, 95% CI −0.19, +4.72, $p = 0.07$). Subgroup analyses per type of sport were not performed due to the fact that groups were too small.

Discussion

The time to clinical healing of fresh clavicle shaft fractures in this study was not influenced by LIPUS. Also secondary endpoints showed no significant differences between treatment groups. Our focus on clinical symptoms of fracture healing has led us away from radiological imaging as a primary endpoint, so we cannot relate these clinical symptoms to radiological fracture (healing) characteristics. Unfortunately we did not use validated functional scoring systems for the objective evaluation of range of motion and function. Despite standardised forms for describing physical examination with range of motion in degrees, in almost all medical files we found remarks describing full recovery, or "left = right".

We intentionally refrained from radiological appraisal of fracture healing, though we realise that this makes comparison with previous studies difficult. We have shown that fracture healing is easily and precisely monitored by both patient and doctor, but we realise that this is not a validated method to measure time to fracture healing.

We believe that the major problem in choosing clinical applications for LIPUS is that the scientific explanation has not been completely elucidated, making it difficult to define which patient groups definitely show a consistent positive clinical influence of ultrasound on fracture healing.[3,4,10,16,21–23] Research on this topic has been conducted by many authors and new theories are emerging and evolving.[6,12,18] Analysis of the clinical literature suggests that LIPUS has the greatest benefit in at-risk patient populations where fracture healing is impaired, either by type of fracture or by patient lifestyle.[5,9,15,19] A future goal might be the identification of these fracture characteristics (fracture gap, immobilisation techniques, anatomic region), in addition to a better explanation on the working mechanism.

Study limitations

With the thousands of non-operatively treated clavicle fractures per year in the Netherlands, we anticipated the patient recruitment would go much more quickly. In contrast to our plan, it took 2 years before sufficient numbers of people for each arm (>50 per arm) were included. One reason for this may be that in the Netherlands, clavicle fractures are also treated outside the hospital and/or without X-rays. This could mean that any extra treatment and out-patient clinic units are regarded as overdone, and did not help to recruit patients for the study. Apart from this we think that Emergency Departments may not be the ideal place to include people for randomised controlled trials, because it takes a considerable amount of time to inform patients and get all the paperwork done. Furthermore, it appeared that, especially in the first months of the study, study-equipment (transducers) was not in stock and eligible patients could not be included in the trial. This demotivated staff to continue recruiting participants in the study.

Conclusion

This study hypothesised that low-intensity pulsed ultrasound accelerates the decrease of clinical fracture symptoms in patients with a fresh clavicle shaft fracture by 20%. With the sample size of 50 patients in each study group we could not confirm this influence.

Acknowledgements

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Conflict of interest

Data collection and data analysis was supported by a financial grant from Smith and Nephew Inc, Memphis, USA. Transducers (placebo and active) were provided free of cost. For this reason the study was designed in cooperation with Smith and Nephew. No author had any financial or personal relationships with people or organisations that could inappropriately influence their work.

References

1. Allman FL. Fractures and ligamentous injuries of the clavicle and its articulation. J Bone Joint Surg Am 1967;49:774–84.
2. Ardan Jr NI, Janes JM, Herrick JF. Changes in bone after exposure to ultrasonic energy. Miner Med 1954;37(6):415–20.
3. Azuma Y, Ito M, Harada Y, et al. Low-intensity pulsed ultrasound accelerates rat femoral fracture healing by acting on the various cellular reactions in the fracture callus. J Bone Miner Res 2001;16:671–80.
4. Busse JW, Bhandari M, Kulkarni AV, Tunks E. The effect of low-intensity pulsed ultrasound therapy on time to fracture healing: a meta-analysis. CMAJ 2002;166(4):437–41.
5. Cook SD, Ryaby JP, McCabe J, et al. Acceleration of tibia and distal radius fracture healing in patients who smoke. Clin Orthop 1997;337:198–207.
6. Dalecki D. Mechanical bioeffects of ultrasound. Annu Rev Biomed Eng 2004;6:229–48.
7. Duarte LR. The stimulation of bone growth by ultrasound. Arch Orthop Trauma Surg 1983;101(3):153–9.
8. Dyson M, Brookes M. Stimulation of bone repair by ultrasound. Ultrasound Med Biol 1983;(Suppl 2):61–6.
9. Gold SM, Wasserman R. Preliminary results of tibial bone transports with pulsed low intensity ultrasound (Exogen). J Orthop Trauma 2005;19(1):10–6.
10. Hantes MW, Mavrodontidis AN, Zalavras CG, et al. Low-intensity transosseous ultrasound accelerates osteotomy healing in a sheep fracture model. J Bone Joint Surg 2004;86-A(10):2275–82.
11. Heckman JD, Ryaby JP, McCabe J, et al. Acceleration of tibial fracture-healing by non-invasive, low-intensity

pulsed ultrasound. J Bone Joint Surg 1994;76-A(1): 26—34.
12. Kokubu T, Matsui N, Fukioka H, et al. Low intensity pulsed ultrasound exposure increases prostaglandin E2 production via the induction of cyclooxygenase-2 mRNA in mouse osteoblasts. Biochem Biophys Res Commun 1999;256(2):284—7.
13. Kristiansen TK, Ryaby JP, McCabe J, et al. Accelerated healing of distal radial fractures with the use of specific low-intensity ultrasound. J Bone Joint Surg 1997;79-A(7):961—73.
14. Legome E, Pancu D. Future applications for emergency ultrasound. Emerg Med Clin N Am 2004;22(3):817—27.
15. Leung KS, Lee WS, Tsui HF, et al. Complex tibial fracture outcomes following treatment with low-intensity pulsed ultrasound. Ultrasound Med Biol 2004;30(3):389—95.
16. Mayr E, Rudzki MM, Rudzki M, et al. Does low intensity, pulsed ultrasound speed healing of scaphoid fractures? Handchir Mikrochir Plast Chir 2000;32(2):115—22.
17. Muller ME, Nazarian S, Koch P, Schatzker J. Comprehensive classification of fractures of long bones. Berlin/Heidelberg/New York: Springer; 1990.
18. Naruse K, Miyauchi A, Itoman M, Gaki YMT. Distinct anabolic response of osteoblast to low-intensity pulsed ultrasound. J Bone Miner Res 2003;18(2):360—9.
19. Nolte PA, van der Krans A, Patka P, et al. Low-intensity pulsed ultrasound in the treatment of nonunions. J Trauma 2001;51(4):693—702.
20. Nowak J, Mallmin H, Larsson S. The aetiology and epidemiology of clavicular fractures. A prospective study during a two-year period in Uppsala, Sweden. Injury 2000;31(5): 335—8.
21. Pilla AA, Mont MA, Nasser PR, et al. Non-invasive low-intensity pulsed ultrasound accelerates bone healing in the rabbit. J Orthop Trauma 1990;4(3):246—53.
22. Rubin C, Bolander M, Ryaby JP, Hadjiargyrou M. The use of low-intensity ultrasound to accelerate the healing of fractures. J Bone Joint Surg Feb 2001;83A:259—70.
23. Tsumaki N, Kakiuchi M, Sasaki J, et al. Low-intensity pulsed ultrasound accelerates maturation of callus in patients treated with opening-wedge high tibial osteotomy by hemicallotasis. J Bone Joint Surg 2004;86-A(11): 2399—405.
24. Valkenberg H. Memo sleutelbeenfracturen. Stichting Consument en Veiligheid (Amsterdam) 2005;1:1—3.
25. Warden SJ, McMeeken JM. Ultrasound usage and dosage in sports physiotherapy. Ultrasound Med Biol 2002;28(8): 1075—80.