Original Research

Dosage and treatment response in randomized clinical trials of therapeutic ultrasound

Valma J. Robertson

Objectives: Effective treatments usually have a known dose-response relationship. For physiotherapists, ultrasound is perhaps the single most widely and frequently used modality. Until now no dose–response relationship for this therapy has been identified. This study provides a first step in that direction by analysing the dosages used and treatment response, in randomized controlled trials investigating therapeutic ultrasound. Design: Dosage related variables from an existing set of randomized controlled trials published in the English-language literature between 1975 and 1999 on the use of ultrasound to treat pain and soft tissue lesions were analyzed. Results: too few details are still provided in most studies to identify a relationship between dosage and treatment responses. An apparently effective treatment window of pulsed ultrasound, 0.16–0.50 W/cm^2 (SATA), proved illusory on closer scrutiny. Conclusions: without a known dose-response relationship users of therapeutic ultrasound can only guess at what dosage might be effective for a patient and how to modify it. Considerably more clinical research is necessary to justify the dosages used in treatment at present.

Dr. Valma J. Robertson School of Physiotherapy, La Trobe University, Bundoora, Victoria, Australia, 3086

Correspondence to: Dr. Valma J. Robertson, School of Physiotherapy, La Trobe University, Bundoora, Victoria 3086, Australia. Tel: +61-3-94795766; Fax: +61-3-94795768; E-mail: V.Robertson@latrobe.edu.au

Introduction

Physiotherapists have used ultrasound frequently and to treat many different types of problems for decades. In many countries ultrasound is one of the single most frequently used treatment modalities, and almost always the most frequently used electrophysical agent (Lindsay et al. 1990; 1995; Pope et al. 1995; Robertson & Spurritt 1998; Robinson & Snyder-Mackler 1988; ter Haar et al. 1988). This is a consistent finding and implies a modality with a well known dose–response relationship and a considerable base of clinical research support.

Dose–response relationship

If a treatment intervention or modality has a consistent and reliable effect there should be an identifiable relation between the dosage (independent variable) and the response or outcome (dependent variable). The form of a particular dose–response relationship depends on the variables involved. The relation might be linear, linear to a certain level of the independent variable, or it might be exponential or more complex. Without knowledge of this relation, practitioners can only guess which dosage might be optimal under particular conditions and how to modify it in others.

Ideally, knowledge of a dose–response relationship is initially obtained from in vitro studies and confirmed in clinical studies. While in vitro studies permit a greater level of control, their relevance to the clinical context has still to be demonstrated. Problems inherent in extrapolating from in vitro studies to in vivo situations have been canvassed elsewhere (e.g. Baker & Robertson 2001; De Deyne 1996; Robertson & Ward 1996). These problems include establishing comparable dosages given size and tissue differences and allowing for the moderating effects of the homeostatic mechanisms of the body. Investigating the

doi:10.1054/ptsp.2002.0107, available online at http://www.idealibrary.com on IDEAL®

1466-853X/02/$ - see front matter

effect of ultrasound on animals partly addresses the problems of in vitro research. For example, many studies of wound healing in animals are done with pigs (e.g. Byl et al 1992; 1993), rather than smaller mammals such as rats, because of their body size and tissue similarities with humans (Forrest & Rosen 1989; Lehmann & Johnson 1958).

Clinical studies are needed to demonstrate if there is a relationship between ultrasound dosages and treatment outcomes in humans. A simpler, first step, is to review the dose-related variables and outcomes in existing clinical studies. Positive outcomes at a certain dosage or dosage range suggest a starting point for controlled clinical studies. This first step is necessary as there is still little agreement in the physical therapy literature as to the dosage required to obtain a desired outcome for specific clinical conditions.

The types of discrepancies between ultrasound dosage recommendations are evident in current textbooks used in entry-level physical therapy courses. One recommends using 0.10–0.25 W/cm^2 (spatial average temporal average [SATA]) for treating acute and post-traumatic lesions with an average duration of 5 min, frequency unspecified (Low & Reed 2000, p. 198). For pain another text recommends 0.50–3.0 W/cm^2 (presumably SATA) with a frequency of 1 or 3 MHz for 3–10 min (Cameron 1999, pp. 282–283). For treating chronic lesions and scar tissue, one textbook recommends 0.25–1.0W/cm^2 (SATA) with a longer time than for acute lesions, frequency unspecified (Low & Reed 2000, p.198). For soft tissue shortening, the other recommends 1.0–2.50 W/cm^2 (presumably SATA) with a frequency of 1 or 3 MHz for 5–10 min (Cameron 1999, p. 282). The differences in the SATA dosage intensities and durations recommended for similar types of lesions supports the argument of a need to revisit the dose–response relationship for therapeutic ultrasound.

Clinical studies

A previous attempt at identifying a dose–response relationship using the information available in a systematic review of randomized controlled trials (RCTs) of ultrasound failed. Gam and Johannsen (1995) identified 293 papers, published between 1950 and 1992, which investigated the use of ultrasound to treat musculoskeletal problems. They were unable to demonstrate even a basic dose–response relationship, because of the inadequacy of the treatment details provided. Further, Gam and Johannsen concluded that the outcomes of the 22 methodologically adequate RCTs they reviewed did not justify the use made of therapeutic ultrasound.

The authors of a more recent systematic review also commented on the inadequacy of dosage details provided in studies of ultrasound (van der Heijden et al. 1997). This particular review was of the physiotherapy treatments of soft tissue lesions in the shoulder. The authors concluded that the use of ultrasound for treating soft tissue lesions of the shoulder should be discouraged as the studies they reviewed provided insufficient evidence that it was effective. This conclusion was subsequently criticised as based on methodologically inadequate studies and the need for adequate dosage details in studies of ultrasound reiterated (Brocknow et al. 1998).

More recent contributions to the discussion of the dose–response relationship for ultrasound have not been identified. Since the attempt by Gam and Johannsen (1995) involved studies only to 1992, the present paper will revisit the possibility by including more recent RCTs but limit it to those which investigated using ultrasound to treat pain or soft tissue lesions.

The present paper analyses the dosage details of all selected RCTs, irrespective of their methodological adequacy. The reason is, dosage choice by investigators is independent of methodological factors such as double blinding and the adequacy of the procedures used for randomization. One limitation is that the methodological inadequacy of a study may mean an effective outcome was not identified because, for example, of a Type 2 error. Alternatively, effective outcomes may have been identified in the absence of adequate randomization procedures. This paper presents the first step in the process of establishing if there is a relationship between dosage and outcome, recognizing the inherent limitations of this process. If successful, this process should provide direction for future, controlled clinical studies of ultrasound.

The aim of the present study was to document the dosage details and treatment responses in RCTs of ultrasound to treat pain and to promote soft tissue healing. This is the first step in establishing if there is a dose–response relationship for ultrasound in clinical studies.

Method

Twenty four RCTs which used therapeutic ultrasound to treat clinically presenting pain or soft tissue damage were identified from sources including databases (MEDLINE, CINAHL), and bibiographies in known systematic reviews. Each was published in the English language between 1975 and 1999 inclusive and detailed at least the frequency and intensity of ultrasound applied. Ultrasound was the major independent variable and not a possibly indistinguishable part of a treatment package. In addition, each study used both placebo and active ultrasound to treat a clinical condition. This sample was chosen for analysis as it has previously been described elsewhere (Robertson & Baker 2001).

Each of the 24 RCTs studies was analysed to ascertain all details of the dosage and outcome provided by the authors. To increase the comparability of each study, if not provided, the SATA intensity was calculated, along with the total energy applied and energy density.

Data analysis and calculations

SATA was calculated as the output (W/cm^2) multiplied by the percentage of on-time (i.e. 1.0 W/cm^2 pulsed at 1:4 = 0.20 W/cm^2 SATA). If continuous, the SATA was the same as the peak output provided (SATP). One paper provided the SATP and noted the output was pulsed but provided no pulsing frequency details (Callam et al. 1987). A range of possible outputs was estimated for this study.

The effective radiating area (ERA) of the applicator was explicitly provided in 6 of the 24 papers (Craig et al. 1999; Everett et al. 1992; Falconer et al. 1992; Gam et al. 1998; Haker & Lundeberg 1991; McDiarmid et al. 1985). Of the remainder nine provided an applicator area (Bradnock et al. 1996; Downing & Weinstein 1986; Ebenbichler et al. 1998; 1999; Eriksson et al. 1991; Hasson et al. 1990; Nykanen 1995; Plaskett et al. 1999; ter Riet et al. 1996). The remaining nine provided no details relevant to the ERA. Estimates of the geometric contact area were made for those papers, based on the size of the area treated, the frequency of the equipment, and the date of publication. For papers published prior to the mid 1990s applicators were assumed to be 5 cm^2 unless information to the contrary was provided.

Total energy (Joules) was calculated as the SATA (W/cm^2) by the applicator geometric contact area (cm^2) by the time of treatment (seconds). This quantity was divided by the size of the area treated (cm^2) to produce the energy density (J/cm^2).

Results

Table 1 shows the dosage intensity (SATA) used by each of the 24 studies by frequency and outcome. The mean intensity (SATA) for studies using 1 MHz ultrasound was 0.69 W/cm^2 (SD 0.82) and for those using 3 MHz, 0.21 W/cm^2 (SD 0.19).

The table shows that of the 15 papers using 1 MHz frequency ultrasound, 5 reported statistically significant improvements in the ultrasound treated group (Binder et al. 1985; Callam et al. 1987; Ebenbichler et al. 1998; 1999; Hasson et al. 1990). Of the nine studies using 3 MHz, two reported a significant improvement for the ultrasound treated group (Dyson et al. 1976; Roche & West 1984). This left 17 of the 24 original studies, with a nonsignificant outcome.

The findings show a clustering of those studies which used ultrasound with a SATA intensity of around 0.20 W/cm^2 and had statistically significant outcomes. This clustering suggests an effective bandwidth for both frequencies of approximately 0.16–0.50 W/cm^2. This SATA was obtained by pulsing 1 W/cm^2 in five of the seven studies (Binder et al. 1985; Dyson et al. 1976; Ebenbichler et al. 1998; 1999; Roche & West 1984), and 0.80 W/cm^2 in another (Hasson et al. 1990). The seventh study (Callam et al. 1987) used a lesser intensity, 0.50 W/cm^2, and pulsed it but did not say at what frequency. This means all seven studies with a statistically significant outcome used pulsed ultrasound. Of those with a nonsignificant outcome, 12 used pulsed, 4 continuous, and 1 provided only the

Table 1 Dosage intensity (W/cm^2, SATA) used in each trial by frequency and outcome

Frequency	
1 MHz	3 MHz
0.05–0.25 Callam et al. (1987)**[a]	0.02 Hashish et al. (1988)
0.05 Lundeberg et al. (1990)	0.02–0.3 Hashish et al. (1986)
0.16 Hasson et al. (1990)**	0.1 ter Riet et al. (1996)[b]
0.16 Craig et al. (1999)	0.12 Grant et al. (1989)
0.2 Haker and Lundeberg (1991)	0.16 McDiarmid et al. (1985)
0.2 Nykanen (1995)	0.2 Dyson et al. (1976)**
0.2 Ebenbichler et al. (1998)**	0.2 Roche and West (1984)**
0.2 Plaskett et al. (1999)	0.25 Everett et al. (1992)
0.2–0.4 Binder et al. (1985)**	0.67 Bradnock et al. (1996)[c]
0.5 Ebenbichler et al. (1999)**[b]	
1.0 Lundeberg et al. (1988)	
1.0 Eriksson et al. (1991)	
1.2 Downing and Weinstein (1986)	
2.4–2.6 McLachlan (1991)[b]	
2.5 Falconer et al. (1992)	

**statistically significant for subjects treated with active ultrasound ($p < 0.05$)
[a]the SATA was estimated as no pulsing frequency was provided
[b]variations in frequency: 3.28 MHz in ter Reit et al. (1996), 0.89 MHz in Ebenbichler et al. (1999), and 1.1 MHz in McLachlan (1991)
[c]only 3 MHz data included

mean SATA dosage and no details of how this was obtained.

Three areas of difference exist between the seven studies which identified a significant effect of ultrasound. Those differences concern the output frequency of ultrasound, the area or problem treated, and the duration of treatment. Five of these studies used 1 MHz frequency ultrasound (Binder et al. 1985; Callam et al. 1987; Ebenbichler et al. 1998; 1999; Hasson et al. 1990) and two, 3 MHz (Dyson et al. 1976; Roche & West 1984). Three studies with significant results treated ulcers: two with 3 MHz frequency ultrasound (Dyson et al. 1976 — chronic varicose ulcers; Roche & West 1984 — venous ulcers), and one with 1 MHz (Callam et al. 1987 — all types of chronic ulcers). The other studies all used 1 MHz frequency ultrasound and treated different problems: epicondylitis (Binder et al. 1985), muscle soreness (Hasson et al. 1990), carpal tunnel syndrome (Ebenbichler et al. 1998), and calcific tendinitis of the shoulder (Ebenbichler et al. 1999). The treatment times used in these seven studies ranged from 5 min (Binder et al. 1985; Dyson et al. 1976; Roche & West 1984) to 40 min (Hasson et al. 1990) and the size of area treated from approximately less than or equal to 2.5 cm^2 (Dyson et al. 1976) to an estimated 72 cm^2 (Hasson et al. 1990).

[1]SPSS for Windows v.9.

Standardized dosages

Dosages were standardised for the 24 studies by calculating total energy (J) applied and energy density (J/cm^2). Table 2 shows that this necessitated the stratification of the studies into four groups according to the extent of data each provided. Group 1 studies provided all data needed to calculate the energy density (seven studies). Group 2 studies required an estimate of the size of the geometric area of the applicator (four studies). In Group 3 (six studies) the size of area treated had to be estimated, based on the description provided. The fourth group required estimates of both the sizes of the applicator and of the area treated (seven studies).

Table 2 also shows that each group included studies with significant findings: Group 1 had one (Hasson et al. 1990); Group 2, one (Callam et al. 1987); Group 3, two (Ebenbichler et al. 1998; 1999); and Group 4 had three (Binder et al. 1985; Dyson et al. 1976; Roche & West 1984).

The mean energy density (J/cm^2) for studies using 1 MHz ultrasound was 144.5 J/cm^2 (SD 336.8) and for those using 3 MHz, 40.8 J/cm^2 (SD 40.4).

The correlation between intensity and energy density was calculated[1] for all studies for both frequencies, and, separately, for those studies with significant findings. When a range of

Table 2 Energy density (J/cm^2) by extent of data provided in each study, equipment frequency, and outcome

1 MHz			3 MHz	
Extent of data provided	J/cm^2	Study	J/cm^2	Study
Group 1 all data provided	28.8 40–48 45 150.9 1356–1341.8	Downing and Weinstein (1986) Plaskett et al. (1999) Falconer et al. (1992) Hasson et al. (1990)* Eriksson et al. (1991)	12.5 18	Everett et al. (1992) ter Riet et al. (1996)
Group 2 size of applicator estimated	5.2–25.9 7.1–14.1 7.9 120	Callam et al. (1987)**[a] Craig et al. (1999) Lundeberg et al. (1990) Lundeberg et al. (1988)		
Group 3 size of area treated estimated	24 40 60 150	Haker and Lundeberg (1991) Nykanen (1995) Ebenbichler et al. (1998)** Ebenbichler et al. (1999)**	40.2 83.2–90.8	Bradnock et al. (1996) McDiarmid et al. (1985)
Group 4 sizes of area treated & of applicator estimated	12–24 93.6–115.2	Binder et al. (1985)** McLachlan (1991)	2–30 4 7.2 60 120	Hashish et al. (1986) Hashish et al. (1988) Grant et al. (1989) Roche and West (1984)** Dyson et al. (1976)**

**statistically significant for subjects treated with active ultrasound ($p < 0.05$)
[a]estimates required of intensity (SATA) as pulsing frequency not given, and of duration of treatment also.

intensities or of total energy was provided, the mean was used when calculating a correlation. For all studies using 1 MHz frequency ultrasound the correlation between intensity and energy density was low ($r = 0.14$), as was that for 3 MHz ($r = 0.13$). When only those studies with significant outcomes were investigated, the correlation for 1 MHz was still low ($r = 0.38$), and for 3 MHz was not calculable, both cases having used the same intensity.

Calibration

The calibration of ultrasound machines is required to ensure that the indicated output is the actual output at the applicator. The most common method of calibration measures the applicator output using a radiation balance (Pye 1996). There is no information available on the general durability of calibrations nor on the factors that affect it.

Details of calibration were checked for all studies with a special focus on those with significant outcomes. The method of checking was provided in 11 of the 24 studies. Of those, nine used a radiation balance (Binder et al. 1985; Dyson et al. 1976; Ebenbichler et al. 1998; 1999; Haker & Lundeberg 1991; Lundeberg et al. 1988; McDiarmid et al. 1985; Roche & West 1984; ter Riet et al. 1996) and two, a radiometer tethered float (Hashish et al. 1988; 1986).

Some studies provided details of the frequency of equipment testing. Seven (Binder et al. 1985; Dyson et al. 1976; Haker & Lundeberg 1991; Hashish et al. 1986; 1988; Lundeberg et al. 1988; Roche & West 1984) reported testing the output of the equipment used either each day or each session and seven (Callam et al. 1987; Craig et al. 1999; Eriksson et al. 1991; Everett et al. 1992; Hasson et al. 1990; Lundeberg et al. 1990; Plaskett et al. 1999) provided no indication as to whether they calibrated the equipment or tested the output. Five tested the equipment ''regularly'' (Bradnock et al. 1996; Ebenbichler et al. 1998; 1999; McDiarmid et al. 1985; Nykanen 1995); one, weekly (Grant et al. 1989); one, every 3 months (ter Riet et al. 1996); two every 6 months (Downing & Weinstein 1986; McLachlan 1991); and one indicated testing but gave no details of how often or when (Falconer et al. 1992). Three of the studies with significant findings (Binder et al. 1985; Dyson et al. 1976;

Roche & West 1984) tested the equipment either each session or day, two tested it ''regularly'' (Ebenbichler et al. 1998; 1999), and two provided no details of any calibration or testing of the output (Callam et al. 1987; Hasson et al. 1990).

Discussion

The main finding of this analysis is there is no clear relationship between the dosage applied and the outcome. Studies with significant findings apparently used a similar range of intensities (SATA), from 0.16 to 0.5 W/cm^2, and pulsing. This, however, is insufficient evidence that this is a window of effective dosage for three reasons. The first reason is because of differences between the seven studies concerned, the second is that other studies used the same range of dosages, and the third relates to the quality and reliability of the data on which these findings are based.

Differences between studies with significant findings

The first difference between these seven studies with significant outcomes concerns the frequency of ultrasound used. Some within the apparently effective treatment window of 0.16–0.5 W/cm^2 used 1 MHz (Binder et al. 1985; Callam et al. 1987; Ebenbichler et al. 1998; 1999; Hasson et al. 1990) and some 3 MHz (Dyson et al. 1976; Roche & West 1984). This means the two sets of measurements are not directly comparable as that produced by 3 MHz equipment is absorbed in approximately one third of the distance of 1 MHz frequency ultrasound. Consequently, 3 MHz ultrasound produces a much higher intensity of heating in the first centimeter of tissue under the skin and much less at a depth of 4 cm (Ward 1986).

The second difference between studies with significant outcomes is that of treatment time. The duration of application is integral to calculations needed for establishing the dose–response of ultrasound. An intensity (SATA) of 0.2 W/cm^2 delivered for 5 min has less time in which to affect deeper tissues or to raise their temperature than if delivered for 15 min. The total energy absorbed in the treated tissue volume will be considerably less with the shorter treatment time. If ultrasound is to affect the rate of healing this may have some relevance to the outcome. For example, to be effective may require a minimum time of exposure to ultrasound. Alternatively, the important factor might be the total energy applied with time important only in so far as too high a rate of application might cause skin burns. This present study, however, while finding a considerable variation in the duration of treatment time used found no relation between successful outcome and duration of treatment, or between outcome and total energy applied. The extent of variation in treatment time does partly explain the very low correlation between intensity and energy density, along with those other dosage parameters, intensity, treatment duration, and size of area treated.

A third difference between studies is the type of problem treated. Why problems of such a seemingly diverse nature as ulcers, epicondylitis, carpal tunnel syndrome and acute muscle soreness would all improve when treated by ultrasound at a particular intensity (SATA) was initially puzzling. As explained above, this is not what actually happens. Instead, the apparent window is an oversimplification. When the type of problem is considered, the added complexities include the staging of treatment for it, the depth of the lesion being treated, and where in the body it is located. Each of these may also affect the outcomes from using ultrasound. The studies analysed in the present paper did not permit exploration of those possibilities nor any way of discriminating the extent to which they might contribute.

The type of problem raises issues of depth of problem and body location. If a superficial problem, a higher frequency of ultrasound should possibly be used because of its lower penetration depth. However, this approach is not apparent in the studies reviewed and the data do not help clarify the issue of when a particular frequency is most effective. With either traditionally used frequency, if the treated area has a relatively superficially located bone, the percentage of ultrasound energy reflected will be higher than if that bone were deeper (Ward 1986). This would effectively increase the dosage received by any area treated between the skin and the bone. A lesion over

much deeper bone would not be affected in the same way. Given the small numbers of trials investigating the same problems, the contribution of depth and location of a treated lesion cannot be effectively examined, nor can that of which frequency should be used when. To resolve these issues requires conducting large trials with patients with similar types of problems, in well specified body locations, being treated with ultrasound of known frequencies and intensities.

Other studies using same dosage range

Table 1 shows some studies with nonsignificant findings used a similar intensity (SATA) or a similar energy density to those in which ultrasound produced a significant outcome. In spite of this they did not identify an effect of ultrasound, even if treating a similar problem. There are three possible reasons for this: the research method used, the type of problem treated in some cases, and the possibility that the effects of therapeutic ultrasound are not sufficiently large or predictable to be reliably identified.

The first possibility concerns the research method used. Possibly, some studies with nonsignificant findings did not have enough statistical power to identify an effect of ultrasound. Group comparison studies need sufficient power. This is obtained either by investigating a large number of subjects or a problem in which the differences in outcome are of a sufficient size (effect size) to identify a difference due to an intervention. Many clinical studies use either too few subjects to identify an effect, or include too heterogenous a patient group in the interests of increasing subject numbers. This compounds the problem of identifying an effect. Some studies with nonsignificant findings (Downing & Weinstein 1986; Gam et al. 1998; McDiarmid et al. 1985) had, in a statistical sense, too few subjects to identify even a large effect. According to Cohen's tables, such studies using two groups require at least 26 subjects per group for an 80% confidence level (Portney & Watkins 1993).

The type of problem is a second possibility to account for nonsignificant findings. Perhaps therapeutic ultrasound was not used at the optimal time (stage) or dosage for the particular problem studied. This might explain why some studies obtained a significant outcome when using ultrasound while others, using the same intensity or the same level of energy density, did not.

The third possibility is that ultrasound used for therapy does not generally have a sufficiently large or predictable effect to be reliably identified. That so few studies report a significant effect of ultrasound suggests it might too often be used to treat inappropriately, either with respect to the types of problem or the manner in which it is applied. Alternatively, the moderating effects of the homeostatic mechanisms of the body may help explain why many fewer studies identify an effect of ultrasound when in vitro and laboratory studies clearly indicate a biological effect under some conditions. Until such a possible reason is identified, and a larger body of comparable clinical trials of ultrasound is available, there is little reason to conclude that ultrasound is clinically effective. This is not to say that the larger number of negative findings increases that probability, but it does raise many questions as to why an effect cannot be consistently and reliably identified in clinical trials of a modality that is used so frequently.

Quality and reliability of data provided

The quality of data provided in some studies is clearly dubious. When basic variables such as equipment frequency, or the ERA and size of an area treated are not documented there is clearly a problem with the relevant body of scientific literature. Without making estimates, as was necessary in the present paper, few studies can be used for establishing a basis for identifying a dose-response relationship. Some estimates will be inaccurate. Also, given few studies provided the ERA, estimates of the geometric area were used. This will have produced a systematic, but very small, overestimate of energy density among the studies examined.

There is also the issue of the reliability of data provided in some studies. In particular, many studies lacked adequate details as to how often the equipment was calibrated as a proportion of time used and the extent to which any adjustments needed to be made. Given the seriousness of previously identified problems with ultrasound equipment (Gledhill 1996;

Pye 1996), this is a major issue and may contribute to this set of studies having such mixed results.

The omission of some relevant data and issues of quality in some of what was provided meant that not all possibly relevant treatment details could be analyzed. For example, few studies provided details of the beam nonuniformity ratio (BNR). Most physical therapy ultrasound machines have a BNR of 5 or 6 to 1 (Cameron 1999, p.296) and those used for fracture healing of 2 to 1 (Hadjiargyrou et al. 1998). Given the apparent lack of a relationship between dosage and outcome, and the omission of much of the data, neither the BNR nor the treatment frequency data were considered further.

Another aspect of the question of quality is that the RCTs used in this study were not examined against the usual criteria for acceptability (Sackett et al. 2000). Many of the studies with significant findings do not meet the ideal criteria for RCTs, as shown in the paper in which they were evaluated (Robertson & Baker 2001). However, the explicit aim of the present study was to obtain information from RCTs about the dosages they used as a means of trying to establish the basis for a dose–response relationship. Excluding studies because of problems with randomisation or blinding of subjects and therapists, for example, would remove possibly useful data. This is only the case because too few studies investigated the same types of problems and provided all relevant dosage details. As this problem is redressed in the literature, future attempts at identifying a dose–response relationship should include only those RCTs that are methodologically adequate. The present paper though, was intended as an initial step in the process.

Limitations

Among the possible limitations of this study is the reliance on published studies using the RCT methodology. Doing RCTs in a clinical context is difficult, especially when the modality being investigated is often used as part of a treatment package rather than by itself. Against this, RCTs should provide the most rigorous method for investigating a clinical therapy. Ultrasound is used so frequently and by so many therapists in so many different countries that it is surprising that relatively few RCTs treating the same problems exist. Similarly, if ultrasound is effective as used now, it is difficult to understand why clinical results still do not permit the identification of a dose–response relationship. The other possible contributors to our knowledge of this relationship, in vitro or laboratory studies or our knowledge of the biophysical properties, all have to be qualified as subject to clinical testing. Whatever assumptions are made, therapists need to conduct reliable clinical trials to ascertain that ultrasound has a consistent effect and to explicate the conditions.

Another possible limitation of this study is that not all RCTs using ultrasound were identified and examined. This might be true but, if a clear dose–response relationship exists then an existing set of 24 studies investigating ultrasound should have provided some clearer evidence with an obvious direction than is the case. Ultrasound has been used clinically by physiotherapists, and others, for decades now. This is in itself puzzling, given the lack of supporting outcome evidence for current dosage practices.

Summary

This study was unable to identify a relationship between the dosage and outcomes by analysing an existing set of 24 RCTs which investigated the use of therapeutic ultrasound. An apparently effective treatment window (0.16–0.50 W/cm^2 SATA) was illusory as it ignored other important variables.

Until sufficient clinical studies are available to start to identify a dose-response relationship, questions about ultrasound dosage will remain unanswered. The situation has apparently not changed since Gam and Johannsen (1995) were unable to develop a dose–response relationship because of a lack of dosage detail in RCTs investigating the clinical uses of ultrasound. A consequence is that currently favoured dosage parameters for ultrasound treatment are difficult to justify. Further, guidelines for practitioners and student physiotherapists can really only aim at reducing the risks of burning or otherwise harming patients. There is still no indication of

what the dose–response relationship might be for clinical ultrasound.

References

Baker K G, Robertson V J, Duck F A 2001 A review of therapeutic ultrasound: biophysical effects. Physical Therapy 81: 1351–1358

Binder A, Hodge G, Greenwood A D M 1985 Is therapeutic ultrasound effective in the treating soft tissue lesins? British Medical Journal 290: 512–514

Bradnock B, Law H T, Roscoe K 1996 A quantitative comparative assessment of the immediate response to high frequency ultrasound low frequency ultrasound ''longwave therapy'' in the treatment of acute ankle sprains. Physiotherapy 82: 78–84

Brocknow T, Franke A, Resch K L 1998 Physiotherapy for soft tissue shoulder disorders. British Medical Journal 316: 555

Byl N N, McKenzie A L, West J M et al. 1992 Low-dose ultrasound effects on wound healing: a controlled study with Yucatan pigs. Archives of Physical Medicine and Rehabilitation 73: 656–664

Byl N N, McKenzie A, Wong T et al. 1993 Incisional wound healing: a controlled study of low high dose ultrasound. Journal of Orthopaedic and Sports Physical Therapy 18: 619–628

Callam M J, Harper D R, Dale J J et al. 1987 A controlled trial of weekly ultrasound therapy in chronic leg ulceration. Lancet. Jul25: 204–206

Cameron M H 1999 Physical agents in rehabilitation. WB Saunders Co, Philadelphia

Craig J A, Bradley J, Walsh D M et al. 1999 Delayed onset muscle soreness: Lack of effect of therapeutic ultrasound in humans. Archives of Physical Medicine and Rehabilitation 80: 318–323

Creates V 1987 A study of ultrasound treatment to the painful perineum after childbirth. Physiotherapy 73: 162–164

DeDeyne P G 1996 Response. Physical Therapy 76: 79

Downing S D, Weinstein A 1986 Ultrasound therapy of subacromial bursitis: a double blind trial. Physical Therapy 66: 194–199

Dyson M, Franks C, Suckling J 1976 Stimulation of healing of varicose ulcers by ultrasound. Ultrasonics 14: 232–236

Ebenbichler G R, Resch K L, Nicolakis P et al. 1998 Ultrasound treatment for treating the carpal tunnel syndrome: randomized ''sham'' controlled trial. British Medical Journal 316: 731–735

Ebenbichler G R, Erdogmus C B, Resch K L et al. 1999 Ultrasound therapy for calcific tendinitis of the shoulder. New England Journal of Medicine 340 (20): 1533–1538

Eriksson S V, Lundeberg T, Malm M 1991 A placebo controlled trial of ultrasound therapy in chronic leg ulceration. Scandinavian Journal of Rehabilitation Medicine 23: 211–213

Everett T, McIntosh J, Grant A 1992 Ultrasound therapy for persistent post-natal perineal pain dyspareunia: a randomized placebo-controlled trial. Physiotherapy 78: 263–267

Falconer J, Hayes K W, Chang R W 1992 Effect of ultrasound on mobility in osteoarthritis of the knee. Arthritis Care Research 5: 29–35

Forrest G, Rosen K 1989 Ultrasound: effectiveness of treatments given under water. Archives of Physical Medicine & Rehabilitation 70: 28–29

Gam A N, Johannsen F 1995 Ultrasound therapy in musculoskeletal disorders: a meta-analysis. Pain 63: 85–91

Gam A N, Warming S, Larsen L et al. 1998 Treatment of myofascial trigger-points with ultrasound combined with massage exercise — a randomized controlled trial. Pain 77: 73–79

Gaul G B 1999 Ultrasound thrombolysis. Thrombosis and Haemostasis 82 Suppl 11: 157–159

Gledhill M 1996 Survey of physiotherapy ultrasound equipment calibrations. National Radiation Laboratory, New Zealand

Grant A, Sleep J, McIntosh J et al. 1989 Ultrasound pulsed electromagnetic energy treatment for perineal trauma A randomized placebo-controlled trial. British Journal of Obstetrics & Gynaecology 96: 434–439

Hadjiargyrou M, McLeod K, Ryaby J, Rubin C 1998 Enhancement of fracture healing by low intensity ultrasound. Clinical Orthopaedics and Related Research 355S: S216–S229

Haker E, Lundeberg T 1991 Pulsed ultrasound treatment in lateral epicondylalgia. Scandinavian Journal of Rehabilitation Medicine 23: 115–118

Hashish I, Harvey W, Harris M 1986 Anti-inflammatory effects of ultrasound therapy: evidence for a major placebo effect. British Journal of Rheumatol 25: 77–81

Hashish I, Hai H K, Harvey W 1988 Reproduction of postoperative pain swelling by ultrasound treatment: a placebo effect. Pain 33: 303–311

Hasson S, Mundorf R, Barnes W et al. 1990 Effect of pulsed ultrasound versus placebo on muscle soreness perception muscular performance. Scandinavian Journal of Rehabilitation Medicine 22: 199–205

Lehmann J F, Johnson E W 1958 Some factors influencing the temperature distribution in thighs exposed to ultrasound. Archives of Physical Medicine and Rehabilitation 39: 347–356

Lindsay D M, Dearness J, Richardson C et al. 1990 A survey of electromodality usage in private physiotherapy practices. Australian Journal of Physiotherapy 36: 249–256

Lindsay D M, Dearness J, McGinley C C 1995 Electrotherapy usage trends in private physiotherapy practice in Alberta. Physiotherapy Canada 47: 30–34

Low J, Reed A 2000 Electrotherapy explained, 3rd ed. Butterworth-Heinemann, Oxford

Lundeberg T, Abrahamsson P, Haker E 1988 A comparative study of continuous ultrasound placebo ultrasound and rest in epicondylagia. Scandinavian Journal of Rehabilitation Medicine 20: 99–101

Lundeberg T, Nordstrom F, Brodda-Jansen G 1990 Pulsed ultrasound does not improve healing of venous ulcers. Scandinavian Journal of Rehabilitation Medicine 22: 195–197

McDiarmid T, Burns P N, Lewith G T et al. 1985 Ultrasound the treatment of pressure sores. Physiotherapy 71: 66–70

McLachlan Z 1991 Ultrasound treatment for breast engorgement: a randomized double blind trial. Australian Journal of Physiotherapy 37: 23–28

Nwuga V C B 1983 Ultrasound in treatment of backpain resulting from prolapsed intervertebral disc. Archives of Physical Medicine and Rehabilitation 64: 88–89

Nykanen M 1995 Pulsed ultrasound treatment of the painful shoulder: a randomized double-blind placebo-controlled study. Scandinavian Journal of Rehabilitation Medicine 27: 105–108

Plaskett C, Tiidus P M, Livingston L 1999 Ultrasound treatment does not affect postexercise muscle strength recovery or soreness. Journal of Sport Rehabilitation 8: 1–9

Pope G D, Mockett S P, Wright J P 1995 A survey of electrotherapeutic modalities: ownership use in the NHS in England. Physiotherapy 81: 82–91

Portney L G, Watkins M P 1993 Foundations of clinical research. Norwalk: Appleton & Lange

Pye S 1996 Ultrasound therapy equipment — does it perform? Physiotherapy 82: 39–44

Robertson V J, Baker K G 2001 A review of therapeutic ultrasound: clinical effectiveness. Physical Therapy 81: 1339–1350

Robertson V J, Spurritt D 1998 Electrophysical agents: Implications of EPA availability use in undergraduate clinical placements. Physiotherapy 847: 335–344

Robertson V J, Ward A R 1996 Dangers in extrapolating in vitro uses of therapeutic ultrasound (Letter). Physical Therapy 76: 78–79

Robinson A J, Snyder-Mackler L 1988 Clinical application of electrotherapeutic modalities. Physical Therapy 68: 1235–1238

Roche C, West J 1984 A controlled investigating the effect of ultrasound on venous ulcers referred from general practitioners. Physiotherapy 70: 475–477

Sackett D L, Straus S E, Richardson W S et al. 2000 Evidence-based medicine how to practice teach EBM, 2nd edn. Churchill Livingstone, Edinburgh

ter Riet G, Kessles A G H, Knipschild P 1996 A randomized clinical trial of ultrasound treatment for pressure ulcers. Physical Therapy 76: 1301–1312

ter Haar G, Dyson M, Oakley S 1988 Ultrasound in physiotherapy in the United Kingdom: results of a questionnaire. Physiotherapy Practice 4: 69–72

van der Heijden G J M G, van der Windt D A W M, de Winter A F 1997 Physiotherapy for patients with soft tissue shoulder disorders: a systematic review of randomized clinical trials. British Medical Journal 315: 25–29

van der Windt D A W M, van der Heijden G J M G, van der Berg S G M et al. 1999 Ultrasound therapy for musculoskeletal disorders: a systematic review. Pain 81: 257–271

Ward A R 1986 Electricity fields and waves in therapy. Marrickville: Science Press