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The Cochrane analyses - can they be improved?

[Jan Tunér DDS](#), Grängesberg, Sweden

Jan.tuner@swipnet.se

The aim of the international Cochrane collaboration is to continuously evaluate new and old medical therapies. The basis for their systematic reviews is the recognition of Randomised Controlled Trials as the "gold standard" for scientific evaluation of small and moderate effects from treatment (1). A thorough search is made for the available literature and the most qualified studies are analysed. The purpose of the analysis is to find out whether or not there is any solid support for a specific medical treatment modality. Such analyses are published in medical journals and extended versions are quarterly updated in the Cochrane Library.

Three systematic reviews of the effectiveness of Laser Therapy have been published in the Cochrane Library. These reviews have evaluated the effect of Laser Therapy for Venous ulcers (1), Osteoarthritis (2) and Rheumatoid arthritis (3). However, the Cochrane style of reviewing has been criticised (9) for not taking into account the variability of diagnoses, treatment procedures and dosage of the included trials. Critical comments are, according to the rules of the Cochrane system, supposed to be included into the ongoing updating of the reviews, but the comments on the venous ulcer analysis by the author of this article have not been published, nor commented.

The impact of the Cochrane Library is profound in medicine. It is therefore essential to "evaluate the evaluation", to find out whether or not these analyses can live up to the prestige of the Cochrane Library. The following text is a critical "analysis of the analyses".

Venous ulcers

Four trials are analysed; two comparing laser with placebo, one comparing laser with non-coherent light and one comparing laser with ultraviolet light. The two studies comparing laser with placebo are (4) and (5). In (4) a 6 mW HeNe laser was used. 4 J/cm² was said to be given to the ulcers. Ulcer size ranged from 3-32 cm². Treatment technique is not stated. Regardless of technique, it would take between 36 minutes and 6 hours to achieve the stated dose, per wound and session. Using a sweep technique with a focused beam, the power density would be

around 0.15 W/cm². If a defocused beam was used to cover the entire largest wound (32 cm²), energy density would be around 0.00019 W/cm², which is lower than the energy density of the normal illumination in an operatory, which is extremely low. A dose miscalculation is probable but the authors of the study have been reluctant to reveal the parameters used. In the absence of such parameters, this study cannot be properly evaluated, but very low power density is a probable reason for negative results. In the second study on venous ulcer (5), GaAs was employed. 4 mW was used for 10 minutes on ulcers ranging from 4 to 52 cm², regardless of ulcer size. The 4-cm² wound would thus receive 0.6 J/cm² and the largest wound 0.046 J/cm², not the 1.96 J/cm² stated by the authors. Energy density as well as dose for larger wounds are thus low. Treatment technique is not indicated. "The laser was held perpendicular to the surface of the wound". This is not a sufficient description of the treatment method. There is a great difference between following the outer border of the wound (active healing area) and spreading the beam over the open wound area. The distance between diode and wound is not indicated.

In summary, the energy said to be applied in these studies must be questioned. The Cochrane evaluators have not observed the essential contradiction between the actual dose and the dose indicated by the authors. In one of the four studies (Crorus and Malherbe, 1988) the laser wavelength and dose is not stated in the original paper. This makes an evaluation impossible.

Osteoarthritis

Five trials were included out of 142 potentially relevant articles. Six abstracts are awaiting assessment, after having contacted the authors for further details. These are our comments on the evaluation:

- a. Bülow (1994) (negative outcome) is a good study with a reasonable energy (22.5 J/session) for painful knee osteoarthritis. However, see discussion on this study in the text on RA.
- b. Basford (1987) (negative outcome) used 0.007 J per point for thumb arthritis. Meaningless dosage.
- c. Jensen (1987) (negative outcome) used 0.2 J in total for painful knee arthrosis. Clearly a meaningless dosage.
- d. Stelian (1992) (positive outcome) used around 11 J per session, twice daily, so 22 J per knee and day, 10 consecutive days. This study has a dose that is acceptable even in the light of to-days experiences, although it was

published already in 1992. The outcome of this study is in sharp contrast to the rather similar study by Bülow. Dose is the same, number of sessions is almost the same (10/9). However, Bülow treated 2-4 times a week, Stelian daily.

- e. Walker (1983) (positive outcome) is a classical positive study, but the use of a less-than 1 mW HeNe laser clearly puts this study in doubt. In our opinion it should not be used as anything but a purely historical reference.

The crucial criticism of the evaluation of the studies above is that there is no discussion about dosage! On the Jadad quality scale (1-5), Basford is given 3 and Bülow 2. However, Basford has used a non-significant dosage for a finger joint, while Bülow has a reasonable dose for knee osteoarthritis. Johansen (see RA below) has been over the generally accepted dosage window. In retrospect, the Bülow trial has been criticised for overlooking a significant short-term effect of active laser treatment by only testing the statistical significance at follow-up (Marks & de Palma 2000). Stelian used 55 times higher energy than Jensen, for knee osteoarthritis! The Jadad quality scale is applied correctly to the studies. But without inclusion of the laser parameters in the scale, the evaluation rather becomes a "study design beauty contest" instead of an evaluation of therapeutical significance.

3. Rheumatoid arthritis

8 out of 191 articles met the inclusion criteria, five were RCT:s. Five studies are waiting assessment, pending answers from the authors. Comments:

- a. Johansen (1994) (negative outcome) used 11.9 J per finger joint, which is a high dose, maybe too high.
- b. Heussler (1993) (negative outcome) used 1.5 J per finger, which is on the low side.
- c. Walker (1987) (positive outcome), see above for relevance. Although Johansen has used 1700 times higher a dose, both studies are "put in the same basket", although a low/high dose evaluation is performed. The wide gap in dosages does not justify a subgroup analysis of merely two groups.
- d. Hall (1994) and Goats (1996) used combined coherent and non-coherent light. Combined single wavelength coherent light and multi-wavelengths non-coherent light

is a poorly studied area and there is no ground for postulating that they produce the same biological effects when used in combination or alone.

- e. The authors quote Seichert (1991): "The laser light loses its coherency completely after only a few tenths of mm in depth". This is not in accordance with laser physics, but a tall tale. Fact is that the length of coherence is considerably reduced but remains within the laser speckles, which can penetrate considerable depth in the infra-red.
- f. The meta analysis by Gam (one of the Cochrane co-authors) (8) is referred to. This analysis did not find any effect of Laser Therapy for musculoskeletal pain. The re-evaluation of the same studies made by Bjordal (9) found a clear effect, since an analysis of the dosage and therapeutic techniques was included. This later meta-analysis is not mentioned. As stated above, critical comments on the Cochrane reviews are supposed to be included.

Review conclusions

The evaluators of the Cochrane groups have been successful in finding many of the relevant studies in the literature. Several interesting observations have been made and a skilful analysis of the design parameters has been performed.

Evaluation of effects is a universal problem for all empirically developed therapies, where consensus of a clearly defined optimal dose range and adequate treatment procedure is lacking. For clinicians practising laser therapy it is hard to understand that the reviewers have disregarded which locations for laser exposure and which laser doses that are being used. The methodology used seems to be that of drug studies. But drugs and LLLT are quite different. While the oral intake of the drug is the only procedure, LLLT has several, such as local irradiation, trigger point irradiation, acupuncture irradiation and irradiation over peripheral nerves. All these methods must be evaluated separately.

The biggest problem has been the fact that most of the reviews have included a variety of diagnoses, doses and treatment procedures and then been "put into the same basket". New treatment methods are often subject to trials where clinicians include all their non-responder patients, and the early laser literature is no exception. The laser literature involves around 100 double blind trials (12). They include a heterogeneous sample of around 20 different diagnoses, which vary widely in

pathology, tissue involved and prognosis. Adding to this are all the inadequate treatment procedures and doses that have been employed in clinical LLLT trials, so we should be very careful about putting all the trial results together, to see if they add up to an effect that is significantly better than placebo. Under such circumstances the majority of these trials will find no effect of active treatment. Future reviews are suggested to analyse the positive studies in order to find out what kind of parameters seem to work. Subgroup analyses are of particular importance. Dosage analysis cannot be limited to the groups "high" and "low" because of the great variations in dosage.

So what have these new Cochrane reviews brought us? Three distinct steps of progress can be identified. The first is the new review limitation to specific diagnosis (2) (3). The second is that in the RA review, attempts have been made to evaluate effects separately for high and low dose. And thirdly, but not least they even give a (conditioned) recommendation: "Low level laser therapy could be considered for treatment of rheumatoid arthritis for its short term effect and lack of side effects".

Future directions

In my opinion both laser researchers and reviewers have common responsibilities in enhancing our understanding of LLLT. The three existing Cochrane reviews on Laser Therapy have drawn a conclusion to which I can subscribe: The literature on the evaluated indications is ambiguous, the average quality of the studies is not high and the number of relevant studies is low. It can therefore be postulated that there is still insufficient scientific support for the general use of Laser Therapy for these indications and that only moderate and short-term effects can be confirmed. However, I would appreciate if reviewing methodology included validity criteria for doses and targets for laser irradiation (synovia, triggerpoints, acupuncture points, peripheral nerve, etc.).

I would also appreciate if the effect calculations were performed for subgroups of different doses, treatment frequencies and laser types. And there is still room for improvement of the literature search. Further, reviewers must make their own dosage calculations, not taking the doses quoted in the studies for granted. Too many of the negative LLLT studies contain serious flaw (11) and such flaw must be firmly investigated in the evaluation of studies. My main impression is that reviewing methodology slowly is improving, but there is still a long way to go before the Cochrane Collaboration can claim propriety over the term "evidence-based medicine" in this field of medicine.

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