Reviewer's report

Title: The effectiveness of extracorporeal shock wave therapy for the treatment of lower limb ulceration: a systematic review

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Reviewer: Robert M Stoekenbroek

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The current manuscript is a systematic review summarizing the evidence on the effectiveness of shock wave therapy in the treatment of chronic lower extremity ulcers. An extensive search was undertaken, but only four studies were considered eligible for inclusion. The authors conclude that the evidence provided by these studies is limited as a result of methodological shortcomings.

Considering that the treatment of (diabetic) foot ulcers has been largely based on clinical experience and ‘beliefs’, rather than on solid evidence, the manuscript addresses a relevant and actual topic. Overall, the review was conducted according to methodological standards.

Some detailed comments below:

Abstract

1. Minor essential revision: It would be good to point out in the abstract that the effectiveness of ESWT as an addition to standard care has only been assessed in one RCT, as the other studies either compared ESWT to HBOT (Wang 2009, Wang 2011) or were not RCTs (Saggini 2008).

2. Minor essential revision: The type of ulcers considered for inclusion could be mentioned, as well as the fact that observational studies were eligible for inclusion (i.e. inclusion was not limited to RCTs).

3. Discretionary revision: The authors may consider adding one sentence on the results of the studies included in the review, as well as the fact that most studies only included diabetic ulcers.

Introduction

1. Discretionary revision: Please consider including a short description of what an ESWT protocol for the treatment of lower extremity ulcers could entail, i.e. number of treatments, frequency, etc.

2. Discretionary revision: Second sentence: please consider rephrasing. Lymphoedema and peripheral vascular disease are not systemic comorbidities. Moreover, I would recommend removing lymphoedema and mentioning peripheral arterial disease and venous insufficiency separately (instead of reporting these combined as peripheral vascular disease), because of the high prevalence of these conditions.
3. Discretionary revision: Regarding the standard ulcer management mentioned in the fourth sentence: please consider revising into “Typically, effective ulcer management involves local wound care, compression therapy, pressure redistribution, infection management and optimization of vascular status”.

4. Minor essential revision: It is stated that “[ESWT] has been shown to be an effective treatment for intermittent claudication”. However, the evidence for ESWT in the treatment is sparse and the authors may wish to rephrase this sentence.

5. Minor essential revision: Please consider referring to the systematic review by Qureshi et al., Plastic and Reconstructive Surgery 238(6), 2011.

Methods

1. Discretionary revision: The authors may wish to remove the age criterion mentioned under participants.

2. Minor essential revision: Did the authors intend to include pressure sores? Although these ulcers are not listed under the exclusion criteria, they were not included in the search strategy.

3. Minor essential revision: The authors may want to state in the text that a predefined data extraction form was used in the extraction process (additional data file 1). It is mentioned in the text that ‘relevant data was extracted’, giving certain examples (‘means, mean differences, standard deviations and p values’). Mentioning only some of the extracted variables may be confusing, and I think the authors should give more details about the variables for which data was sought.

4. Major compulsory revision: No mention is made in the methods section about the outcome measures for which data was sought. It becomes apparent from the results section that the included studies used a wide variety of outcome measures. I would recommend choosing some of the most patient-relevant outcome measures (e.g. wound healing and change in ulcer size), and summary measures to report these outcomes (e.g. relative risk). These could then be mentioned in the methods section.

5. Discretionary revision: Although I agree with the authors that a narrative approach best fits the heterogeneous data, I think the authors should mention in the methods section whether the narrative approach was chosen a priori or only after obtaining the research data.

Results

1. Minor essential revision: The authors state that 555 studies were identified. However, only 123 articles remained after removal of duplicates. I suppose the authors mean that their searches yielded 555 results, not studies.

2. Minor essential revision: Please mention the number of venous, diabetic and posttraumatic ulcers in the study by Saggini et al.

3. Discretionary revision: Under ‘Trial characteristics’, second sentence, the
authors describe a study as a randomized, prospective, controlled trial. As randomized controlled trials are always prospective, please remove ‘prospective’.

4. Major compulsory revision: Referring to the trial by Moretti et al., the authors state that patients in the control group received standard therapy that also included pressure relief and treatment of infection where present, and imply that patients in the ESWT group did not. However, it is stated in the original article that (1) “[…] two groups that received standard care […] ESWT group also received ESWT”, (2) “each patient was provided with an orthopedic device”, and (3) “wound infection was treated by appropriate antibiotics”. Moreover, in the results section it is mentioned that a patients with an infection in the ESWT group was treated by antibiotics. My interpretation is that all patients included the study received these treatments, and I do not read from the original article that standard therapy differed between both groups.

5. Minor essential revision: In table 2, the authors provide a clear overview of the ESWT characteristics and patient- and ulcer characteristics. However, the information provided on each study in the text is rather non-uniform. For example, the number of ESWT treatments and the treatment frequency are not provided for the Saggini study, as opposed to the other studies, although far more technical details on the ESWT are given for this study. In addition, both studies by Wang et al. were not blinded, although this is only mentioned for the newest study.

6. Minor essential revision: The authors may wish to separately report the significance for the different outcome measures for the first trial by Wang et al. Outcomes for the number of ulcers completely healed, >50% improvement and unchanged are reported with one p-value (0.001). However, the difference in complete healing (11/36 vs. 8/36) is not statistically significant, although this is not mentioned in the original article, which I find somewhat misleading.

7. Minor essential revision: Regarding the newest study by Wang et al.: patients were randomized to 6 ESWT treatments or 20 HBOT sessions. Some patients received a second course of ESWT or HBOT. However, the review authors state that 40 HBOT sessions were given. This is valid, however, for only part of the study population.

8. Major compulsory revision: Referring to comment 4 on the methods section, I think it would be useful if the authors would limit the outcome measures reported on to some patient-relevant measures. Currently, the authors mention all outcome measures reported in the primary studies, although I consider outcome measures such as ‘re-epithalization index’, ‘improvement in the healing process’ and ‘amount of exudates’ rather ambiguous.

9. Minor essential revision: Saggini et al. included diabetic, venous and posttraumatic ulcers, and separately report outcomes for each of these groups. It may be worth mentioning the number of patients in each group, along with the healing rates, as these where quite different for posttraumatic vs. diabetic / venous ulcers.

10. Minor essential revision: The authors do not mention the long-term follow-up results of the first study by Wang et al. (J Surg Res 2014, June 2014), probably
because this was published after the search. It may be worthwhile including these results.

11. Major compulsory revision: The authors excluded the study by Schaden et al. (2007) because this study also included burn wounds and surgical wounds. However, results are separately reported for ulcers of other etiology (e.g. venous, arterial), and I therefore think the authors should include information from the Schaden study. It may also be observed that, as in the study by Saggini et al., healing rates were best in the group with posttraumatic ulcers.

Discussion

1. Major compulsory revision: It would be good to point out that only two studies (only one of which was an RCT) investigated the effect of ESWT versus standard treatment, as Wang et al. compared ESWT to HBOT. Moreover, one sentence could be added on the small number of patients in the studies.

2. Major compulsory revision: Regarding the section on the internal validity of the Moretti study, please refer to comment number 6 in the method section.

3. Minor essential revision: The authors mention the lack of description on standard treatment for the studies by Moretti et al. and Saggini et al. However, in my opinion, standard of care is poorly described in all four studies (including those by Wang et al.). Moreover, it may be noted that lack of standardization may be of particular importance given the non-blinded design of the studies.

4. Discretionary revision: Regarding the section on heterogeneity of ulcer classification, I think the problem is not so much variation in ulcer classification, but lack of reporting of ulcer characteristics in general. For example, little information is given on the presence of infection and vascular status.

5. Major compulsory revision: The authors state that “the treatment dosage for each participant in the second study by Wang et al. was dependent on the size of the ulcer”, which is indeed stated in the original article, referring to the number of impulses per session. However, I think the number of impulses always depends on ulcer size, and the number of impulses is expressed per unit of wound surface area in all of the four studies. Am I correct?

6. Minor essential revision: The authors could add a sentence to the ‘recommendations for future research’ section regarding the fact that the optimal ESWT regimen remains to be established.

7. Discretionary revision: Regarding the limitations of the review: although heterogeneity between the included studies and inconsistent outcome measures in the included studies do limit the strength of any conclusions that could be drawn based on the results, I do not consider these limitations of the current review, but rather of the original studies.

Level of interest: An article of importance in its field

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests