Author's response to reviews

Title: A randomized clinical trial comparing hydrocolloid, phenytoin and simple dressings in the treatment of pressure ulcers

Authors:

Mohammad TAGHI Hollisaz (hollisaz@bmsu.ac.ir)
Dr Hossein Khedmat (h_khedmat@hotmail.com)
Fatemeh Yari (yari1672@yahoo.com)

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PDF covering letter
**CONSORT item 1:** Title and abstract. "How participants were allocated to interventions. (e.g., "random allocation," or "randomly assigned")

**Reviewer comment:** the abstract describes the design as "simply randomized." The title does not mention random allocation, (Minor compulsory Revisions)

**Authors response:** Title and abstract were revised accordingly

**CONSORT item 2:** "Scientific background and explanation of rationale"

**Reviewer comment:** “Authors describe pressure ulcer prevalence, cost, and treatment. In most circumstances, the authors provide appropriate reference for their text. However, the reference for cost (reference 5) is from 1987 and may be out of date. In the last paragraph of the introduction, the authors assert morbidity and mortality associated with pressure ulcers. I ask the authors to provide references for their assertions regarding morbidity and mortality. The last sentence of the introduction suggests extrapolation and generalization of the results to other surface wounds. I believe text about "generalizability" (external validity) of the trial findings belongs in the Discussion section (please see CONSORT item 21 below) (Minor compulsory Revisions).”

**Authors response:** 1."The reference for cost …": New reference were addressed (References ----to ----) and the text was revised.
2. "to provide references for … morbidity and mortality": There are several references in this regard including: A. sugarman B. Infection and pressure sores. Arch Phys Med Rehabil 1985; 66:177-9.


To avoid a long list of references, we only cited two references (A. and B)

3. "I believe text about generalizeability…": The issue of generalizability was omitted from the Introduction section and moved to the Discussion section as was recommended.

**CONSORT item 3:** “Eligibility criteria for participants and setting and locations where data were collected”.

**Reviewer comment:** “The authors described the eligibility criteria and setting for the trial.”

**CONSORT item 4:** "Precise details of the interventions intended for each group and how and when they were actually administered”.

**Reviewer comment:** who administered treatment intervention? Who assured the treatment intervention was administered with comparable adherence in each treatment group? In Patients and Methods section, paragraph 4, the control therapy appears to be dry sterile gauze. Since maintenance of a moist wound environment is the standard of care, the dry sterile gauze group may not have received standard therapy. Comparisons to the dry sterile gauze group will need to emphasize any deviations from the standard of care that might exaggerate differences between treatment groups. (Major compulsory revisions)

**Authors response:** At the beginning of the study, medical records of all war SCI victims were reviewed by the authors and all pressure sore patients were recruited and those who met eligibility criteria were enrolled in the study.

Two general practitioners and nine nurses who were trained for treatment interventions administered treatment protocols.
Simple dressing patients were visited twice a day, phenytoin group were visited once a day and hydrocolloid group were visited twice a week. All participants were visited and examined by general practitioners every two weeks to make sure of the proper administration of treatment intervention with comparable adherence in each treatment group.

In the simple dressing group, the following steps were taken with due care twice a day: The ulcer was cleaned and washed 3 times with normal saline serum, then dried out with a sterile gauze and depending on the size of ulcer, it was covered by wet saline gauze dressing. In case of existence of necrotic tissue, it was debrided before dressing. Wet saline gauze dressing is an accepted and frequently used method and if carefully done, the injury to the wound bed is minimized, although epithelial cell growing into the gauze fibers and embeded cotton fibers in the wound have reported. Details of other interventions have been mentioned in the text (Methods section).

**CONSORT items 5:** "Specific objectives and hypotheses".

**Reviewer comment:** “The text dose not contain precise statements of the primary and secondary objectives or hypotheses. My review of the Results section leads me to believe the primary objective was a comparison of complete healing rates between patients with pressure ulcer treated with hydrocolloid, phenytoin, or dry sterile gauze. I assume the secondary objectives were comparisons of complete healing rates within subgroups defined by ulcer and location. (Major compulsory revisions).”

**Authors response:** primary and secondary objectives are now defined at the end of the Introduction section.

**CONSORT item 6:** "Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurments(e.g. multiple observations, training of assessors) "

**Reviewer comment:** “I could not find an explicit statement of the primary outcome in the Methods section. Was the primary outcome complete healing within 8 weeks? What was definition of complete healing for stage I ulcers?"
What was the definition of complete healing for stage II ulcers? The authors calculated ulcer area. Was ulcer area a secondary outcome? (Minor compulsory revisions)

Authors response: The primary outcome was whether complete ulcer healing happened or not within 8 weeks. Complete ulcer healing is defined as:
- For stage I ulcers: Intact epidermis, no red area
- For stage II ulcer: Intact dermis and epidermis, no abrasion or ulceration.

Primary and secondary outcomes were appropriately explained in the Methods section. Ulcer area measurement was done to match all three treatments groups under study in terms of the ulcer size. Data analysis of partial ulcer healing i.e. decreased measurements of ulcer surface area was not included in this manuscript.

CONSORT item 7: How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules

Reviewer comment: “I did not find text in the Methods section to describe a rationale for the sample size. If the study did not have a formal sample size analysis, then it would be appropriate to call the study a pilot study in the title and methods and discussion (Minor compulsory revisions).”

Authors response: Before the study, we assumed the response rates of 30%, 40% and 80% for simple dressing, phenytoin and hydrocolloid dressing, respectively. Thus, based on the effect size of 40%, power of 0.85, confidence level of 95% and estimated loss to follow-up of 10%, 29 patients were required for each study group. The number of ulcers that met eligibility criteria totalled to 91, all of which were enrolled in the study. (revised in Methods section).

CONSORT item 8: “Method used to generate the random allocation sequence. including details of any restriction (e.g. blocking, stratification)”
Reviewer comment: “I did not find text in the Methods section to describe the technique for random sequence generation. (Minor compulsory revision)”

Authors response: Random-number table was used to generate the random allocation sequence and in order to achieve balance between treatment groups and subgroups (ulcer stages and locations) blocked randomization was done. (revised in Methods section).

CONSORT item 9: "Method used to implement the random allocation sequence (e.g. number containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned."

Reviewer comment: “I did not find text in the Methods section to describe the presence or absence of allocation concealment(Major compulsory Revisions).”

Authors response: the statistician working with us generated the random allocation sequence using a random-number table. He was aware of the patients list (numbers only) and ulcer stage and locations and the number of each subgroup. The treatment category of each patients was determined by the statistician and was announced in an opaque sealed envelope bearing on the outside only the number given to each patients. These sealed envelopes were received by the authors and delivered to the general practitioners along with the list of patients numbers and names. After visiting every patient, the appropriate numbered envelope was opened by the general practitioner to determine whether he would be treated by simple, phenytoin or hydrocolloid dressing method. Then the appropriate intervention was started.

CONSORT item 10: “Who generated the allocation sequence. Who enrolled participants, and who assigned participants to their groups.”
Reviewer comment: “I did not find text in the Methods section to describe the implementation of random allocation. (Minor compulsory revisions).”

Authors response: Generation of the allocation sequence and assignment of participants (according to their numbers) to trial groups were made by the statistician. Enrollment of participants to the study was done by the authors according to eligibility criteria. (mentioned in Methods section).

CONSORT item 11: “whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.”

Reviewer comment: “the methods section describes the study as "single blind". I could not find text to tell me who was blind. If outcome assessors were blind, then I would like to know if they were blind to treatment assignment when they assessed the primary outcome and/or secondary outcome. (Minor compulsory revisions).”

Authors response: The authors were blind to patients assignment to trial groups. The general practitioners were also blind to treatment intervention of each patients up to the start of the study, when they opened the sealed envelopes made by the statistician as mentioned above. With the start of the intervention both general practitioners and nurses knew the trial groups because of the existance of significant differences between. Three treatment methods which precluds any blinding. The patients were also aware of the treatment method although at the beginning, they had equal chance to enter to any of the trial groups. Thus, the study was single blinded and the authors who enrolled the patients to the study were blind to treatment assignment. The authors were also the final assessors of the outcomes and they were again blind to the trial group of each patient when they assessed the outcomes. (Methods section)
**CONSORT item 12: **“Statistical methods used to compare groups for primary outcome…”

**Reviewer comment:** “the text does not state the primary outcome for analysis and does not state the method of analysis for the primary outcome. The text state ANOVA and chi-squared tests for all data gathered from patients preliminary and complementary questionnaire. The text does not give me enough information to assess fulfillment of CONSORT item 12. The authors analyzed 91 ulcers from 83 patients. When analysis involves more than one ulcer per patient, then there is a violation of the statistical assumptions of independence and of random sampling from the population. The statistical test chosen by the authors do not permit more than one ulcer per patient. If the authors wish to analyze two ulcers per patient, then they need to have a matched design that will allow the use of appropriate tests like MCNemars test(Major compulsory revision).”

**Reviewer comment: the text does not state the primary outcome for analysis and …)**

**Authors response:** As mentioned in the Methods section, 91 ulcers of 83 patients were assigned to three trial groups by restricted blocked randomization. If a patient had more than one ulcer, all of them were treated by one treatment method to avoid any treatment interactions. Thus we avoided two different treatment methods in a single patient. To keep the strength and dependability of the study, we performed a second analysis considering only one ulcer per patient. The findings had no significant difference with the original analysis.

**CONSORT item 13: **"Flow of participants through each stage (a diagram is strongly recommended) "

**Reviewer comment:** “I did not receive a flow diagram to review. I could not assess drop-outs or withdrawals.(Major compulsory revision).”

**Authors response:** Flow diagram of participants through each stage of the study was added to the manuscript. All patients completed the study and there
was no lost to follow-up, no treatment withdrawal, no trial group change and no major adverse events.

**CONSORT item 14:** "Dates defining the periods of recruitment and follow-up"

**Reviewer comment:** “I found the dates of spinal cord injury in the text. I did not find dates requested in CONSORT item 14 (Minor Compulsory Revisions)"

**Authors response:** the study proposal was designed in November 2001, recruitment of patients began in March 2002 and lasted about 2 months. Then the patients were allocated to trial groups and followed up for another 2 months and then all the gathered data were analyzed within 2 months. Thus the total length of the study from proposal to final analysis was about 10 months (i.e. up to September 2002) (Results section).

**CONSORT item 15:** "Baseline demographic and clinical characteristics of each group”.

**Reviewer comment:** “I found these items in table 1. The text dose not state if the trial included men or women or both. Please note. Figure 1 and figure 2 were distorted and were hard to read. I assume the distortion occurred during the process of uploading or downloading from the internet. Either way, both figure 1 and figure 2 appear to be superfluous because they display baseline characteristics that belong in table 1 or in the text. (Minor Compulsory Revisions).”

**Authors response:** All the patients were men who were SCI victims of Iran-Iraq war. Distribution of patients in trial groups according to the ulcer location (gluteal, ischial and sacral) and ulcer stage (I and II) have been demonstrated in figures. (Results section).

**CONSORT item 16:** “Number of participants (denominator) in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible (e.g., 10 or 20, not 50%).”
Reviewer comment: “The text dose not state if the analysis was according to intention to treat. In the Results section, there are numerous examples of percentages that lack numerator and denominator data. In the abstract, there are P values without numbers of participants. Please note. The Results section mentions Table 2. I did not receive Table 2 in the documents submitted for review. (Minor Compulsory Revisions)"

Authors response: All the data were revised accordingly in the Results and Abstract sections. We had no lost to follow-up, no treatment withdrawal, no treatment group change and no important adverse events during the study. Thus all the participants completed the protocol and all were included in the analysis (we assume in our study intention to treat equals perprotocol)

CONSORT item 17: ”For each primary and secondary outcome a summary of results for each group and the estimated effect size and its precision (e. g. 95% confidence interval).“

Reviewer comment: “I did not find 95% confidence intervals in the text submitted for review”

Authors response: All the data were revised accordingly in the Results section.

CONSORT item 18: ”Address multiplicity by reporting any other analyses performed, including subgroup analyses, including those prespecified and those exploratory.“

Reviewer comment: “I found subgroup analyses within ulcer stage and within ulcer location. The text does not state if these analyses were prespecified or exploratory. (Minor Compulsory Revisions)”

Authors response: All the analyses were prespecified in the trial protocol, including subgroup analyses for secondary outcomes (ulcers stages and locations), and there were no exploratory analyses. The only additional analysis which was done, was on the case with more than one ulcer. As was mentioned, there was no significant difference between the analyses.
**CONSORT item 19:** “All important adverse events or side effects in each intervention group”.

**Reviewer comment:** “I did not find adverse event data in the text submitted for review”.

**Authors response:** Fortunately, there had been no adverse events or side effects during the study.

**CONSORT item 20:** "Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes“.

**Reviewer comment:** The Discussion section mentions the mechanisms of action of phenytoin and hydrocolloid. The third paragraph contains several assertions about hydrocolloid that require references. The references at end of the paragraph (25-27) do not appear to pertain to hydrocolloid. I could not check the references from the journal named HELIOS because this journal is not indexed by the National Library of Medicine (PUBMED) or by Science Citation Index. The authors did not address potential biases. I cannot tell from the text if there are biases related to randomization, execution of the blind, drop outs-withdrawals, generation of random numbers or allocation concealment. (reference Moher D. Pham B, Jones A. Cook DJ. Jadad AR. Mohr M, Tugwell P, klassen TP. Lancet 1998: 352:609-613) (Minor Compulsory Revision)

**Authors response:** The reference section was revised and other references used in the study were addressed.

**CONSORT item 21:** ”Generalizability (external validity of the trial finding).”

**Reviewer comment:** "In the Discussion, Paragraph 6, the authors make generalizations and assertions regarding hydrocolloid cost and comfort. Since the outcomes were not measured in their trial, I ask the authors to provide reference citations to other trials.“

**Authors response:** other reference were citations provided in the reference section.
Reviewer: Catherine Ratiff

Reviewer report:

“I have several comments about the manuscript. There is a difference between a stage I and stage II ulcer (www.npuap.org) and often times since
with a stage I, where there is no break in the skin some people do not even consider it an ulcer and even if they do, often do not treat it. However, you need to make sure your readers know what staging system was used. Hydrocolloid dressing are not really new as they have been available here in the US for about 20 or so years. You might also want to mention the support surface and the amount of turning and repositioning as this will also effect healing. Generally, a stage II ulcer should show evidence of healing and/or be healed in 2 weeks. How did you determine healing? Measurements?”

Authors response:
1. Fortunately, the ulcer classification system used in our study is the one recommended by you (i.e. National Pressure Advisory Panel Classification).

2. The data regarding SCI victims were accessed through the mediation and assistance of the Jaonbazan Medical and Engineering Research Center (JMERC), the medical and research section of the official governoental body which is responsible for SCI war victims. JMERC has a rich and precise data bank containing all medical and surgical records of war victims. Thus, pressure ulcer patients were easily accessed. In unreliable or doubtful cases, home visit was done to determine the existence of stage I ulcers.

3. Details of ulcer Classifications used in the study are now presented in table 1.

4. Although hydrocolloid usage in pressure ulcer dates bank to about 20 years ago, New studies are still being conducted, some of them have been cited in the Reference section. Our investigation is justified because of uniformity of the sampled and study populations and good adherence to methodological principles.

5. All the participants were appropriately trained with respect to turning and repositioning to keep all trial groups identical in this regard.
6. Although many of stage II ulcer heal within two weeks, our pilot study indicated a healing range of 1-8 weeks. Thus we followed our patients for 8 weeks.

7. Measurements were explained in the Methods section.