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Letter to the Editor

The Responsibility of the Institutional Review Board in Good Clinical Practice: First, Do No Harm

Dear Editor,

I read with interest the article on outpatient management of burn wounds published in a recent issue of the *IJMS*.[1] There are many questions that arise which are worth mentioning. Under the methodology section, no description was provided on how patients were randomized into the two treatment arms and, therefore, it is not possible to assess how confounding variables were controlled. Based on the data presented in table 3 of the article, the pain score before dressing was significantly lower in the "amnion group" than the "control group". This might reflect degrees of bias in assigning patients to the study groups. Consequently, as expected, the pain score measured after dressing and the dose of analgesics consumed were lower in the "amnion group" than in the "control group" (table 3 of the article).

Another point to be mentioned is that according to Article 32 of the Declaration of Helsinki code of ethics,[2] "the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention." While numerous brands of synthetic dressings have been readily available in Shiraz, where the principal investigator practices, it is not clear why the researchers treated the control group with silver sulfadiazine ointment.

Under the methodology section, it is also not clear how the amniotic membrane was processed; it is stated that "the amniotic membranes were placed in a sterile pot containing normal saline and 80 mg gentamicin," but the volume of normal saline is not mentioned. Did the authors think that an undetermined dose of gentamicin could eradicate all possible infectious organisms? "VDRL, HIV, and HCV and HBS antigens" were tested; the membranes were also cultured for identifying probable bacteriologic contamination. Did all these efforts eliminate the likelihood of transmission of infectious diseases?

As the authors, themselves, state in the very first paragraph of the Discussion, dressing with the amniotic membrane was introduced almost a century ago, but for concerns about the transmission of infections, it soon became obsolete in most developed countries. Nonetheless, based on its physiologic properties, synthetic dressings have been manufactured and used widely. The authors do not explain why their patients who were treated with amniotic membrane developed a "relatively high fever" for a few days soon after application of the membrane. As authors mentioned, amniotic membrane does not cause serious inflammatory response; so what was the cause of that fever? Have these patients been followed up for a reasonable period of time to identify whether they developed any health problem? Although it is mentioned that all the participants provided informed consents to take part in this study, because of marked differences between the knowledge of physicians and patients, it is not acceptable to put the patients' health in danger. Note that Ravishanker, whose work had probably influenced the authors of this article, used long-term glycerol preserved amniotic membranes for dressing since glycerol has antibacterial and antiviral properties.[3] Furthermore, Ravishanker used the membranes only for dressing of superficial wounds.

Finally, I believe that the Ethical Committee of Shiraz University of Medical Sciences is the most responsible body in this study for approving conduction of such an appalling and sketchy clinical trial. Over the past decade, we have witnessed an increasing trend in the number of scientific and biomedical publications from Iran.[4] Thanks to incorporation of many Iranian journals in major indexing systems, most of our publications are now readily accessible to the entire world. The world community judges us by our work. Doing a misconduct,[5] publishing a plagiarized article,[6] or conducting a poor research will seriously jeopardize this national movement.[7] I, for one, believe that all the bodies supervising research activities in our country should be more cautious in managing this critical situation.

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The Authors' Reply

Dear Editor,

I carefully read the letter about our manuscript that you sent to me.[1] There were questions about our work, which I have answered below;

1- Randomization was done using random allocation software.[2]

2- I think there was a misunderstanding about table 3. Pain score before dressing means average score before all dressings in both groups, which was interpreted by Dr. Habibzadeh as the pain measured at the beginning of the study. Obviously when the time between dressings becomes longer, patients have less pain, and this is one of the advantages of amnion dressing.

3- Dr. Habibzadeh states that according to the article 32 of the Declaration of Helsinki code of ethics, a new intervention must be tested against the best current proven interventions. According to all textbooks related to "Burn", the most effective and common treatment of burn in all burn centers is silver sulfadiazine.[3-5] And almost always, in all controlled clinical trials in burn patients in the world, the control group receives silver sulfadiazine.[6,7] On the other hand, all brands of synthetic dressing have many advantages and disadvantages. And no synthetic dressing has been suggested as the standard treatment in burn patients. Synthetic and biological dressings are alternatives to antimicrobial dressing.[5] Also, synthetic dressings are very expensive and are used in selected patients and rare circumstances, even in developed countries. For example; Integra (Integra lifeSciences corporation, USA) costs about 4500 US dollars for covering one percent of body surface area. It means that in a patient with 50% burn in his/her body surface area only one dressing with Integra would cost 225000 US dollars. With Acticoat (Smith&Nephew Healthcare Pvt.Ltd, USA), the cost is 2500 US dollars and with Biobrane (Smith&Nephew Healthcare Pvt.Ltd, USA) it is about 10000 US dollars.

4- Each amniotic membrane in our study was placed in 100 ml of normal saline and 80 mg of gentamycin. There are many preservation methods for amniotic membrane.[8] According to new studies, all preservation methods of amniotic membrane might have strong influences on cell viability. For example, glycerol preservation method leads to immediate cell death.[8] Therefore, we used a new and easy method (saline preservation method) with consideration of all precautions; by selection of placenta from HCV, HIV, HBS, and VDRL negative mothers,[7,8] with elective caesarean deliveries.[9] Additionally, we checked HCV, HIV, HBS, and VDRL of umbilical cord and performed bacteriologic study and used only the sterile membranes. Therefore, it is obvious that we did not put the patients' health in danger.

Dr. Habibzadeh wishes to know why fever developed in our patients who were treated with amniotic membrane. Hyperthermia is a component of the physiological response to burn. Hyperthermia (≥38.50) is routinely present following thermal injury, and is a poor indicator of infection.[10,11] In our study, many patients in the amniotic membrane group had a slightly higher fever during the first days of treatment,

which may be related to accumulation of burn discharge caused by the delay in changing the dressings. However, this fever was not associated with any other clinical manifestations and disappeared after dressing change without any other interventions, and the patients were discharged uneventfully.

5- Dr. Habibzadeh believes that the amniotic membrane is a discarded treatment for burn and only has a historic value. However, this is a wrong idea. Human amniotic membrane is known to be an effective dressing since John Staige Davis used it in 1910. But, since then, in spite of some concerns about the transmission of infections, extensive studies on amniotic membrane performed worldwide have proved it to be an excellent biological dressing with almost all the qualities of an ideal dressing.[12,13] Nowadays, in addition to wide use in ophthalmology,[14,15] amniotic membrane is widely applied in a variety of clinical applications, including intra-abdominal and reconstructive surgery, as well as dressing for burns and chronic ulcers,[16-22] reconstruction of artificial vagina,[23] head and neck surgery,[24] prevention of tissue adhesion in surgical procedures of the abdomen and pelvis,[25,26] insulin-producing cells,[27] and graft fixator.[28]

Amniotic membrane dressing has been a routine practice in our center since 3 years ago and in this period we have treated a considerable number of patients and had no health problem in their follow-up.

The last paragraph of Dr. Habibzadeh's letter is very strange. I believe that we passed all usual ethical and scientific stages to conduct our study, and that the Ethical Committee in Shiraz University performed its duty very well. Calling this clinical trial, which helps us to solve many problems in our burn patients as an appalling trial and using sentences such as plagiarized article or poor research about this study and calling it jeopardous for Iranian national scientific movement is very illogical and without scientific value. So, I think, silence is the best answer to such discriminations.

Finally, sorry to say that I think this letter has been written under the influence of some commercial medical companies that their benefits have been threatened by such studies.

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