Author’s response to reviews

Title: A Multi-center, Randomized, Clinical Study to Compare the Effect and Safety of Autologous Cultured Osteoblast Injection to Treat Fractures

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Author’s response to reviews: see over
Reviewer's report

Title: A Multi-center, Randomized, Clinical Study to Compare the Effect and Safety of Autologous Cultured Osteoblast Injection to Treat Fractures

Version: 4 Date: 21 July 2008
Reviewer: Jennifer Westendorf

Reviewer's report:
Kim and colleagues report the results of a multi-center randomized clinical trial that compared the effect and safety of autologously cultured osteoblasts on fracture treatment. The trial seems to have been successful; however, additional data need to be added to the manuscript to make it acceptable for publication.

1. Examples of x-rays from representative patient populations should be shown to demonstrate the degree of fracture healing. For example, in a particular age group, the samples representing median results should be shown.

→ We added the X-ray, as you recommended.

2. In Figure 2, there are a number of problems. First, the scale should be set to zero and error bars need to be included. Second, it is unclear why the data from one month after injection was averaged with data from two months after injection. These are not comparable and should be separated into distinct data points.

→ We added the figure and corrected the figure, as you suggested.

3. The fracture healing data should be broken down into age groups. Do the younger patients (with younger cells) respond better to osteoblast injection than older patients?

→ We added this data. And There was no statistical difference in the osteoblast injection response between the younger age group and the older age group(Fig. 6)

4. The culture techniques for expanding osteoblasts need to be described. How long were they grown in vitro? What medium was used?

→ We added this information, as you recommended.

5. Did the control group get only fibrin injections?

→ No. Nothing was applied as it is ethically problematic to inject to patients with ineffective substances. In addition, fractures usually heal over time without any treatment.

6. There are a few sentences that need to be rewritten on page 3, second paragraph. The sentence beginning with “However” is a run-on sentence. The last sentence of that paragraph has some typographical errors.

→ We edited it as you recommended.
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests.

Reviewer's report
Title: A Multi-center, Randomized, Clinical Study to Compare the Effect and Safety of Autologous Cultured Osteoblast Injection to Treat Fractures
Version: 4 Date: 2 August 2008
Reviewer: Peter Ebeling
Reviewer's report:
Kim S-J et al have conducted a multi-center, randomized, clinical study to compare the effect and safety of autologous cultured osteoblast injections to promote fracture healing. Callus formation was accelerated by autologous osteoblast injections.

This reviewer suggests the following compulsory revisions:
1. More detail is required regarding the autologous osteoblast cultures. What was the duration and method of culture? How was sterility assured? This section on page 4 needs to be expanded considerably to include these and other details.

➔ We expanded the contents as you recommended.

2. Does a callus formation score of < 3 at 6 weeks represent delayed fracture healing? This should be specified here on page 5.

➔ Many fractures showed delayed healing when the callus formation score was lower than three, 6 weeks after the fracture surgery, according to the Catholic University Hospital fracture patient data in 2004. The Korean FDA recommends considering this condition as part of the patient selection criteria in order to avoid unnecessary surgery.

3. What were the side effects of local fracture site injection of osteoblast cultures?

➔ There were no side effects of the osteoblast injection.
4. It is unclear why 77 patients were enrolled when 74 was the number originally planned (Page 7). Please clarify.

⇒ Because many patients were dropped from the study, it was very difficult to accurately determine the exact enrollment number. During the process of enrolling the study patients, this factor became inevitable.

5. A Figure should be included to show the recruitment pathways and reasons for exclusion, drop-out, etc.

⇒ We added a figure showing the pathways as Figure 2.

6. One decimal point is adequate for age and two orders of significance for p-values. These should be changed throughout, including the Tables.

⇒ We changed this information, as you recommended.

7. The meaning of the comparisons at different time points is unclear. A table could be added for the comparisons between osteoblast injection and control groups at different time points.

⇒ We explained this in Figure 4.

8. Figure 2: What does sum of the difference in callus formation scores mean? The standard errors should be included in the Figure as well as the significance of the difference.

⇒ It indicates the sum of the increased callus formation score both one month and two months after cell injection.

To clarify our intended meaning, we added a Figure, i.e. Figure 4, to explain the callus formation score at each time point, as you recommended.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published.
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.