Comparing Treatment of Focal Articular Cartilage Defect using Mesenchymal Stem Cell to Autologous Chondrocytes

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INTRODUCTION:
The use of autologous chondrocyte implantation (ACI) has demonstrated promising results for the repair of cartilage defects. However, several limitations to this technique have been identified. A major drawback is the various stages of the procedures required to complete the treatment, which include harvesting of chondrocytes from patients’ own knee, chondrocytes expansion in the laboratory and, re-implantation of these cells into the defective areas. Technical limitations have also been associated with its use, including low cell viability and re-occurrence of the defect after approximately four years post surgery. To overcome these problems, the use of mesenchymal stem cells (MSCs) as an alternative potential treatment modality in substitute of autologous chondrocytes has recently been considered. MSCs have the advantage of being multi-potent and having higher cell proliferation rate. However, there has not been any previous direct comparison of treatment outcomes between these two sources of chondrocytes in any in vivo model. A study was thus conducted to investigate the efficiency of mesenchymal stem cell embedded in alginate beads in repairing damaged focal cartilage in vivo compared to that of ACI and no treatment.

METHODS:
Thirty male New Zealand white rabbits (18 treated with ACI; 12 with MSCs) aged between 5 to 6 months were used in the study. Three rabbits were sacrificed to harvest bone marrow derived MSCs. The study was approved by University of Malaya animal ethics committee and the experiments were carried out in accordance to the regulations imposed by the University and appropriate Malaysia government body.

Focal articular cartilage defect was created in both knees of the 30 animals (n = 60 knees) as described in our previous study (1). All defects were created on the weight-bearing portion of medial femoral condyle. The remainder of cartilage within the defective areas were removed superficial to the subchondral bone. The extracted cartilage tissues from both knees were processed to harvest chondrocytes as previously described (2). MSCs were obtained and processed as described by Pelttari et al. (3). Chondrocyte and MSCs alginate beads were prepared in 1.2% low viscosity alginate (1).

After 4 weeks, the defects on the right knees were filled with alginate beads containing the autologous chondrocytes (ACI group) or MSCs (1 x 10^6 cells) (MSC group). Left knees were left untreated (control). All knees were evaluated and bisected after 24 weeks of in vivo implantation. Qualitative observations were made using gross assessments (Brittberg score) carried out by trained surgeons, while quantitative analyses were based on the sulfated glycosaminoglycans (GAG) assays. Half of each specimen was also fixed for histological (O’Driscoll scoring) and immunostaining analyses.

Statistical analysis was performed using SPSS statistical software (version 15.0). The mean values of Brittberg, GAG and O’Driscoll scores were calculated based from the samples obtained from the left and right knees. Parametric analyses were performed accordingly. Significance level was set at p value less than 0.05.

RESULTS:
Both the MSC (Figure 1a) and ACI (Figure 1b) treated groups displayed good filling of the defect areas, with the surface appearing flush and smooth. In the left knee, none of the untreated areas showed complete filling of the defects after 6 months (Figure 1c).

Figure 1: Articular cartilage of MSC treated (1a), ACI treated (1b) and control knee (1c).

Paired-sample T-test showed significant differences in the Brittberg and O’Driscoll scores as well as the GAG content between the treated and untreated knee of the same animals for both MSC and ACI groups (P value < 0.01) (Figure 2).

Figure 2: Mean and SD of MSC and ACI group separated into treatment and control knee.

In the left knee (control), no significant differences in the above-mentioned parameters were found between the MSC and ACI treated groups (P value > 0.05).

Inter-group analysis using Independent sample T-test revealed significantly higher Brittberg score in the MSC group as compared to the ACI group (Table 1).

<table>
<thead>
<tr>
<th>Experiment Treatment</th>
<th>MSC (n=12)</th>
<th>ACI (n=18)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Brittberg score</td>
<td>8.50 ± 1.537</td>
<td>6.61 ± 1.650</td>
<td>0.04</td>
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<tr>
<td>GAG content (µg GAGs/mg protein)</td>
<td>1.6719 ± 0.6386</td>
<td>1.7841 ± 1.0103</td>
<td>0.736</td>
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<tr>
<td>O’Driscoll score</td>
<td>11.17 ± 1.528</td>
<td>13.50 ± 4.768</td>
<td>0.66</td>
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</table>

Table 1. Evaluation of focal articular cartilage defect treatment after 6 months. Values are means ± 1 standard deviations. MSC = Mesenchymal stem cell treatment; ACI = Autologous chondrocyte implantation

DISCUSSION:
The results obtained from the biochemical and histological analyses in the present study appears to be in support of previous independent clinical studies indicating comparable outcomes between the MSCs and ACI treated knees for the repair of cartilage defects (4). The present study is superior to the clinical outcome-based study as it incorporated many other aspects which were previously lacking including objective measurements of the repair sites, comparison to non-treated damaged cartilage, and standardized subjects and defect size. The significantly higher Brittberg scores in the MSC repaired sites would suggest that further improvements in the GAG contents and histological appearance could be expected if a more prolonged duration of experiments was allowed. In conclusion, MSC appears to be a suitable alternative source of chondrocytes with comparable regenerative ability as ACI. Considering that the use of MSC will reduce the treatment to a single-stage procedure, provide better and faster cell yield and prevent donor site morbidity, this technique may potentially be the preferred therapeutic option in the near future.

REFERENCES: