

Cervical Interbody Fusion Is Enhanced by Allogeneic Mesenchymal Precursor Cells in an Ovine Model

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Study Design. An experimental study using a sheep cervical spine interbody fusion model.

Objective. To compare allogeneic mesenchymal precursor cells combined with hydroxyapatite and tricalcium phosphate (HA/TCP) with HA/TCP alone or iliac crest autograft (AG) for cervical interbody fusion.

Summary of Background Data. We investigated the effect of mesenchymal precursor cells on cervical fusion because of the shortcomings of using iliac crest (donor site morbidity), bone substitute (poor osteoinductive properties), and bone morphogenetic proteins (serious complications).

Methods. Thirty ewes were divided randomly into four groups of six having C3–C4 anterior cervical discectomy and fusion using a Fidji cage packed with, AG, HA/TCP, HA/TCP containing 5 million MPCs, and HA/TCP containing 10 million MPCs. MPCs were derived from a single batch of immuno-selected and culture-expanded MPCs isolated from bone marrow of out-bred sheep. The fifth group were nonoperated controls. Safety, fusion parameters, and biomechanics were assessed.

Results. No cell-related adverse events were observed. No significant differences were found between the five or 10 million MPC groups. Evaluation of fusion by CT scan at 3 months showed that 9 of 12 (75%) MPC-treated animals had continuous bony bridging compared with only 1 of 6 AG and 2 of 6 HA/TCP ($P = 0.019$ and $P = 0.044$, respectively). By quantitative CT, density of new bone in MPC-treated animals was 121% higher than in HA/TCP ($P = 0.017$) and 128% higher than in AG ($P < 0.0001$).

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Functional radiology at 3 months revealed that MPC-treated animals had significantly reduced macromotion at C3/4 compared with AG and HA/TCP groups combined ($P = 0.007$).

Conclusion. Implantation of allogeneic MPCs when combined with HA/TCP and an interbody spacer facilitates new bone formation after discectomy without any cell-related complications. The earlier and dense new bone formation observed with MPCs relative to autograft and HA/TCP alone suggest that this approach may offer therapeutic benefit.

Key words: cervical spine, stem cells, mesenchymal stem cells, interbody fusion, osteoinductive graft, animal model, sheep.

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Anterior cervical discectomy and fusion accounts for up to 40% of all spinal fusion procedures and is the most common surgical approach employed for treating cervical spondylosis or discopathies.^{1,2} Although iliac crest autograft bone has traditionally been the gold standard source material for cervical fusion, it is associated with the potential for donor site morbidity.³ Alternatives, such as bone graft substitutes^{4,5} and allograft, have limited osteoinductive properties and, whereas they eliminate donor site morbidity, they are considered to result in fusion rates inferior to autograft.^{6,7} Use of allograft has also been associated with resorption, infection, and collapse.^{7–9} Bone substitutes are osteoconductive as they provide a matrix into which local cells, including endogenous mesenchymal stem cells (MSC), blood borne cells, and osteoblasts can engraft and produce new bone. Levels and bioactivity of endogenous MSCs decline with age, an issue that can reduce bone fusion.¹⁰ Multilevel surgery, rheumatoid arthritis,¹¹ smoking^{12,13} the use of anti-inflammatory medications¹⁴ can all independently decrease fusion rates. Nonunion or pseudoarthrosis after anterior cervical discectomy generally results in recurrent radiculopathy and neck pain, which may require reoperation.¹⁵ Recombinant human bone morphogenetic proteins (rhBMPs) have been used as osteoinductive agents aimed at increasing cervical interbody fusion rates, but have been reported to result in life-threatening complications, including airway and neurological compression.¹⁶ Allogeneic mesenchymal precursor stem cells (MPCs) have recently been shown to increase bone fusion rates in clinical¹⁷ and preclinical indications.^{18,19} In the present study, we evaluated the capacity of allogeneic MPCs to promote fusion in the cervical interbody space in an ovine model.

MATERIALS AND METHODS

Study Design

Thirty-two-year-old, Boarder-Leicester/Merino ewes were divided randomly into five groups of six animals. Four groups were subjected to C3–C4 anterior cervical discectomy and prepared for fusion with a Fidji interbody cage (Abbott Spine, Austin, TX). The C3–C4 segment was used due to its similarities to the human cervical spine.²⁰ The interbody cage was packed with either (a) iliac crest autograft (AG) alone, (b) hydroxyapatite-tricalcium phosphate containing 15% hydroxyapatite and 85% tricalcium phosphate, (HA/TCP, Mastergraft Granules, MG, Medtronic, Minneapolis, MN) alone, (c) HA/TCP containing 5 million MPCs group, (d) HA/TCP containing 10 million MPCs group. The fifth group were aged match nonoperated controls.

Mesenchymal Precursor Cells

Allogeneic ovine MPCs (Mesoblast Limited, Melbourne, Australia) were isolated from bone marrow of out bred sheep using immunoselection with monoclonal antibodies²¹ to STRO-3+ and manufactured by Lonza Incorporated (Walkersville, MD) under good manufacturing practice (GMP) guidelines. The MPCs were derived from a single batch and culture-expanded to passage 4. The MPC surface marker characteristics have been previously reported.²²

The cells were frozen and maintained in the vapor phase of a liquid nitrogen tank until thawed and used within 30 minutes. Cellular viability was greater than 85% using trypan blue exclusion.

Interbody Cage and Carrier

The interbody cage (7.7 mm × 12 mm × 15 mm) was made from polyetheretherketone (PEEK). It was packed with iliac crest autograft cancellous bone in the AG control group (group A). The HA/TCP carrier was mixed with autologous blood and then packed into the cage in the HA/TCP alone group (group B). In the cell treated groups, the MPCs were added to the carrier, which was already mixed with autologous blood and packed into the cage (groups C and D). The MPCs then soaked into the granules avoiding spillage (Figure 1).

Surgical Technique and Postoperative Care

All procedures were carried out with institutional ethics approval (School of Biomedical Sciences, Monash University). Animals were fasted 12 to 24 hours before surgery and were allowed water ad libitum. Sheep were anaesthetized by intravenous injection of thiopentone 20 mg/kg and anaesthesia maintained by Isoflurane (1%–3%) inhalation and were positioned supine. Local anesthetic (0.5% bupivacaine with 1:200,000 adrenaline) was injected prior to a right anterolateral approach thorough a longitudinal neck incision. The longus coli muscle was elevated bilaterally with diathermy and the position of C3–C4 level was confirmed with fluoroscopy. Distraction was achieved with 16 mm Caspar pins followed by a total discectomy and removal of the cartilaginous end plates with a high-speed drill to reveal bleeding bone. The posterior longitudinal ligament was

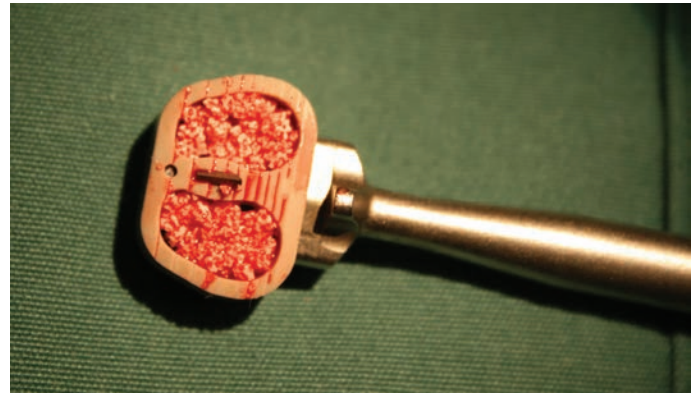


Figure 1. Fidji cervical PEEK interbody cage packed with mastergraft granules and mesenchymal precursor cells.

opened until the dura was visualized to directly simulate the clinical procedure and to investigate any effects of the MPCs around the neural elements. In sheep receiving autograft, the left iliac crest cortical bone was elevated and cancellous bone curetted and packed into the cage. All cages were inserted and countersunk by approximately 3 mm. The longus colli muscle was then approximated by suture, followed by layered closure and subcuticular suture to skin.²³

A fentanyl patch was administered postoperatively. After extubation, the sheep were transferred to a metabolic cage for observation. After 3 days, the sheep were transferred to open pastures, for the duration of the study where regular observations were made. The sheep were allowed to graze ad-libitum and supplemented with Lucerne chaff. Clinical pathology was performed on day 0, 1, and 3 months after surgery for standard hematological, comprehensive biochemical, and coagulation assays.

Radiographic Analysis

Fusion was assessed by plain and functional radiography, multislice thin cut (0.6 mm) CT and quantitative CT. Fusion was defined by continuous bridging of trabecular bone and the absence of radiolucent lines at 3 months on CT.^{24,25} Continuous bridging of trabecular bone was further subdivided into less than or more than 30% of the interbody cage area as assessed by three blinded observers using a semiquantitative score (Table 1 and Figure 2). All animals had plain lateral and selected anteroposterior digital radiographs (Radlink, Atomscope

TABLE 1. Scoring System for Computed Tomographic Evidence of Fusion

Grade	Description
Grade 0	No new bone formation
Grade 1	New bone formation but not continuous between C3 and C4 (cleft of discontinuity)
Grade 2	Continuous bridging new bone but comprises <30% of fusion area
Grade 3	Continuous bridging new bone formation of >30% of fusion area

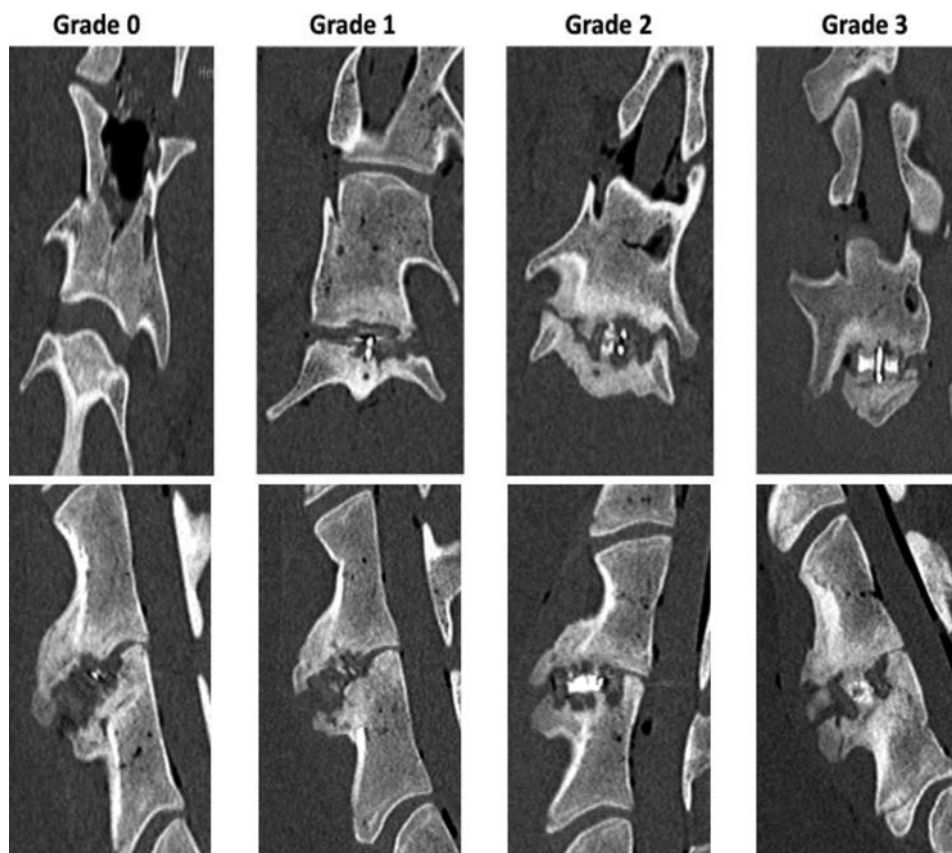


Figure 2. Computed tomography, in the coronal plane above and sagittal plane below, giving an example of each scoring grade see table 1.

HF 200A, Redondo Beach, CA) taken of the cervical spine preoperatively, within 24 hours after surgery and at 1, 2, and 3 months postoperatively. This was performed under sedation (using metomidine (0.025 mg/kg intravenously) and reversal using atipamezole (0.125 mg/kg intravenously).

Functional radiography was conducted by the method of Kandziora.²⁰ After sacrifice the superficial musculature of the explanted fresh spine was removed, carefully sparing all ligaments. T1 was rigidly fixated and a 60-Newton load was applied through C1. Lateral flexion and extension radiographs were taken and the intervertebral angle (IVA) and lordosis angle (LA) measured²⁰ (Figure 3) and calculated



Figure 3. Functional radiography demonstrating the measurement of the intervertebral and lordosis angles in flexion and extension.

as the difference between flexion and extension by three blinded assessments.

Multiplanar images were acquired with 0.6 mm collimation on a 64-slice-scanner (Siemens Sensation-64, Malvern, PA) and reconstructed in the sagittal, axial, and coronal planes. Fusion was assessed for evidence of bridging of trabecular bone as described earlier. Quantitative CT was performed on the basis of the methods of Kandziora^{26,27} and Burkuss.²⁴ Specifically, the coronal slice 3.6 mm (6 slices) anterior to the cage's posterior radiolucent marker was identified to ensure that an identical location was analyzed for each sample. A standardized elliptical region of interest (ROI), with an area of 183 mm², was selected at this point (Figure 4). The ROI was used to measure the bone mineral density (BMD) of the callus formation in hounsfield units. To account for the BMD contribution from the HA/TCP or autograft implanted within the cage, these BMD values were ascertained from control animals and subtracted from the mean BMD to give the BMD of the callus formation alone, referred to as bone callus density (BCD). The control animals were implanted with either autograft alone or HA/TCP alone and sacrificed at 1 week to allow time for artefacts such as intraoperative air to be reabsorbed but at a time-point before fusion would occur, thus establishing the background density of the autograft and HA/TCP alone, respectively.

Biomechanical Analysis

Biomechanical testing was performed in a similar manner to the nonconstrained method described by Gal.²⁸ As we have



Figure 4. Quantitative computed tomography in the coronal plane, showing the region of interest (ROI) measuring bone mineral density.

previously described,²⁹ pure bending moments were applied to the cervical spine using a custom made rig. Four degrees of movement, namely flexion, extension and left and right lateral bending, were tested at incremental forces of 0.75 Nm to a maximum of 12 Nm after a 15 Nm preload.

Colored markers, placed into the corpora of C1 to C7 inclusively, were detected with biplanar digital photography. A computerized motion analysis system (Track Eye Motion Analysis 3.0 [TEMA], Qualysis Inc, Provo, UT) was used to track and measure marker positions across the total range of motion. Load-displacement curves were generated to determine stiffness of the C3–C4 segments for each degree of movement. Total displacement of the C3–C4 joint was calculated from these curves.

Postmortem Analysis

Clinical veterinarians performed comprehensive autopsies in a blinded fashion. Samples from all organs and tissues from the perisurgical site were reviewed by a blinded, board certified veterinary pathologist.

Histomorphological, Histomorphometric, and Fluorochrome Analysis

Fluorochromes, calcein green 10 mg/kg, oxytetracycline 50 mg/kg, and alizarin complexone 30 mg/kg, were administered intravenously at 3, 6, and 9 weeks, respectively. Undecalcified bone histology was performed as previously described.³⁰ After sacrifice, the C3–C4 segment was excised and fixed in 10% normal buffered formalin, followed by dehydration in ascending concentrations of ethanol under agitation. The blocks were cleared in butanol prior to embedding in glycol-methacrylate (Technovit 7100, Kulzer, Wehrheim, Germany) using a slow embedding and hardening protocol.

For fluorochrome analysis, the mid sagittal section, was ground to approximately 40 μ m thickness, using a diamond blade Macrotome (MR Limited, Cambridge, United Kingdom). For light microscopy, the 10 μ m sections were cut with a sledge microtome (Leitz, Wetzlar, Germany). Histological sections were stained with Haematoxylin and Eosin, Safranin-O/lightgreen, Von Kossa, Alcian Blue, and Masson-Goldner the later being used for histomorphometric analysis (Figure 5). Masson Goldner's Trichrome staining was found to be superior to Von Kossa for this application as it allowed differentiation of new bone from the ceramic which is also stained by the Von Kossa dyes.

Slides were scanned with the Olympus dot slide System (with BX51 Microscope), at 2 \times magnification for each fluorescent label, using U-MNIBA3, U-WIG3, U-MWU2 filters,

A 10 micron cut section stained with Masson Goldner's Trichrome at 10 \times magnification, showing examples of the different stages of bone formation around remnants of tricalcium phosphate/hydroxyapatite granules within the cage

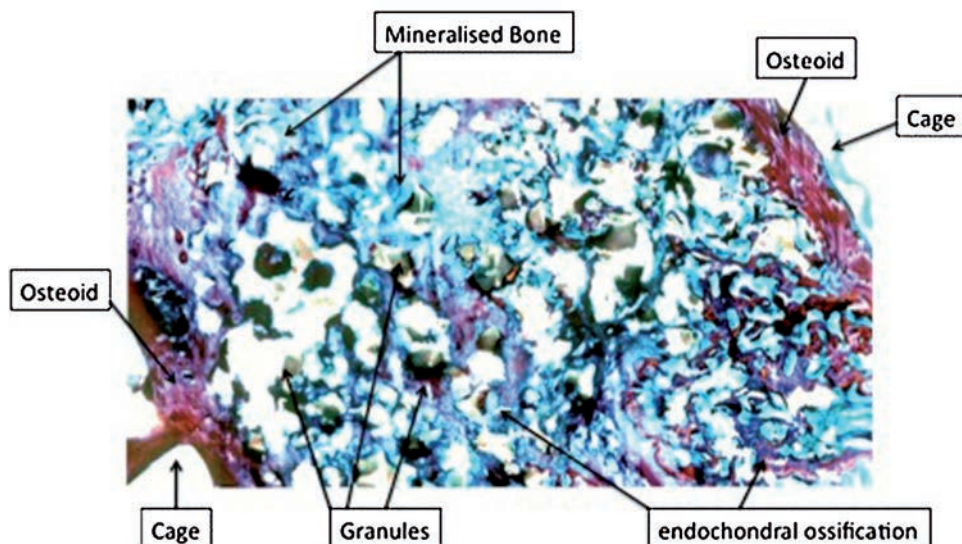


Figure 5. Example of undecalcified histological section stained with Masson Goldner's Trichrome.

and a Peltier-cooled high sensitivity camera, at consistent exposure. The images were then uploaded into the Metamorph quantitative analysis software program (version 7.6, Molecular Devices, MDS Inc, CA) and the area within the cage marked out on the program. The intensity of each fluorescent label within the cage was measured and expressed as intensity per unit area (μ^2). This gave a quantitative assessment of the amount of bone deposition at each time point.

A certified veterinary pathologist performed a semiquantitative analysis of the histological sections in a blinded fashion. A score, using the criteria of Zdeblick³¹ to assess fusion was assigned separately to the Cage—Vertebral Interface (CVI) and the tissue inside the cage (CI) using the system empty (score 0), fibrous tissue (score 1) and bone (score 2). Four points indicate a successful fusion and three points represents a developing fusion.

Histomorphometric analysis was performed using quantitative image analysis for percentage of osteoid formation relative to mineralized bone within the cage area. This was conducted on the midsagittal slice stained with Masson-Goldner in a blinded fashion. Consistent inclusive threshold mapping was then used to measure the threshold percentage within the total cage area containing red staining regions representing osteoid volume (OV), and green staining regions representing mineralized bone volume (MdV), respectively.³²

Statistical Analysis

Comparison of nonparametric data was evaluated by the Kruskal Wallis test on the median values followed by Dunn's Multiple Comparison test, where significant differences were observed. Parametric data were analyzed using one-way Anova followed by Dunnett's Multiple Comparison test where significant differences were observed. The two-tailed Student *t* test was used for comparison of parametric data and the Fisher exact test was used for contingency data when comparing cell treated animals with controls. Prism 5.0 (Graph Pad Software) was used for analysis. Interobserver reliability was assessed using the Kappa score calculated by a custom made algorithm in Excel (2008, Microsoft Corporation, CA) based on the method of Landis and Koch.³³ Values were expressed as means and range unless otherwise stated. Graphs show means with standard deviation. A *P* of < 0.05 was considered statistically significant.

RESULTS

Adverse Events

No procedural or cell related adverse events were observed during the study or at postmortem. One ewe developed pneumonia and hypoproteinaemia that resolved under close veterinary treatment. Two ewes, both from the autograft group, lost significant weight during the study period. Veterinary assessment, clinical pathology, grosspathological and histopathological analysis showed no differences between groups.

All outcomes for low and high dose MPC treated ewes (Groups C & D) were not significantly different and were subsequently treated as a single group.

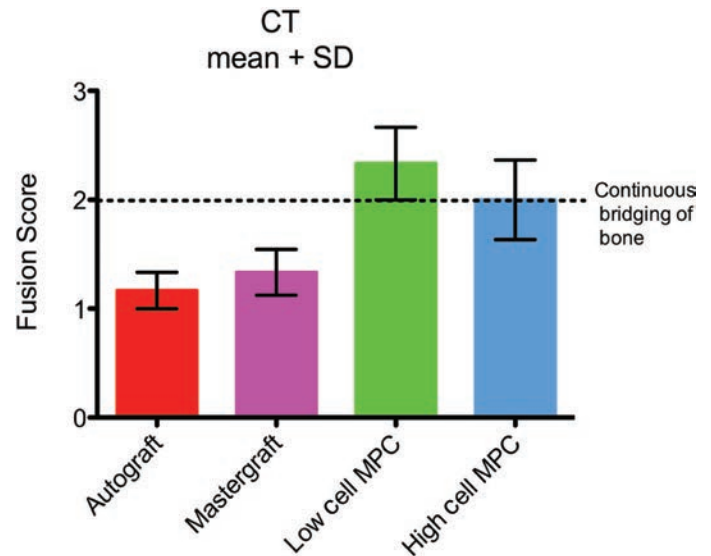


Figure 6. Graph of computed tomography results of 3 months.

Radiographic Results

The three blinded observers, overall, had interobserver reliability with Kappa scores ranging from 0.59 to 0.87 being moderate to almost perfect according to the classification of Landis and Koch.³³ A consistent observation by all observers was that a score of three was never awarded to a noncell treated animal. By CT scan at 3 months, 9 of 12 (75%) MPC-treated animals had continuous bony bridging compared with only 1 of 6 AG and 2 of 6 HA/TCP (*P* = 0.019 and *P* = 0.043, respectively) (Figure 6). This was confirmed by objective quantitative CT revealing that cell-treated animals had significantly higher BCD compared with HA/TCP (*P* < 0.017) and Autograft (*P* < 0.0001) (Figure 7, Table 2).

Functional radiography scores obtained for intervertebral angle (IVA) had an interobserver discrepancy of less than 1 degree, whereas the scores obtained for lordosis angle (IVA) had an interobserver discrepancy of 2.8°. There was a reduction in the intervertebral angle in all operated groups compared with

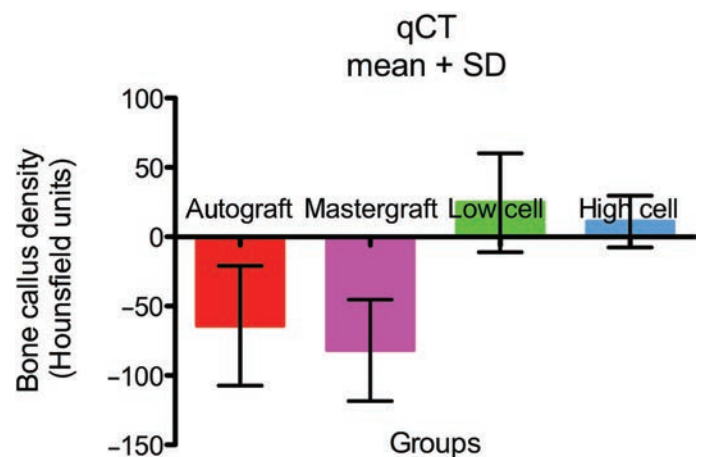


Figure 7. Graph of quantitative computed tomography results of 3 months.

TABLE 2. Quantitative CT Results Mean Hounsfield Units (Range)

Group	Autograft	Mastergraft	Low cell	High cell
Bone mineral density (BMD)	591.8 (459–704)	758.2 (621–882)	864.5 (801–1032)	851.0 (784–917)
Control BMD	656	840	840	840
Bone Callus Density	−64.17 (−197 to 47)	−81.83 (−219 to 42)	24.50 (−39 to 192)	11.00 (−56 to 77)

nonoperated controls ($P < 0.0001$). Cell-treated animals had a significant reduction in IVA compared with HA/TCP ($P < 0.001$) and Autograft ($P < 0.012$) treated animals (Figure 8 and Table 3). Lordosis angle was not significantly reduced in operated animals compared with nonoperated controls. Cell-treated animals, however, had a significantly reduced LA compared with Autograft ($P < 0.05$) but not compared with HA/TCP ($P < 0.08$).

There was no radiological evidence of ectopic bone formation posteriorly around the spinal canal or at the neural exit foramina in any animals. In controls that received HA/TCP alone, bone callus formation was noted at the anterior of the interbody space at a mean maximal distance of 6.67 mm anterior to the cage. Similar reactive bone formation was seen in all of the cell-treated groups at a mean maximal distance of 5.94 mm anterior to the cage (Table 4). There was no significant difference in the maximal distance of new bone formation anterior to the cage between any of the groups. There was no evidence of calcification within the muscles or ligaments anterior to the spine.

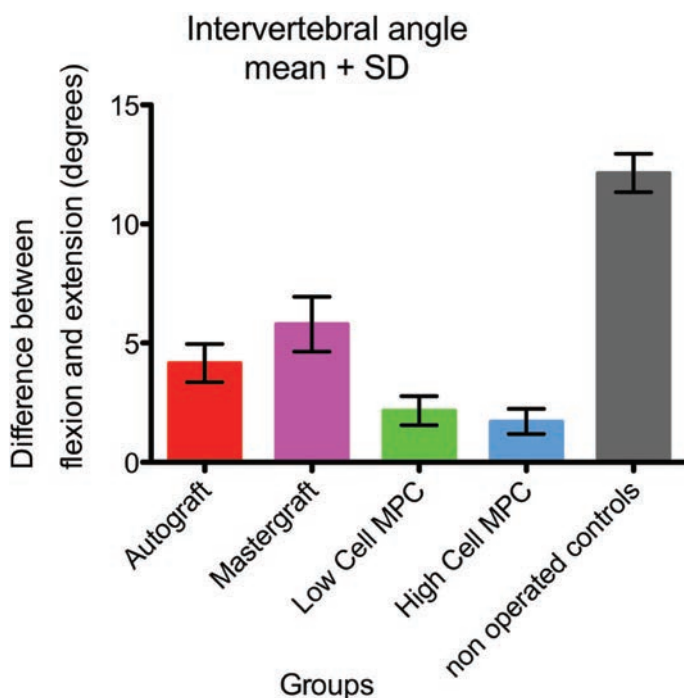


Figure 8. Difference between flexion and extension of intervertebral angle (degrees).

Biomechanical Result

Significantly more stiffness at the C3–C4 level was observed in operated groups compared with nonoperated controls in flexion ($P < 0.015$), however, this did not achieve significance in extension or in lateral bending. No significant difference between operated groups was observed in any of the four degrees of motion.

Histological Results

There was no evidence of inflammatory or neoplastic changes in any specimen within the fusion area as reviewed by the veterinary pathologist. The semiquantitative histological scoring system revealed that 11 of 12 (92%) cell-treated animals had either developing or complete fusion as compared to three of 6 (50%) treated with HA/TCP alone ($P = 0.02$) and one of six (17%) autograft animals ($P = 0.0007$). Significantly, however, the percentage of cell-treated animals with complete fusion was 5 of 12 (42%) compared with zero of six in either control group ($P = 0.03$). (Table 5) This finding was supported by the histomorphometric analysis, which demonstrated significantly more mineralized bone in the cell-treated groups *versus* HA/TCP ($P < 0.008$) and autograft ($P < 0.0001$) (Figure 9).

At 3 weeks postoperatively, the fluorochrome showed more prominent deposition of mineralized bone in cell-treated

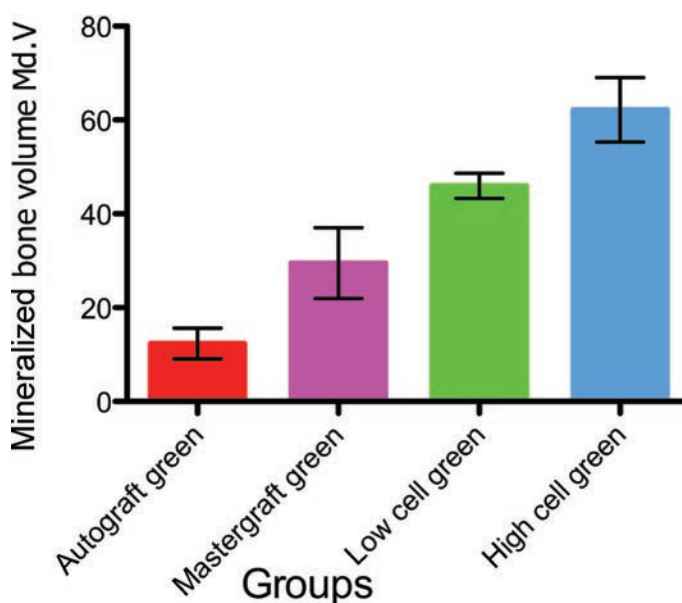


Figure 9. Graph of histomorphometric results of mineralized bone volume within the cage on mid sagittal section stained with Mason Goldner's Trichrome.

TABLE 3. Functional Radiography at 3-Month Difference Between Flexion and Extension in Degrees Mean (Range)

Group	Autograft	Mastergraft	Low cell	High cell	Nonoperated control
IVA	4.16 (2.71–8.09)	5.79 (2.84–10.6)	2.17 (0.54–4.92)	1.71 (0.56–3.99)	12.14 (10.10–15.17)
LA	6.83 (2.45–11.99)	5.78 (2.01–8.48)	4.23 (2.04–5.50)	4.15 (2.58–5.38)	7.248 (4.42–9.25)

IVA indicates intervertebral angle; LA, lordosis angle.

TABLE 4. Mean of Maximal Bone Distance Anterior to the Cage Millimetres (Range)

Group	Autograft	Mastergraft	Low cell	High cell
Bone anterior to the cage	6.11 (4.79–6.7)	6.67 (3.94–8.70)	4.90 (2.53–8.16)	5.94 (2.74–8.76)

groups compared with autograft ($P < 0.004$) and HA/TCP ($P < 0.03$). Although there were no significant differences between the groups at 6 weeks, by 9 weeks significant differences were observed for the cell-treated groups *versus* autograft ($P < 0.02$) and a trend observed *versus* HA/TCP ($P < 0.06$).

DISCUSSION

These results show that anterior cervical implantation of allogeneic MPCs together with HA/TCP and an interbody spacer safely and effectively facilitate new bone formation after discectomy. Significantly, these MPC-mediated osteogenic activities were not accompanied by cell-related adverse events.

The bone formation seen anterior to the cage was similar to that shown in previous preclinical studies.^{26,31,34} It has been suggested that the countersinking of the cages results in exposed reamed bone lacking cartilaginous endplates, which acts as a source for new bone formation.³¹ In the current study, the cages were countersunk by approximately 3 mm and the thick periosteum in sheep, along with significant neck mobility, may act as a potent osteogenic stimulus. As this occurred equally in both control and cell-treated animals, we postulate that this is a phenomenon related to the animal model or procedure and was not specifically related to the use of MPCs.

The multiple modalities of assessment used in this study showed that MPCs resulted in increased fusion compared to controls representing the current standard of care. It has been said that the ideal graft should be osteogenic, osteoconductive, and osteoinductive, as well as mechanically stable and disease free.^{10,35} Autograft can fulfil these criteria but has the potential for donor site morbidity, as well as prolonged operation time and increased blood loss.^{3,35} Allograft has the

potential for collapse and, like autograft, can undergo resorption^{7,9} which does not occur with carriers such as tricalcium phosphate and hydroxyapatite.³⁶ Currently, it is unclear from the literature if these osteoconductive carriers result in fusions rates equivalent to autograft.^{37–39} Recombinant bone morphogenetic proteins have been used as an additive osteoinductive agent to promote fusion.^{40,41} There are, however, reports of adverse effects of their use in the cervical spine.^{7,16,41,42} Biologically, there is an interplay between the 14 naturally occurring BMPs involved in osteogenesis⁴³ and MPCs secrete many of these growth factors (Zannettino oral communication). This paracrine effect of MPCs, in addition to a direct effect of osteogenic differentiation at the fusion site, could account for the beneficial effects mediated by the MPCs in the current study.⁴⁴ In combination with the HA/TCP, MPCs are likely osteogenic, osteoconductive, and osteoinductive.

Mesenchymal stem cells have been defined by the International Society of Cellular Therapy by their characteristic plastic adherence, fibroblastic morphology, and by cell marker expression of CD105, CD73, CD90 and lack of lacking expression of CD45, CD34, CD14, CD11b, CD79a, CD19, and HLA-DR.⁴⁵ It should be emphasized that the term MSCs refers to a heterogeneous population of cells with variable characteristics.^{46–48} The issue of heterogeneity, in cell characterization and differentiation, becomes significant if these cells are to be used clinically.⁴⁹

The stromal stem cells used in this study have been designated as mesenchymal precursor cells (MPCs), which are a purified monoclonal population of cells derived by immunoselection.⁵⁰ These MPC have a greater potential for differentiation into the tissues of the mesenchymal lineage and are

TABLE 5. Histopathology Results, no with Developing or Complete Fusion Based on Zdeblick⁵³ Scoring System

Group	Autograft (n = 6)	Mastergraft (n = 6)	Low cell (n = 6)	High cell (n = 6)
Developing fusion	1	3	3	3
Complete fusion	0	0	2	3

more potent with respect to ability for self-renewal.⁵¹ The homogeneity and low immunogenicity of the MPCs make them an attractive prospect for clinical use in spinal surgery. They exhibit low levels of cell surface markers such as the MHC class and lack surface expression of immune costimulatory molecules.⁵² MPCs also lack the ability to induce an allogeneic mixed lymphocyte reaction (MLR)^{53,54} and secrete multiple anti-inflammatory and immunosuppressive cytokines, for example, IL-10.⁵³ These anti-inflammatory properties possibly have a beneficial effect on radiculopathy or myelopathy, which are the common underlying problems necessitating cervical fusion. The potential beneficial properties of MPCs reported in this animal study require evaluation in a human clinical setting.

CONCLUSION

The more robust bone formation observed with MPCs, relative to autograft and HA/TCP bone substitute in this study suggest that this biological approach may offer a therapeutic benefit when rapid fusion of the cervical interbody space is indicated. This would obviate the donor site morbidity associated with autograft harvest and the potential life-threatening complications associated with the use of bone morphogenetic proteins. The potential mechanisms by which MPC mediated spinal fusion could include promotion of osteoblast differentiation and their secretion of trophic factors, such as multiple BMPs and other growth factors, which are known to upregulate osteogenesis.

➤ Key Points

- ❑ MPCs are a pure population of stem cells derived by monoclonal antibody immunoselection.
- ❑ Together with a tricalcium phosphate and hydroxyapatite carrier MPCs enhance cervical fusion.
- ❑ MPCs may have a therapeutic role for certain patients requiring cervical interbody fusion.

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This preclinical study demonstrates that anterior cervical implantation of allogeneic mesenchymal precursor cells when combined with hydroxyapatite and tricalcium phosphate (HA/TCP) in an interbody spacer, safely and effectively facilitate new bone formation after discectomy in an ovine model relative to autograft or HA/TCP alone. This approach may offer a clinical benefit in selected patients.

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