REVIEW ARTICLE

Stem cells in degenerative lumbar spine disease: a review and focus on utility in Low- and Middle-Income Countries

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Abstract

Stem cell therapy is a common adjunct in regenerative medicine and has recently seen greater adoption in spinal surgery. Arthrodesis is typically achieved with iliac-crest bone grafts with several adverse events, leading to the development of alternative biomaterials. One such biomaterial is stem cells, which may be equal in terms of effectiveness but with significantly fewer complications. Low- and Middle-Income Countries (LMICs) have seen slow adoption of stem cell therapy due to resource constraints but may benefit the most from these techniques. We conducted a comprehensive review of literature in the PUBMED, Scopus, and Cochrane Library databases on the use of stem cells and stem cell-based biomaterials in spinal surgery. Our review showed promising results, from a variety of methods including augmentation of existing scaffold with mesenchymal stem cells or concentrated bone marrow aspirate. With minimal complications, stem cell augmentation can be a good alternative to existing biomaterial use for spinal fusion and repair.

Keywords: Spinal Fusion, Mesenchymal, Stem Cell, Transplantation.

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Introduction

Spinal surgery, particularly from a reconstructive standpoint, is a complex field that heavily relies on prosthetics, biomaterials, and mechanical stability to promote arthrodesis and achieve maximal postoperative functionality. Until recently, stem cells have been primarily underutilized due to poor biochemical and physical control. As technological and genetic engineering techniques evolve, these stem cells have become a fixture of regenerative medicine[1]. Stem cells harvested from blood, bone marrow, or adipose tissue retain the ability to undergo mitosis and multipotent differentiation into cell lineages of all three germ layers. While artificial alternatives are limited in their ability to replace and regenerate tissue, stem cells have the potential to replace diseased or disrupted tissue without eliciting foreign body reactions and subsequent graft failure. Treatment for disorders such as degenerative spinal disc disease and spinal cord injury has had promising results through the implantation of stem cells and subsequent regeneration of the spinal disc or injured nerve[2]. These advances have become possible due to advances in material and genetic engineering through a three-dimensional scaffold to retain cells and facilitate growth factors in tissue reconstruction[3].

The gold standard to induce arthrodesis is iliac crest bone grafting (ICBG) due to its osteogenic, osteoinductive, and osteoconductive properties[4]. However, donor site pain, numbness, and impaired ambulation have been common complaints post-iliac crest bone grafting[5,6]. It has also been linked to longer in-hospital stay, extended operating time, and higher blood transfusion rates after surgery[7]. Synthetic materials cannot overcome factors contributing to bone- factors such as age, autoimmune conditions, organ function impairment, systemic illness (such as diabetes mellitus and hypertension), and malignancy[8,9]. Other osteobiologics include allografts, which are being augmented with stem cells, such as in cellular bone matrices, to overcome these factors.

Literature has shown that comorbidities and other systemic factors do not adversely affect outcomes with stem cell product lines which makes them favourable compared to synthetic materials[10]. Thus, stem cell therapies such as bone marrow aspirate (BMA) composed of mesenchymal stem cells (MSC) are increasingly shown to be at least equally, if not more, effective as other operative adjuncts for fusion success rates[10]. The main disadvantage of BMA is the impact comorbidities and age have on MSC numbers and differentiation potential[11]. Improper fusion after spinal surgery is a major contributing factor to patient morbidity and decreased quality of life. Stem cell therapy can reduce healing time and improve outcomes post-surgery particularly for fusion, with equivalent or in certain cases, better uptake than standard materials[3].

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Low and middle-income (LMIC) countries have typically seen slow adoption of stem cell treatments due to the high cost of procurement, storage, and modification. Some strides in haematological malignancy and neuroblastoma treatment have been made recently to offer lower-cost high-yield stem cell-based treatments in low resource settings, but a disparity in outcomes still remains between high income countries (HICs) and LMICs[12,13]. Spine surgery has not yet seen a ready adoption of stem cells as a biomaterial for arthrodesis. In this review we aim to synthesize and critically appraise evidence in clinical trials of stem cell use in spine surgery. We also seek to explore the possible barriers in the utilization of stem cells as osteo-biological materials in LMICs and avenues to improve outcomes where it is used.

Methods

We conducted a review of the available literature on clinical trials in stem cell therapy for the spine. A bibliographic search was conducted through three major electronic databases with no restriction on the age of the study on the 15th of August 2022. The MEDLINE (PUBMED), the Cochrane Library, and Scopus were the databases used with Medical Subject Headings (MeSH) terms (((spine surgery) OR (spinal surgery) OR (spine instrumentation)) AND ((stem cells) OR (mesenchymal cells) OR (pluripotent stem cells) OR (IPSCs))). Most studies in the search originated from high income countries (HICs) but studies from low and middle-income countries (LMICs) were emphasized where possible. Abstract, title, and full text review were concluded on August 28th 2022.

Discussion/Review of Evidence

A series of clinical trials and comparative studies are available in the current literature regarding stem cell use for a variety of spinal diseases (Table 1). The most common pathologies that undergo surgery with stem cell adjuncts are degenerative disc disease, thoracolumbar fracture, and spondylosis. Additionally, a spectrum of surgical techniques is reported, from transpedicular instrumentation to un-instrumented fusion. Instrumentation in PLF has generally been shown to produce stability in the short-term although no impact has been demonstrated in long term outcomes[14].

Demographics and Patient-related factors

There is no reported difference between outcomes based on most demographic factors. Ajiboye et al.[15] demonstrated in two separate studies that gender was not a significant factor in fusion rates or complication rates between stem cell groups and ilac bone crest graft or other osteobiologic groups, a finding corroborated by other studies in this review[15–17]. Gan et al. also found no differences in nucleated cells between males and females; the prevalence of mesenchymal stem cells and subsequent outcomes of intervention were also similar between the two groups[18].

Age had been a concern in the use of multipotent progenitor stem cells as it affects the viability of the cell culture[19]. While several studies saw no difference in efficacy of stem cell therapy with age[15,17], they were usually within a specific narrower age range. Ajiboye et al. in their 2018 study, investigated the effect of age on the efficacy of demineralized bone matrix (DBM) with concentrated bone marrow aspirate (BMA) in lumbar fusions. They reported that in their cohort of 51 patients, nonsolid union odds in patients aged 65 and older who underwent Posterior Lumbar Fusion (PLF) were significantly higher than those below 65 years of age (OR=16.3, p=0.03)[16].

The typical factors affecting arthrodesis with use of synthetic biomaterials can be circumvented with augmentation with stem cells, particularly bone marrow aspirate and mesenchymal stem cells. In both their 2015 and 2018 studies Ajiboye et al. demonstrated that gender, Charlson comorbidity index (CCI)[20], smoking, osteoporosis, multilevel fusion, and length of follow-up were not significant in their cohort[15,16,21]. Other studies have also reported no effect of pre-existing conditions such as diabetes, osteoporosis, or use of steroids on outcomes for spinal repair with stem cells[22]. This is particularly important in the context of increasing comorbidities, especially in developing countries which are shifting from higher infectious disease prevalence towards non-infectious disease prevalence. Stem cells can be a viable alternative to traditional spinal fusion methods due to their tendency to adapt better to the organic chemistry regardless of other systemic disease processes[2,6].

Posterior Lumbar Fusion

Stem cells in the form of mesenchymal stem cells and bone marrow aspirate have generally demonstrated positive outcomes. Hart et al. investigated the efficacy of allograft alone versus allograft with bone marrow concentrate. Of the 80 patients enrolled in the study, 40 had simple PLF with allograft and 40 had PLF with allograft augmented with MSCs. Patients in the MSC groups achieved higher rates of fusion at both 12 (p=0.041) and 24 months (p=0.011) in comparison to the control group[23]. Similarly, Ajiboye et al. reported favourable results in their cohort of 31 patients in which concentrated bone marrow aspirate (BMA) with allograft

Table-1: Results of scoping review of studies on stem cell therapy in degenerative lumbar spine disease.

Year	Author	Country	Sample Size	Study design	Summary
2008	Gan et al.[18]	China	41	Prospective cohort	"The enrichment of autologous marrow MSCs combined with porous b-TCP peri-operatively is as effective as autologous bone for the purposes of grafting for instrumented posterior spinal fusion surgery."
2008	Vaccaro et al. [26]	USA	36	Prospective cohort	"The efficacy and safety profile of OP-1 Putty appear to be comparable to that of the autograft controls, suggesting that this material may potentially represent a viable bone graft substitute for fusion applications that avoids the significant morbidity associated with the harvesting of autogenous bone."
2011	Kerr et al.[28]	USA	52	Retrospective cohort	"The use of Osteocel allograft is safe and effective in adult patients undergoing lumbar interbody spinal fusion procedure. Increased age and habitual smoking delays fusion but gender, previous surgery at the index level, type of procedure and number of levels do not affect the fusion rates."
2012	Tohmeh et al[30]	USA	40	Prospective cohort	Extreme Lateral Interbody Fusion using Osteocel Plus, an allograft cellular bone matrix, has excellent radiographic and clinical results and provide a viable alternative to conventional biomaterials.
2013	Ammerman et al.[21]	USA	23	Retrospective cohort	"OsteoCell Plus results in robust and reproducible interbody fusion, comparable to other available fusion substrate options, with a favorable complication profile. This effect was observed in the majority of patients seemingly independent of age, sex or potential risk factors for nonunion."
2014	Hart et al.[22]	Czech Republic	80	Case Control study	"The use of autologous MSCs in form of BMC in combination with allograft is an effective option to enhance the PLF healing."
2015	Mochida et al.[31]	Japan	9	Prospective cohort	"There seems to be minimal efficacy of activated nucleus pulposus treatment to slow the further degeneration of human intervertebral discs."
2015	Ajiboye et al.[15]	USA	31	Prospective cohort	"Autologous concentrated BMA mixed with allograft and DBM in posterolateral and interbody fusions can achieve successful fusion rates with good clinical outcomes and low complication rates."
2016	Chotivichit et al.[23]	Thailand	12	Randomized Control Trial	"Bone marrow concentrate augmentation in this small randomized controlled trial failed to demonstrate positive effects on autologous local bone graft in posterolateral lumbar fusion relative to both quality and quantity. "
2017	Yousef et al.[25]	USA	21	Retrospective cohort	"The use of bone marrow mesenchymal stem cell concentrate obtained with selective cell retention technology could be considered as an effective means for augmenting spinal fusion."
2017	Fomekong et al.[29]	Belgium	3	Control Trial	"A scaffold-free 3D graft made of AMSCs can be manufactured and used as a promising alternative for spinal fusion procedures."
2017	Lee at al.[27]	USA	41	Retrospective cohort	"Map3 allograft demonstrates equivalent fusion rates to rhBMP-2 as well as a favorable surgical cost profile. It is therefore a better alternative than rhBMP-2 for spinal fusion."
2018	Ajiboye et al.[16]	USA	51	Retrospective cohort	"DBM enriched with BMA may be an ineffective graft option in elderly patients (>65 years) and needs further study."
2019	Blanco et al.[24]	Spain	11	Randomized Control Trial	"The use of autologous MSCs for spine fusion in patients with monosegmental degenerative disc disease is feasible, safe, and potentially effective."
2020	Frutos et al.[17]	Spain	72	Randomized Control Trial	"The use of expanded bone marrow MSCs combined with cancellous allograft is a feasible and effective technique for spinal fusion, with no product-related adverse events found in the study."
2021	Xu et al.[20]	China	45	Prospective cohort	"It is feasible and effective to repair lumbar IVD defects using SCR-enriched BMSCs with gelatin sponges, which warrants further study and development as a cell-based therapy for IVD repair."

and demineralized bone matrix (DBM) was used for posterolateral and interbody fusion[15]. They reported a solid fusion rate of 83.9%. specifically, the rate of posterior lateral fusion was 83.9% while the rate of interbody fusion was 96.8%. In their study Ajiboye et al. achieved excellent or good results in 83.9 % of patients in accordance with the modified Odom's criteria[15]. In a follow up study, they similarly achieved excellent or good results in 10 of 14 (71.4%) patients in group >65 who had BMA with DBM, 13 of 17 (76.5%) patients <65 who had BMA with DBM, and 15 of 20 (75%) of patients >65 who had ICBG (P = 1)[16]. The mean follow-up time differed with each group from a range of 86 months to 113 months. Overall, their results seemed promising although they did not have a control group to directly compare to. In contrast, Chotivichit et al. conducted a randomized control trial with 12 patients comparing posterolateral lumbar fusion with and without bone marrow concentrate augmentation[24]. Patient-reported outcomes did not differ significantly between the control and the intervention group, using the Oswestry low back pain disability questionnaire (ODI). While all patients in the non-BM group achieved complete bridging bone fusion at six months, 50% of patients with bone marrow did not achieve complete bridging bone fusion. There was only one complication in which a patient from the bone marrow group had inflammation at the aspiration site but no fever and was subsequently treated with antibiotics. In their experience, bone marrow concentrate augmentation failed to demonstrate positive effects on autologous local bone graft in poster lateral lumbar fusion. However, the low sample size, and the lack of measurement of cell quantity and viability may have been a significant factor in the results of this study.

Gan et al. did a study on 41 patients who was scheduled for posterior spinal fusion with transpedicular spinal instrumentation and enriched mesenchymal stem cell (MSC) implantation[18]. Their aim was to investigate the clinical utility of enriched bone marrow stem cells combined with porous beta tricalcium phosphate in posterior spinal fusion. The number of nucleated cells were similar between patients with degenerative disc disease and thoracolumbar fractures (TLF), but MSCs were significantly higher in TLF patients. They also found that the MSC volume was significantly more in younger patients less than 40 years old. None of the patients experienced any pain on follow up and none needed reoperation. The authors found that there was a positive correlation not only between NCs' recovery rate (yn) and the volume recovered (r 1⁄4 0.6712, P 1⁄4 0.0001), but also between MSCs' (CFUs- ALPþ) recovery rate (yc) and the volume recovered (r1⁄40.3557, P 1⁄4 0.0225). The enrichment of autologous marrow MSCs combined with porous b-TCP peri-operatively was as effective as autologous bone for the purposes of grafting for instrumented posterior spinal fusion surgery. Blanco et al. also looked at the clinical efficacy of the implantation of autologous MSCs embedded with tricalcium phosphate as an alternative to bone graft in patients with degenerative disc disease[25]. Eleven patients, with a mean age of 44 years, underwent surgery, and radiological solid fusion was obtained in nine out of 11 cases. No adverse effects were observed, and ODI and VAS scores increased in the literature's most extended follow-up (5 years). Thus, the potential complications associated with the harvesting of bone grafts from the iliac crest can be avoided through stem cell therapy. Frutos et al. also conducted a prospective clinical trial to study the feasibility of using bone marrow MSCs loaded onto allograft bone for spinal fusion in degenerative disc disease[17]. From their cohort of 62 patients (with 31 patients in the control and intervention group respectively) they determined that MSC augmentation achieved a higher rate of spinal fusion and early response to treatment. The Mental Component Summary score which is indicative of quality of life was also significantly higher at 3 months (p=0.009). No adverse events were linked to the intervention. There were no significant differences in ODI score.

Some studies have used commercial products (such as the BMA extraction device from Cellect or the Osteocel Plus device) to investigate the efficacy of stem cell therapy with PLF. Yousef et al. conducted a retrospective review of 40 patients who underwent PLF with BMA concentrate[26]. They found that all patients achieved successful solid bilateral fusion but unilateral fusion with bridging bone (Grade II) was detected in one patient. Interestingly, interbody fusion was detected in another three patients without usage of cage, at L4-L5 level in one patient, and at L5-S1 level in another patient. They also saw more complications than most of the other studies. Degenerative lumbar scoliosis was detected in two patients, and residual right dorsolumbar scoliosis was observed in one patient. Also, loss of lumbar lordosis was observed in one patient with a burst fracture of L4. Mechanical displacement of the vertebral body above/below the fused segment in the form of listhesis had been observed in four patients including retrolisthesis in three patients and anterolisthesis in one patient. Adjacent segment degeneration was detected in 11 patients, but it was not statistically associated with VAS score or ODI score. Strong association was detected between the development of listhesis and VAS score using binary logistic regression with odds ratio of 4.4.

Also, a weak association was detected between the development of lithesis and Oswestry Disability Index (ODI) score using binary logistic regression with odds ratio of 1.47. However, there was no use of a scaffold, HEALOS strips were soaked with bone marrow aspirate and heparin and implanted. The use of a scaffold is an important feature as it allows the stem cells to stay contained in the area of damage and regenerate tissue.

Ammerman et al. also investigated the role of Osteocel Plus in minimally invasive transforaminal lumbar interbody fusion[22]. They found that of the 23 patients, 91% had achieved radiographic evidence of solid bony arthrodesis at 24 of 26 levels by 12 months post-op. Six of the patients exhibited evidence of interbody bone growth within 6 months of surgery as well. No adverse events were reported in their study.

Recombinant human bone morphogenetic protein has also been postulated to be an alternative biomaterial but has shown higher rates of adverse effects than other biomaterials[2,27]. Lee et al. compared the outcomes of anterior lumbar interbody fusion between allografts with either recombinant human bone morphogenetic protein-2 (rhBMP-2) and multipotent adult progenitor (map3) cells[28]. They found no significant difference between the two group and an overall fusion rate of 91%. There were improvements in ODI and VAS overall but no significant difference between the groups. However, the rhBMP-2 group had twice as many post-operative complications than the map3 group, which leaned towards significance (p=0.058) but may have been limited due to low frequency. Another study by Kerr et al. also investigated the clinical effectiveness of mesenchymal stem cell allograft (Osteocel)[29]. They found that solid arthrodesis in 92.3% of their cohort was achieved in a median of 5 months. Age greater than 50 years (p=0.017), and habitual smoking (p=0.015) were reported as the only factors that led to delayed fusion time and higher risk of pseudoarthrosis. However, this was the only study that reported smoking as a risk factor and warrants further investigation.

Interbody fusion

While several studies discuss posterolateral as the primary outcome, focus on interbody fusion as a primary outcome is relatively rare[15]. Fomekong et al. applied a three-dimensional (3D) graft made of adipose-derived mesenchymal stem cells (AMSCs) in patients undergoing minimally invasive transforaminal lumbar interbody fusion[30]. At 12 months, all four operated AMSC levels could be assessed (n = 4). Grade 3 fusion could be confirmed at two levels out of four. The mean VAS score improved from 8.3 to 2, and ODI also improved from 47 to 31%. No donor site complication was observed. The final AMSC osteogenic product was thus a promising alternative to the iliac bone crest graft, which has been the most prevalently used biomaterial previously. In the 2015 study from USA, Ajiboye et al. also investigated the rates of interbody fusion, in conjunction with posterior lumbar fusion using MSCs. They found an interbody fusion rate of 96.8%, which is higher than the posterior lumbar fusion rate. From these two studies we can surmise that interbody fusion rates are generally high using stem cell therapy and thus can present a viable alternative to traditional spinal fusion models. Another study using Ostecel Plus also demonstrated no complications in their cohort of 40 patients while investigating Extreme Lateral Interbody fusion rates[31]. They found complete interbody fusion in 90.2% of patients, while the latter 9.8% were partially fused at 12 months post-operatively.

Degenerative Disc Disease

Degenerative disc disease with activated nucleus pulposus cell transplantation was investigated by Mochida et al. at their center in Japan[32]. Their cohort of 9 patients reported no adverse effects and slight improvement in 1 case on MRI. More evidence however is needed to determine the efficacy of the treatment. Xu at all conducted a controlled trial on the repair of intervertebral disc (IVD) defects after micro endoscopic discectomy with selective retention of bone marrow stromal cells with gelatin sponge[21]. They found that the bone marrow stromal cells group had a significantly improved VAS score at final follow up than groups with just annulus fibrosis suture or mobile micro endoscopic discectomy alone. ODI improvement also showed a significant difference, being significantly better in patients with bone marrow stromal cells. There was however no difference in quality of life or imaging using the Pfirmann classification (which is used to evaluate the severity of IVD degeneration based on T2-weighted images). There were no complications in their study. Their research demonstrated that IVD defect repair with SCR-enriched BMSCs combined with gelatin sponge provides a feasible cell-based therapy for IVD defects after discectomy.

Barriers in use in LMICs

The major barrier in the use of stem cells therapy in LMICs has been cost. Although few studies report cost to patients, or to the funding institution, stem cell therapy can incur greater cost than traditional therapy[33]. As with any relatively new modality, we can expect these costs to

decrease with greater adoption and optimisation. The direct costs however are not that significantly different from other commonly used options. The hidden costs in processing, activation, testing for infections, and other tasks associated with high sterility procedures are big barriers to implementation[34]. A major benefit of stem cell therapy use in LMIC's would be minimisation in indirect costs to the patient, less time off particularly for daily labourers and lower socioeconomic impact groups could have a big impact on patient satisfaction and outcomes. Some of the issues foreseeable in stem cell use for degenerative spinal disease is the cost of activating and mobilizing agents, as seen with haematopoietic stem cell transplant. The use of generic drugs as opposed to expensive brand named may alleviate some of this financial burden, however the generation of these drugs, approval by local authorities, and infrastructure to ensure quality are costs that will need to be met as well.

Additionally, research and investment in stem cell therapy needs to be prioritized on a systemic governmental level to fully realize its potential. In this respect some LMICs such as Iran and India have seen significant increases in research and practice using stem cells, but Pakistan has seen low growth in this sector[35]. For reference, stem cell therapy in haematopoietic cells can reach up to $15,749 for the first year alone[36], and in Pakistan where the GDP per capita is $1,193.73 (2020), it may be a distant dream[37]. Fortunately, spinal stem cell therapy costs significantly less that haematopoietic stem cell therapy, but the barriers to entry remain similar in both fields.

Currently, a few dedicated research centres within the region have focussed on developing viable stem cell lines and translation from bench to bedside. The use of dental pulp and human amniotic membrane as two viable, novel substitutes in biomedical applications present promising opportunities for many LMICs[38]. The ease of procurement, with relatively low-cost storage, and long-term viability shows the capacity for integration of stem cells in surgical practices.

Conclusion

Spinal fusion with augmented stem cells is a promising alternative and shows equal or greater efficacy than lilac bone crest graft and other biomaterials with lower rates of adverse effects. Most clinical trials are small; phase III and IV clinical trials are needed to investigate the long-term efficacy of stem cells and viability in different populations. LMICs may stand to gain the most from stem cell therapy in spinal fusion due to decreased indirect costs and better outcomes.

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