The Management Growth Plate Injury in Animal Studies with Stem Cells Technique: Systematic Review

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doi: 10.5455/aim.2022.30.53-56
ACTA INFORM MED. 2022 MAR 30(1): 53-56
Received:  Feb 05, 2022
Accepted:  Mar 16, 2022

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ABSTRACT

**Background:** Injury of growth plate may lead to serious complications such as bone bridge formation, deformity, growth disturbance, and limb length discrepancy. Stem cell therapy is one of the fields studied to mitigate this problem. There are various types and techniques which can be implemented. **Objective:** This systematic review aims to review the most common techniques used in the experimental animal study about the application of stem cells to treat growth plate injury. **Methods:** This study was conducted according to PRISMA guidelines. The following strategy was used. The terms used on the search engine were “stem cell growth plate injury” in PubMed database. A bibliometric evaluation was done on all the search results. **Results:** The initial PubMed search yielded 74 results, but 5 articles were eliminated because they could not be accessed. From the remaining 69 articles, 50 were excluded after abstract and full-text review. Further, 7 articles were eliminated because they did not meet the inclusion criteria. Most studies are experimental animal studies, and there is no human trial regarding this matter. **Conclusion:** There are still a few studies evaluating the application of stem cell in treating growth plate injuries, but the present results are generally satisfactory. Hopefully, clinical trials could be conducted in the near future.

**Keywords:** Animal experimental study, Growth plate, Stem cell, Injury, Systematic Review.

1. BACKGROUND

Physis and epiphysis are two most important parts responsible for longitudinal growth in children. Injury of these anatomical regions usually results in excellent outcomes if treated properly. However, more severe injuries and improperly treated cases may lead to severe complications such as bone bridge formation, deformity, growth disturbance, and limb length discrepancy. This issue becomes more pressing because more children and youths participate in sports nowadays, increasing the risk of injuries (1).

Thus, recent researches aim to minimize the risks of such complications. In the last 20 years, many studies tried to elucidate the basic molecular mechanism of growth plate injury repair responses. The main responses are inflammatory, fibrogenic, osteogenic, and remodeling phases. Many cytokines play a role in these responses, including IL-6, TNF-alpha, PDGF (Platelet-derived growth factor), along with some common pathway such as Wnt/β-catenin pathway. These lead to new targets for therapy in preventing said complications (2, 3).

Many studies utilize the application of stem cells to attenuate the degree of injury, ensuring proper continuation of growth in affected children. There are many types of stem cells used in studies: bone marrow mesenchymal stem cell (bmMSC), chondrogenic stem cell, hepatic mesenchymal stem cell (hMSC), neural stem cell, a stromal vascular fraction (SVF), and various others (4–10). There are also various techniques used to apply stem cells in treating growth plate injury. The stem cell can be used independently or combined with various growth factors.
such as bone morphogenic protein (BMP). Likewise, there are various ways to apply the cells, by implantation, transplantation, scaffold, isolation, and others (12, 13).

2. OBJECTIVE
The aim of this systematic review is to review the most common techniques used in the experimental animal study about the application of stem cells to treat growth plate injury, especially regarding the methods to induce the injury, the anatomical location of the injury, and the technique used to prepare the stem cell.

3. MATERIALS AND METHODS
The following strategy was used: the terms used on the search engine were “stem cell growth plate injury”. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to perform the comprehensive data collection. A bibliometric evaluation was done on all the search results. After searching with those keywords, the authors conducted a review of abstracts to select the appropriate journals. Then, the authors extracted the necessary data from the selected journals to be further analyzed (Figure 1).

This research includes these types of studies: in-vitro study, experimental animal study, clinical study, review article, systematic review, and meta-analysis. The studies above were searched regardless of the language used in the publications. Microsoft Excel was used to create a database, the demographic data from PubMed were loaded, analyzed, and visualized using this software.

4. RESULTS
The initial PubMed search yielded 74 results, but 5 articles were eliminated because they could not be accessed. From the remaining 69 articles, 50 were excluded after abstract and full text review. Further, 7 articles were eliminated because they did not meet the inclusion criteria. Figure 2 depicts the type of studies. The most common type of study is experimental animal study (n=12). The second most common is the review article (n=5). The least common type is in-vitro study (n=2).

Animal Samples
The most common type of animal model used is NZ white rabbits (n=7). The second most common is the rat model (n=3). The other animal model used are lambs (n=1) and miniature pigs (n=1). Figure 3 depicts the type of animals used.

Injury site
The most common injury site used in the animal models is proximal tibia (n=8). From those 8 tibial models, 7 induced injury in the medial part of the proximal tibial epiphysis, and only one induced injury in the central part. The second most common is the lateral part of distal femur (n=3), and one study induced injury in another region (iliac crest). Figure 4 depicts the injury site induced in the animal models.

Injury Type
The most common injury type induced is excision (n=5). The second most common injury type is drilling (n=4). The other types of injuries are incision (n=2) and trocar removal (n=1). Figure 5 depicts the methods of injury induced.

Stem Cell Type
From all the experimental animal studies, the most common type of stem cell used was bone marrow mesenchymal stem cells (MSC) (n=5). One study used synovial stem cells, and another one used periosteum stem cells. Four remaining studies used other types. Figure 6 depicts the stem cell types used.
Stem cell technique

From the 12 studies, 4 studies used direct implantation technique, and another 4 used tissue-engineered disks. Two studies used direct transplantation, and two studies did not mention the technique used. Figure 7 depicts the techniques used.

5. DISCUSSION

There are various types of stem cell that can be used in treating growth plate injury. Likewise, there are various preparation techniques that can be implemented. From all the studies we included in this systematic review, all are either experimental animal studies, in-vitro studies, or secondary articles (7, 14, 15). To the authors’ knowledge, there is currently no human trial conducted regarding this matter.

The most common type of animal model used is New Zealand white rabbit. This is understandable because NZ white rabbit is known for its easy handling, high reproduction rate, and docile temperament. Thus, the application of this model is quite economically advantageous (16).

Regarding the injury site, the most common growth plate injured is the proximal tibial growth plate, especially the medial part (17, 18). Other part injured is the distal femoral growth plate (14). The tibial growth plate injury model is an established model and has been used extensively in various animals (19).

The most common type of stem cell used as bone marrow mesenchymal stem cells (MSC). The main characteristics of this type of stem cell are multipotentiality, self-renewal, tissue regeneration, population heterogeneity, plasticity, lineage priming. This type of stem cell is proven to be versatile in its application to treat musculoskeletal problems in translational study (20).

One study used synovial stem cells. Recent studies have elucidated the specific markers of this stem cell type, and some protocols have been established to isolate this stem cell. Synovial stem cell shows promising result in the treatment of meniscal and growth plate damage (9, 21, 22). Further studies are still needed to evaluate the potential of this cell type.

One study used periosteum stem cells. Periosteum-derived cells and BMSC shows superior result compared to cells isolated from fat in forming hyaline cartilage. Other than that, this type of cell can be used in combination with growth factors such as BMP-2 in order to promote desired cell type differentiation (2, 10, 23).

From the 12 studies, 4 studies used direct implantation technique, 2 studies used direct transplantation. The problems associated with the transplantation of stem cells to growth plate are primarily due to the innate difficulty of growth plate healing and the difficulty of chondrocyte regeneration from the stem cells (3, 7). Currently, there is still no effective way to properly program the stem cell differentiation into desired cell type differentiation. Many techniques are still developed to ensure better repair with stem cell application (24).

Four remaining used tissue-engineered disks. The tissue-engineered disk is, in fact, a type of scaffold engineered using various compounds such as chitosan, collagen, et cetera. The results showed that the beneficial effect of these scaffold applications appeared in more concentrations of cells (25). The main goal of scaffold is to improve stem cell survival which in turn promotes its differentiation into the desired cell type (26).

6. CONCLUSION

There are still a few studies evaluating the application of stem cell in treating growth plate injuries, but the present results are generally satisfactory. Hopefully, clinical trials could be conducted in the near future.

- Patient Consent Form: This study did not perform in human.
- Author’s contribution: PS, and Y.I. gave substantial contributions to the conception or design of the work in acquisition, and analysis. Y.I. and R.D. had a part in article preparing for drafting or revising it critically for important intellectual content. P.S and M.A. gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- Conflicts of interest: There are no conflicts of interest.
- Financial support and sponsorship: None.
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