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Mesenchymal Stem Cell Therapy for Sports Injuries - From Research to Clinical Practice

(Terapi Sel Stem Mesenkima untuk Kecederaan Sukan - Daripada Kajian kepada Amalan Klinikal)

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ABSTRACT

The number of sports-related injuries is on the rise as more people are involved in sports, especially the extreme sports that are prone to injury. A serious sports injury might end the career of an athlete. Thus, prompt and effective treatment is very important for these injuries. Cell-based therapy is becoming more popular as a potential new treatment for sports injuries that are refractory to conventional therapy. Mesenchymal stem cells (MSCs) are commonly used in the treatment of sports injuries as they are safe and will not be rejected by the recipient. MSCs secrete paracrine factors that modulate the host immune response, promote angiogenesis, enhance cell migration and survival as well as prevent fibrosis. The safety and efficacy of MSC therapy in treating sports injuries involving the muscle, ligament, tendon, bone, cartilage, and nervous tissues have been demonstrated in many preclinical and clinical studies. However, more studies especially the large-scale randomized clinical trial need to be done in order to determine the adequacy of MSC therapy in treating different sports injuries. In this review, we discussed the treatment for sports injuries, focusing on MSC therapy, using data from preclinical and clinical studies.

Keywords: Mesenchymal stem cell; orthopedics; regenerative medicine; sports injury; stem cell therapy

ABSTRAK

Bilangan kes kecederaan berkaitan dengan sukan semakin meningkat sejajar dengan peningkatan bilangan orang yang aktif dalam sukan, terutamanya sukan lasak yang senang tercedera. Kerjaya seorang atlet mungkin ditamatkan oleh kecederaan berkaitan dengan sukan yang serius. Oleh yang demikian, rawatan segera dan berkesan amat penting untuk kecederaan ini. Terapi sel menjadi semakin popular sebagai rawatan baharu untuk kecederaan berkaitan dengan sukan yang refraktori kepada terapi konvensional. Sel induk mesenkima (MSC) kerap digunakan untuk rawatan kecederaan berkaitan dengan sukan kerana ia adalah lebih selamat dan tidak akan ditolak oleh sistem imun penerima. MSC merembeskan faktor parakrin yang memodulasi tindak balas imuniti, merangsang angiogenesis, migrasi sel dan kemandirian sel serta mencegah fibrosis. Keselamatan dan efikasi terapi MSC dalam merawat kecederaan berkaitan dengan sukan yang melibatkan tisu otot, ligamen, tendon, tulang, rawan dan saraf telah ditunjukkan dalam banyak kajian praklinikal dan klinikal. Namun demikian, lebih banyak kajian terutamanya percubaan klinikal terawak berskala besar perlu dijalankan untuk mengenal pasti kepadanan terapi MSC dalam menangani kecederaan berkaitan dengan sukan yang berbeza. Di sini kami membincangkan rawatan untuk kecederaan berkaitan dengan sukan menggunakan data daripada kajian preklinikal dan klinikal dengan fokus diberikan kepada terapi MSC.

Kata kunci: Kecederaan berkaitan dengan sukan; sel induk mesenkima; ortopedik; perubatan regeneratif; terapi sel

Introduction

The term 'sports injury' is often defined differently between articles. Generally, a sports injury is defined as a medical injury where the patient's body loses the capacity to perform certain functions or body structure abnormality resulting from sports activity following the diagnostic of a medical examiner (Timpka et al. 2014). Common sports injury sites include the knee, shoulder, ankle, elbow, and wrist.

There are six criteria to determine the severity of sports injuries which consists of nature of the sports injury, treatment duration, permanent damage, cost, working and sporting time lost (Hespanhol Junior et al. 2015). Management of sports injuries is very complicated as inappropriate treatment may affect an athlete's health and career. Despite the existent of standard treatment plan such as PRICE (protection, rest, ice, compression, and elevation) therapy, anti-inflammatory drugs, physiotherapy, and surgery, more effort is needed to develop a safer and more efficacious alternative treatment for the management of sports injuries in order to achieve rapid recovery without the loss of body function.

The term 'tissue engineering' was first mentioned by Wolter and Meyer during the 1980s (Wolter & Meyer 1984). Subsequently, Kaiser (1992) advocated a new treatment strategy which involves regeneration or restoration of the impaired tissue or organ. This new concept later developed into a new branch of medicine known as regenerative medicine. Regenerative medicine is an advanced medicine approach where various techniques are implied to facilitate the regeneration of damaged cell, tissue or organ by triggering the body's own repair mechanism (Figueroa et al. 2014).

The stem cell is a natural biological cell which is capable of self-regeneration and differentiates into other cell types. Stem cell therapy represents a novel approach in regenerative medicine for sports injuries as stem cells can intervene at the physiological levels through cell differentiation and the molecular level through secretion of various cytokines, hormones, and growth factors that mediate tissue repair (Spees et al. 2016). Mesenchymal stem cell (MSC) are widely explored as a potential cell-based therapy for the treatment of sports injuries as they are safer compared to embryonic stem cell (ESCs) and induced pluripotent stem cell (iPSCs) (Liau et al. 2019). This review paper discusses the treatment of sports injuries with MSCs using data from preclinical and clinical studies.

TREATMENT FOR ACUTE SPORTS INJURIES

Conventional treatment of sports injuries includes the PRICE principle, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs).

PRICE principle

Generally, the PRICE principle is used during the initial phase of soft tissue injury (including muscle, ligament, and tendon) to reduce hemorrhage into the affected area and thereby reduce swelling and pain (Fernandes et al. 2015). Protection is to prevent the tissue from further damage. Resting is advised to minimize additional stress for rapid healing while cooling or cryotherapy using ice, frozen gel, or other vapocoolants is to decrease bleeding and also serving as a counterirritant to reduce pain (van den Bekerom et al. 2012). Lastly, compression and elevation are to reduce the swelling at the injury site.

Corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are widely used in the management of sports injuries as they are potent anti-inflammatory drugs that inhibit the inflammatory cascade through down-regulation of immune responses. However, recent studies indicated that long-term application of NSAIDs is associated with numerous notable side effects (Rotunno et al. 2016). Cohen et al. (2016) showed that indomethacin and celecoxib that are commonly used to treat sports injuries have a negative effect on rotator cuff tendon-to-bone healing and affect the organization of collagen fibrils in an animal model. Furthermore, NSAIDs such as COX-2 inhibitors, diclofenac, ibuprofen and naproxen were linked with a higher risk of gastrointestinal ulcers (Drini 2017).

Coombes et al. (2010) conducted a meta-analysis to compared the safety and efficacy of corticosteroids and other nonsurgical interventions in the treatment of tendon injury and found that corticosteroids only provided better short-term (0-12 weeks) pain relief and no differences were found in the intermediate and long terms. In a randomized placebo-controlled trial of unilateral epicondylalgia, the corticosteroid group gives better outcome compared to the placebo group at the initial stage (4 weeks) (Coombes et al. 2013). However, at 26 weeks and 1 year, patients underwent corticosteroid treatment have a poorer outcome compared to the placebo group. The recurrent rate also significantly higher in the corticosteroid group compared to the placebo group at 1 year. Based on these findings, it is very clear that NSAIDs merely provide short-term pain relief and interfere with tissue regeneration. The key to successful treatment in most sports injuries is a continuous rehabilitation program stressing restoration of the normal range of motion, strength, and functionality.

REGENERATIVE MEDICINE

The application of the concept of regenerative medicine in the treatment of musculoskeletal injuries can be traced back to as early as the 1930s (DeChellis & Cortazzo 2011). The goal of regenerative medicine is to heal an injury by augmenting the body natural potential for self-healing or by means of bioengineering (Malanga & Nakamura 2014). The current practice of regenerative medicine in the treatment of sports injuries includes platelet-rich plasma (PRP), prolotherapy, and stem cell therapy. The current review focuses on the potential and application of stem cell therapy, especially the MSCs in sports injuries.

PROLOTHERAPY

Prolotherapy, also known as proliferative therapy, is an injection-based treatment used to introduce an irritating agent to the joint, tendon, and ligament to promote healing (Hauser et al. 2016). The exact mechanism of prolotherapy remains unclear but researchers postulated that the irritants stimulate an inflammatory response that ultimately leads to fibroblast proliferation and collagen synthesis. Dextrose is the most commonly used irritant in prolotherapy, with polidocanol, zinc, manganese, ozone, glycerin, phenol, guaiacol, pumic acid, and sodium morrhuate also being used occasionally (Hauser et al. 2016; Malanga & Nakamura 2014). The irritants are

normally delivered to the injured sites multiple times in a period of several weeks to several months (Rabago et al. 2010). Published human trials reported that prolotherapy is effective in pain relief in several types of sports injuries including Achilles tendinosis, groin pain, and plantar fasciitis with minimal adverse effect (Ryan et al. 2009; Topol & Reeves 2008; Yelland et al. 2011).

PLATELET-RICH PLASMA

PRP is defined as the blood plasma with platelet concentration higher than the physiological level (Law et al. 2017; Lim et al. 2019). In recent years, many studies have showed the importance of growth factors in promoting tissue repair and regeneration (Maarof et al. 2016; Yamakawa & Hayashida 2019). Therefore, the application of PRP which is rich in growth factor is thought to be useful in treating sports injuries. PRP is typically prepared via a two-step centrifugation process, i.e. first centrifugation to remove the red blood cells and followed by the second centrifugation to concentrate the platelets (Xian et al. 2015). Till now, the clinical efficacy of PRP is ambiguous despite many effort and attempts, likely due to the differences in the preparation process which renders the PRP quality to vary from one study to another. The presence of various preparation methods, lack of standardization as well as other variables such as activation modalities are confounding factors which hindered the evaluation of PRP effectiveness.

STEM CELL THERAPY

The self-renewal and differentiation ability of stem cells render them ideal for regeneration medicine. Stem cell was first discovered in mice bone marrow at the year 1963 and the hematopoietic stem cells are now widely used to treat blood diseases (Becker et al. 1963). Over the decades, multiple types of stem cells have been discovered, including MSCs, ESCs, and iPSCs. Currently, there is a lack of evidence to support ESC and iPSC usage in orthopedic injuries.

MSCs can be harvested from many tissues including bone marrow, fat, peripheral blood, and umbilical cord (Hafez et al. 2018; Liau et al. 2018; Lim et al. 2018; Zhang et al. 2018). The multipotent nature of MSCs allows them to differentiate into the bone, cartilage, nerve, tendon, and ligament cells (Cortés-Medina et al. 2019; Dai et al. 2015; Li et al. 2017; Lim et al. 2016). Thus, MSCs are suitable for the treatment of orthopedic injuries. Importantly, transplantation of allogeneic MSCs is very safe as the cells have very low efficacy to induce an immune response in the recipient as they express a low level of major histocompatibility complex (MHC) class I and do not express MHC class II (Ankrum et al. 2014; Liau et al. 2019). In addition, MSCs also have a very low risk of tumor formation after transplantation due to their limited replication lifespan (Kim & Park 2017). MSCs are capable of modulating the cell-cell signaling pathway through the secretion of various cytokines and growth factors. One of the main functions of MSCs in tissue repair and regeneration is to suppress the inflammation (Sharma et al. 2017). MSCs can modulate the immune response of B cells, T cells, and NK cells via secretion of paracrine factors and cell-to-cell contact (Gao et al. 2016). At the same time, MSCs also promote cell survival and angiogenesis while preventing tissue fibrosis (Xu et al. 2016). At present, the literature supporting MSC therapy for orthopedic and musculoskeletal injuries consists of *in vitro* and animal studies along with case reports, case series, and clinical trial results in human.

RESEARCH ON MESENCHYMAL STEM CELL THERAPY

There are thousands of clinical trials that have been completed, actively conducted or in the planning worldwide to examine the safety and efficacy of MSC therapy and many of the aforementioned trials investigate on the injuries of bone, cartilage, tendon, and skeletal muscle, therefore having implication for sports injuries.

ARTICULAR CARTILAGE

Many preclinical studies have shown the benefits of MSCs in cartilage regeneration. Marquass et al. (2011) investigated the efficacy of bone marrow-derived MSCs (BMSCs) and chondrogenic-differentiated BMSCs in cartilage regeneration using a sheep model. Their results indicated that chondrogenic-differentiated BMSCs embedded in a collagen matrix significantly improved structural repair of a chronic osteochondral defect in an ovine stifle joint without signs of cell hypertrophy after 12 months compared to the undifferentiated BMSCs. In addition, Al Faqeh et al. (2012) also reported better regeneration of osteoarthritis (OA) knee in the sheep model when using chondrogenic-differentiated BMSCs compared to the undifferentiated BMSCs. However, no clinical data on the efficacy of chondrogenic-differentiated MSCs has been reported thus far.

As for clinical research, many studies have proven the benefits of MSC therapy in cartilage regeneration. Table 1 lists the clinical studies applied MSCs for the treatment of cartilage injuries. Koh et al. (2015) used adipose-derived MSCs (ADSCs) to treat knee OA in elderly patients above 65 years old and found that the therapy improved the cartilage structure and function. Freitag et al. (2017) reported the treatment of an athlete with post-traumatic patella chondral defect that fails to heal 12 months after the surgery with autologous ADSCs and found that the chondral defect regenerated and functional score improved. Wong et al. (2013) evaluated the efficacy of BMSCs in treating patients with unicompartmental OA and genu varum. Results showed that patients received BMSC therapy exhibited

improvement in various clinical outcomes, including the Lysholm, Tegner, and International Knee Documentation Committee (IKDC) scores. Emadedin et al. (2018) applied BMSC therapy on OA patients and found that the patients showed significant improvement in visual analog scale (VAS) score, Western Ontario and McMaster Universities Arthritis Index (WOMAC) score and painless walking distance compared to the patients received placebo. Park et al. (2017) used combination of umbilical cord blood-derived MSCs and hyaluronate hydrogel in treating patients with Kellgren-Lawrence grade 3 OA and International Cartilage Repair Society grade 4 cartilage defects and found that the clinical outcomes improved as early as 24 weeks and lasted for 7 years. Interestingly, Nejadnik et al. (2010) demonstrated that BMSC therapy is as effective as autologous chondrocyte implantation (ACI) in articular cartilage repair.

Several clinical studies compared the efficacy of high and low cell dosage for the treatment of knee OA. While most of the studies reported that high dose group achieved better results in term of pain reduction, functional recovery, and cartilage regeneration (Chahal et al. 2019; Jo et al. 2014; Lamo-Espinosa et al. 2018), Pers et al. (2016) found that only those received low dose of MSCs achieved significant improvement in WOMAC, VAS and Knee Injury and Osteoarthritis Outcome Scoring (KOOS) scores. These discrepancies may be due to the variation in the initial OA severity and small sample size (6-30 subjects).

Generally, results from the clinical studies reported thus far found that MSC therapy is safe, feasible, and beneficial in improving the functionality, reducing the pain, and promoting the regeneration of damaged cartilage.

TABLE 1. Trials applied MSC therapy for the treatment of cartilage injuries

Disease	No. of patient	Cell source	Dosage	No. of infusion	Key findings	References
Knee osteoarthritis	30	ADSCs in SVF	4.2×10^7	1	Improvement in Lysholm, VAS and KOOS scores. 87.5% of patients maintained their cartilage status at least 2 years	(Koh et al. 2015)
Post-traumatic chondral defect	1	ADSCs	1.05×10^8 & 1.12×10^8	2 (6 months apart)	Improvement in functional score (WOMAC and KOOS) and reduction of pain (NPRS). MRI showed patella chondral regeneration	(Freitag et al. 2017)
Unicompartmental osteoarthritic knee and genu varum	56	BMSCs	$1.46 \pm 0.29 \times 10^7$	1	Improvement in the Lysholm, Tegner and IKDC scores compared to the control group	(Wong et al. 2013)
Knee osteoarthritis	43	BMSCs	4×10^7	1	Improvement in VAS score, WOMAC score and painless walking distance compared to the control group	(Emadedin et al. 2018)
Knee osteoarthritis	7	UC-MSCs	2.5×10^6 / cm^2 of defect area	1	Improvement in the IKDC score and increment in GAG content indicated cartilage regeneration	(Park et al. 2017)
Knee osteoarthritis	72	BMSCs	$1\text{-}1.5 \times 10^7$	1	Comparable improvement in SF-36 questionnaire, IKDC, Lysholm and Tegner scores compared to ACI treatment	(Nejadnik et al. 2010)
Knee osteoarthritis	12	BMSCs	1×10^6, 10×10^6 or 50×10^6	1	Improvement in KOOS and WOMAC scores. MRI showed insignificant changes in WORMS and synovitis scores. High dose group showed better results compared to the medium and low dose groups	(Chahal et al. 2019)
Knee osteoarthritis	24	BMSCs	1.3×10^7	1	Improvement in arthroscopic and histology grading score. Not different in clinical evaluation	(Wakitani et al. 2002)
Knee osteoarthritis	5	BMSCs	2×10^6 / cm^2 of defect area	1	Improvement in Lysholm and RHSSK scores. MRI showed cartilage regeneration	(Haleem et al. 2010)

Knee osteoarthritis	12	BMSCs	4×10^7	1	Improvement in pain (VAS) and functionality (WOMAC and Lequesne index). MRI showed improvement in cartilage quality	(Orozco et al. 2013)
Knee osteoarthritis	50	BMSCs	$4 \pm 0.1 \times 10^7$	1	Improvement in pain (VAS) and functionality (Lequesne index and WOMAC). MRI showed improvement in cartilage quality	(Soler et al. 2015)
Knee osteoarthritis	15	BMSCs	$40.9 \pm 0.4 \times 10^6$	1	Improvement in pain (VAS) and functionality (Lequesne index, WOMAC, and SF-36 questionnaire for bodily pain, role physical and physical functioning). MRI showed improvement in cartilage quality	(Soler et al. 2016)
Knee osteoarthritis	30	BMSCs	1×10^7 or 10×10^7	1	Improvement in pain (VAS) and functionality (WOMAC). MRI showed improvement in cartilage quality (WORMS). High dosage group showed better results compared to the low dose group	(Lamo-Espinosa et al. 2018)
Knee osteoarthritis	10	BMSCs (with 10-20% cartilage-derived cells)	-	1	Improvement in pain (VAS) and functionality (KOOS). MRI showed cartilage regeneration	(de Windt et al. 2017)
Knee osteoarthritis	50	ADSCs	1.89×10^6	1	Improvement in pain (VAS) and functionality (Lysholm and Tegner activity scale) compared to the control group	(Koh & Choi 2012)
Knee osteoarthritis	91	ADSCs in SVF	-	1	Improvement in pain (VAS)	(Pak et al. 2013)
Knee osteoarthritis	18	ADSCs	1.18×10^6	1	Improvement in pain (VAS) and functionality (Lysholm and WOMAC). MRI showed improvement in cartilage quality (WORMS)	(Koh et al. 2013)
Knee osteoarthritis	18	ADSCs	1×10^7, 5×10^7 or 10×10^7	1	High dose group showed improvement in pain (VAS) and functionality (WOMAC and KSS) compared to the medium and low dose groups. MRI showed cartilage regeneration	(Jo et al. 2014)
Knee osteoarthritis	56	ADSCs	3.8×10^6	1	Improvement in functionality (IKDC and Tegner activity scale)	(Koh et al. 2014a)
Knee osteoarthritis	54	ADSCs	3.9×10^6	1	Improvement in functionality (IKDC and Tegner activity scale)	(Kim et al. 2014)
Knee osteoarthritis	30	ADSCs	1×10^8	1 or 2 (second injection at 6 months)	Improvement in pain (NPRS) and functionality (KOOS and WOMAC)	(Freitag et al. 2019)

Knee osteoarthritis	6	ADSCs	2×10^6, 10×10^6 or 50×10^6	1	The low dose group achieved better improvement in pain (VAS) and functionality (WOMAC and KOOS) compared to the medium and high dose groups	(Pers et al. 2016)
High tibia osteotomy	44	ADSCs	4.11×10^6	1	Improvement in pain (VAS) and functionality (KOOS). Arthroscopy showed better cartilage regeneration compared to the control group	(Koh et al. 2014b)
Partial medial meniscectomy	55	BMSCs	5×10^7 or 15×10^7	1	MRI showed better improvement in meniscal volume compared to the control group	(Vangsness et al. 2014)
Torn meniscus	5	BMSCs	1×10^6 / cm^2 of scaffold	1	3/5 patients treated with BMSCs + collagen scaffold showed improvement in functionality (IKDC, Tegner activity scale and Lysholm) and MRI showed meniscal repair	(Whitehouse et al. 2017)

BMSCs- bone marrow-derived mesenchymal stem cells, UC-MSCs- umbilical cord-derived mesenchymal stem cells, ADSCs- adipose-derived mesenchymal stem cells, SVF- stromal vascular fraction, VAS- visual analog scale, WOMAC- Western Ontario and McMaster Universities Arthritis Index, GAG- glycosaminoglycan, IKDC- International Knee Documentation Committee, WORMS- Whole-Organ Magnetic Resonance Imaging Score, NPRS- Numeric Pain Rating Scale, RHSSK- Revised Hospital for Special Surgery Knee Score, SF-36- Short Form-36 questionnaire, ACI-autologous chondrocyte implantation, , KOOS- Knee Injury and Osteoarthritis Outcome Scoring, KSS- Knee Society Score

MENISCUS

The meniscus is the crescent-shaped fibrocartilage structure between the femoral condyles and tibial plateau of the knee (Mordecai et al. 2014). Meniscus tear is a very common pathology of the knee. Cell-based therapy directed toward meniscus regeneration has manifested in many forms, including intraarticular injection, direct surgical injection or through scaffolding vehicle. Hatsushika et al. (2014) conducted an animal study using a pig model. In the study, a total of 50 million synovial MSCs were administered through intraarticular injection 2 weeks after bilateral resection of the anterior half of the medial meniscus. MRI, macroscopic and histologic evaluation showed that meniscal regeneration was significantly better in the MSCs-treated group compared to the control group. The benefit of MSC therapy in meniscus repair also has been reported in other animal studies (Horie et al. 2012; Nakagawa et al. 2015).

Vangsness et al. (2014) reported a randomized double-blind controlled trial involving 55 patients that underwent a partial medial meniscectomy at seven institutions. The patients received an intraarticular injection of allogeneic BMSCs within seven to ten days after the surgery. The study reported a reduction in pain and an increment in volume of the meniscus in the BMSC-treated patients that were followed-up for 2 years. Surprisingly, the authors also reported that a higher dosage (150 million cells) did not provide additional benefits compared to the lower dosage (50 million cells). Whitehouse et al. (2017) treated torn meniscus with BMSCs + collagen scaffold. Three patients showed improvement in functionality and meniscal repair, while the remaining 2 patients required meniscectomy due to retear or non-healing of the meniscal tear after 15 months.

LIGAMENT

Many preclinical studies have gleaned into the mechanism of MSC-based therapy for ligament regeneration. Soon et al. (2007) analyzed the effect of BMSCs on the quality and rate of osteointegration by coating the allograft at the tendon-bone interface with BMSCs during the anterior cruciate ligament reconstruction process in 36 rabbits. The results showed that treatment with BMSCs improved osteointegration and ligament biomechanical strength compared to the control group. Figueroa et al. (2014) treated the transected anterior cruciate ligament (ACL) with BMSCs seeded type I collagen scaffold and reported that the presence of BMSCs is critical in ACL repair as no regeneration was observed in ACL treated with type I collagen scaffold alone.

To the best of our knowledge, there is no clinical data reported the use of stem cells for tendon repair. However, few trials (NCT02469792, NCT02755376, NCT03294759, NCT03294720, NCT01088191, and NCT01850758) were found when the search was done on the clinical trial database (clinicaltrials.gov by United States National Library of Medicine). From the information, we can summarize that the application of stem cells in treating ligament injury is still new and the safety and efficacy of stem cell therapy for ligament injury remain unknown until the results are reported.

TENDON

Tendon has similar cell composition with ligament and mainly functions as an attachment point between muscle and bone. Daher et al. (2011) treated suture repair transected Achilles tendon in Sprague-Dawley rat with allogeneic circulating stem cells seeded on a biodegradable scaffold. They found that the aligned collagen fibers formed a bridge at the transection site by 2 weeks and the mechanical strength of the tendon was better compared to the control group with suture alone. Similar findings have been reported in a few other studies that reported that stem cells improved biomechanical properties and collagen organization of damaged Achilles tendon (Adams et al. 2014; Chong et al. 2007). Furthermore, studies also showed that the culture environment is vital in MSCs-based therapy for tendon regeneration. Huang et al. (2013) conducted a study on the effect of hypoxic condition toward the efficacy of MSCs in repairing injured Achilles tendon. The results showed that hypoxic MSCs have significantly higher healing capacity compared with those cultured in the normoxic environment. Besides the culturing environment, the source of MSCs also played an important role in determining the efficacy of MSC in the treatment of ligament injury. Utsunomiya et al. (2013) investigated MSCs isolated from several different shoulder tissues of patients with rotator cuff injuries. It was found that tissue from the subacromial bursa showed the greatest expandability, yield, and osteogenic potential, suggesting that MSCs isolated from this tissue might be the best source of MSCs for treatment of ligament injury. Nonetheless, the study did not test the efficacy of the MSCs *in vivo*. Interestingly, Pietschmann et al. (2013) found that tenocytes were better than BMSCs when the cells were seeded on the polyglycol acid-collagen type I scaffold for the treatment of full-size Achilles tendon rupture in a rat model.

Clinical potential of MSC therapy in tendon repair have been demonstrated in several clinical studies. Treatment of tennis elbow with bone marrow-derived mononuclear cells (BMMCs) significantly improved the Patient-rated Tennis Elbow Evaluation (PRTEE) score of the patients (Singh et al. 2014). Kim et al. (2017) reported that application of ADSCs significantly enhanced the rotator cuff repair by reducing the pain, improving the functionality and lowering the retear rate. Hernigou et al. (2014) treated rotator cuff injury with BMMCs and found that tendon healing was faster and the tendon quality was better compared to those received the surgical repair alone. Importantly, the MSCs treated patients also have lower rate of recurrent compared to the control group. Similarly, Ellera Gomes et al. (2012) also reported that application of BMMCs enhanced the healing of rotator cuff injury. Pascual-Garrido et al. (2012) treated chronic patellar tendinopathy with BMMCs and found that the functionality of the knee improved as indicated by the increase in Tegner activity scale, IKDC score and KOOS score. Safety of MSC therapy for tendon repair also have been demonstrated in several other studies (Havlas et al. 2015; Ilic & Atkinson 2014). Table 2 summarize the clinical studies applied MSCs for the treatment of tendon injuries.

TABLE 2. Trials applied MSC therapy for the treatment of tendon injuries

Disease	No. of patient	Cell source	Dosage	No. of infusion	Key findings	References
Tennis elbow	30	BMMCs	-	1	Improvement in functionality (PRTEE)	(Singh et al. 2014)
Rotator cuff injury	70	ADSCs	4.46×10^6	1	Improvement in pain (VAS) and functionality (UCLA shoulder rating scale and Constant score). Lower jhhjed recurrent rate compared to the control group	(Kim et al. 2017)
Rotator cuff injury	90	BMMCs	$5.1 \pm 2.5 \times 10^4$	1	Ultrasound and MRI showed enhanced tendon healing and quality =. Lower rate of recurrent compared to the control group	(Hernigou et al. 2014)
Rotator cuff injury	14	BMMCs	3.81×10^8	1	Improvement in functionality (UCLA shoulder rating scale). MRI showed tendon regeneration	(Ellera Gomes et al. 2012)
Chronic patellar tendinopathy	8	BMMCs	3×10^4	1	Improvement in functionality (Tegner activity scale, IKDC, and KOOS)	(Pascual-Garrido et al. 2012)
Chronic refractory Achilles tendinopathy	6	P-MSCs	1×10^6 or 4×10^6	1	Safe and feasible	(Ilic & Atkinson 2014)

BMSCs- bone marrow-derived mesenchymal stem cells, P-MSCs- placenta-derived mesenchymal stem cells, ADSCs- adipose-derived mesenchymal stem cells, BMMCs- bone marrow-derived mononuclear cells, KOOS- Knee Injury and Osteoarthritis Outcome Score, IKDC- International Knee Documentation Committee, PRTEE- Patient-rated Tennis Elbow Evaluation, VAS- visual analog scale

BONE

Rest and immobilization are the standard medical procedure used to manage bone fractures, particularly fragility fractures that could not heal in the appropriate time frame. Treatment for such fracture is often challenging due to the complex biological environment. Previous studies showed that MSCs secreted various paracrine factors such as vascular endothelial growth factor (VEGF), bone morphogenetic protein-4 (BMP-4) and bone morphogenetic protein-6 (BMP-6) which enhanced angiogenesis and bone formation (Peng et al. 2002; Sheyn et al. 2011). The aforementioned researches demonstrated increased bone formation rate and bone volume and shorter recovering time in the MSCs-treated group compared to the control group.

Kim et al. (2009) reported a randomized clinical trial examined the safety and efficacy of osteogenic-differentiated BMSCs in treating 64 patients with long bone fracture. They found that patients receiving osteogenic-differentiated BMSCs healed faster compared to those without treatment. Leibergall et al. (2013) reported a clinical trial assessing the safety and efficacy of BMSCs + PRP + demineralized bone matrix combination in treating patients with distal tibial fracture. They found that the intervention group healed faster but no significant difference was detected in the VAS and Short Form-12 scores. Ismail et al. (2016) applied BMSCs to patients with long bone fracture and found that treatment with BMSCs + hydroxyapatite granules hasten the functional recovery and radiographic improvement. Gómez-Barrena et al. (2019) used BMSCs with calcium phosphate bioceramic granules to treat femur, tibia and humerus diaphyseal and metaphysodiaphyseal and reported that healing was seem in 26 of 28 patients.

Zhao et al. (2012) treated femoral head osteonecrosis with BMSCs and found improvement in the Harris hip score and higher reduction in volume of necrotic lesion compared to the control group. Recently, Kang et al. (2018) reported the application of BMMCs to patients with femoral head osteonecrosis and found that the treatment lowered the total hip replacement arthroplasty conversion rate but did not affect the Association Research Circulation Osseous stage progression. Several other clinical studies also recorded improvement in hip function as well as reduction in pain and size of necrotic lesion upon received BMMCs for their femoral head osteonecrosis (Gangji et al. 2011; Sen et al. 2012; Tabatabaee et al. 2015; Wang et al. 2010). Table 3 lists the clinical studies applied MSCs to treat bone injuries.

TABLE 3. Trials applied MSC therapy for the treatment of bone injuries

Disease	No. of patient	Cell source	Dosage	No. of infusion	Key findings	References
Long bone fracture	64	BMSCs (Osteogenic differentiated)	1.2×10^7	1	Bone fracture healed faster compared to the control group (callus formation score)	(Kim et al. 2009)
Distal tibial fractures	24	BMSCs	1×10^8	1	Treatment with BMSCs + PRP + DBM significantly reduced bone healing time compared to the control group	(Liebergall et al. 2013)
Tibial fracture	1	BMSCs	5×10^6	1	Combination of BMSCs + calcium phosphate pellet promoted bone healing	(Bajada et al. 2007)
Long bone fracture	10	BMSCs	1.5×10^7	1	Treatment with BMSCs + HA granules hasten the functional recovery (LEFS or DASH) and radiographic improvement (Lane-Sandhu and Tiederman radiological scores)	(Ismail et al. 2016)
Femur, tibia or humerus diaphyseal or metaphysodiaphyseal	28	BMSCs	1×10^8 or 2×10^8	1	Treatment with BMSCs + calcium phosphate bioceramic granules healed 26/28 bone injuries	(Gómez-Barrena et al. 2019)
Femoral head osteonecrosis	100	BMMCs	2.1×10^8	1	Lowered the THA conversion rate but did not affect the ARCO stage progression	(Kang et al. 2018)
Femoral head osteonecrosis	19	BMMCs	$1.9 \pm 0.2 \times 10^9$	1	BMMC transplantation reduced pain and joint symptoms and slow downed the ARCO stage progression	(Gangji et al. 2011)
Femoral head osteonecrosis	45	BMMCs	1.5×10^9	1	Improvement in Harris hip score and slow downed disease progression	(Wang et al. 2010)

Femoral head osteonecrosis	18	BMMCs	$5 \pm 2 \times 10^8$	1	Treatment with BMMCs + core decompression improved the ARCO, VAS and WOMAC scores	(Tabatabaee et al. 2015)
Femoral head osteonecrosis	40	BMMCs	5×10^8	1	Treatment with BMMCs + core decompression improved the Harris hip score and mean hip survival	(Sen et al. 2012)
Femoral head osteonecrosis	100	BMSCs	2×10^6	1	Improvement in the Harris hip score and reduction in volume of necrotic lesion compared to the control group	(Zhao et al. 2012)

BMSCs- bone marrow-derived mesenchymal stem cells, BMMCs- bone marrow-derived mononuclear cells, PRP- platelet-rich plasma, DBM- demineralized bone matrix, HA- hydroxyapatite, LEFS- Lower Extremity Functional Scale, DASH- Disabilities of the Arms, Shoulder and Hand score, THA- total hip replacement arthroplasty, ARCO- Association Research Circulation Osseous, VAS- visual analog scale, WOMAC- Western Ontario and McMaster Universities Arthritis Index

MUSCLE

Muscle injuries are challenging to address, particularly through surgical method. Ota et al. (2011) conducted an animal study to examine the effects of muscle-derived stem cells transplanted at 1, 4, and 7 days after muscle contusion in a murine model. The MSCs-treated group showed a high level of vascular endothelial growth factor (VEGF) and angiogenesis at 1 week, increased muscle strength at week 2 and decreased fibrosis formation at week 4. These findings indicated that stem cells may have the potential to accelerate the muscle healing process and decrease the formation of scar tissue that affects normal muscle function. Results reported by Brickson et al. (2016) and Utomo et al. (2018) also supported the use of MSCs in treating muscle injuries. Only 1 clinical trial (NCT03068988) on muscle repair using MSCs is found in the clinical trial database (ClinicalTrials.gov). Unfortunately, there is no report available regarding the safety and efficacy about this study.

PERIPHERAL NERVE

Cell-based therapy has been studied for the treatment of critical-size peripheral nerve defect. In the preliminary animal-based experiments, researchers have shown that the application of MSCs gives positive effects on nerve regeneration. In these studies, the MSCs were delivered with a scaffold such as a chitosan/poly(lactic-co-glycolic acid)-based scaffold, collagen tube, inside-out vein graft and polycaprolactone conduit into the host (Ding et al. 2010; Ladak et al. 2011; Mohammadi et al. 2012; Oliveira et al. 2010). These studies claimed that a 2-50 mm nerve growth was observed within 3 weeks to 6 months along with an increment in number and diameter of myelinated nerve as well as improvement of muscle mass and nerve functional recovery. Currently, there is no study that evaluates the safety and efficacy of MSC therapy in peripheral nerve injury registered in ClinicalTrials.gov. Nonetheless, MSCs have been clinically tested in many studies for the treatment of central nervous system injury, especially the spinal cord injury.

CURRENT LIMITATIONS AND FUTURE PERSPECTIVES

To date, many clinical studies have reported the safety and efficacy of MSC therapy in promoting sports injuries. Most of the clinical studies are phase I and phase II trial with small sample size. Furthermore, most of the studies do not have a control group. Thus, randomized phase III clinical study with large sample size should be conducted in future to confirm the safety and efficacy of MSC therapy in treating various sports injuries. In order to achieve the best therapeutic results, the sources of MSC, and the timing, dosage and number of MSC administration are very crucial. Currently, there is no consensus on the best sources of MSCs and the optimal timing, dosage and number of MSC administration for different sports injuries. Future research should also focuses on the preconditioning of MSCs before administration. Preconditioning can modulate the biological activities of MSCs to render them more effective in promoting tissue repair and regeneration. Using the animal models, few studies have showed that differentiated cells are more effective compared to the undifferentiated MSCs in tissue repair and regeneration. However, very few clinical studies used the differentiated cells. Thus, future clinical studies should consider comparing the safety and efficacy undifferentiated and differentiated MSCs.

Just like other narrative review articles, this paper does not performed meta-analysis to combine the results from multiple studies in order to determine the common effect of MSC therapy.

CONCLUSION

Cell-based therapy directed at tissue repair represents an opportunity to promote the regeneration of damaged tissue that is difficult or slow to heal. Thus far, results from most of the human trials showed that MSC therapy is safe and effective in treating sports injuries. Even though cell-based therapy is a promising new therapy for tissue regeneration, nonetheless, the effectiveness of cell-based therapy varies from one study to another. Larger phase III clinical trial should be conducted in future and more

fundamental study is needed to understand the mechanism of action and the new findings should be translated as soon as possible.

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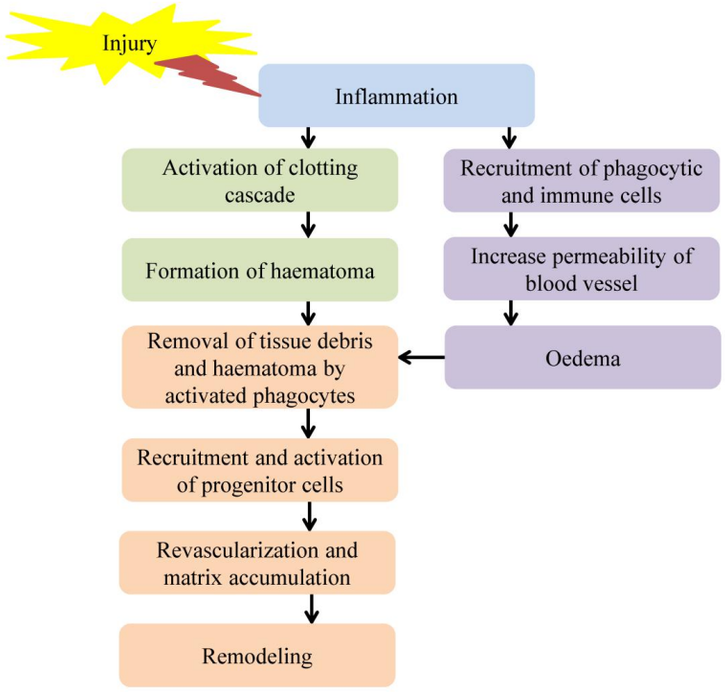

SUPPLEMENTARY 1. General sequence of events of tissue repair after injury. Immediate response of inflammation including the recruitment of M1 macrophage and other immune cell involved in innate immunity. Activated immune cells secrete growth factors, chemokines and cytokines that are responsible in the increment in blood vessel permeability, which subsequently lead to the efflux of immune cells into the inflammation site. Aggregation of body fluid and immune cells leads to the formation of edema. In addition, injured blood vessel will activate the blood coagulation cascade which involved in the stimulation, adhesion and accumulation of platelets and eventually formation of hematoma. Afterwards, M2 macrophages recruited will contribute towards the wound healing and tissue repairing process by releasing the pro-inflammation cytokines with the participation of MSCs or progenitor cells. MSCs are responsible for revascularization, tissue regeneration and remodeling through cell differentiation to replace the damaged cell and produce a broad range of growth factors and cytokines