Research Article

Combined administration of platelet rich plasma and autologous bone marrow aspirate concentrate for spinal cord injury: a descriptive case series

https://doi.org/10.4103/

Received: February 23, 2020

Peer review started: February 26, 2020

Accepted: May 21, 2020

Published online: 2020

Joseph A. Shehadi[1, *], Steven M. Elzein[2], Paul Beery[3], M. Chance Spalding[3], Michelle Pershing[4]

Abstract

Administration of platelet rich plasma (PRP) and bone marrow aspirate concentrate (BMAC) has shown some promise in the treatment of neurological conditions; however, there is limited information on combined administration. As such, the purpose of this study was to assess safety and functional outcomes for patients administered combined autologous PRP and BMAC for spinal cord injury (SCI). This retrospective case series included seven patients who received combined treatment of autologous PRP and BMAC via intravenous and intrathecal administration as salvage therapy for SCI. Patients were reviewed for adverse reactions and clinical outcomes using the Oswestry Disability Index (ODI) for up to 1 year, as permitted by availability of follow-up data. Injury levels ranged from C3 through T11, and elapsed time between injury and salvage therapy ranged from 2.4 months to 6.2 years. Post-procedure complications were mild and rare, consisting only of self-limited headache and subjective memory impairment in one patient. Four patients experienced severe disability prior to PRP combined with BMAC injection, as evidenced by high (> 48/100) Oswestry Disability Index scores. Longitudinal Oswestry Disability Index scores for two patients with incomplete SCI at C6 and C7, both of whom had cervical spine injuries, demonstrated a decrease of 28–40% following salvage therapy, representing an improvement from severe to minimal disability. In conclusion, intrathecal/intravenous co-administration of PRP and BMAC resulted in no significant complications and may have had some clinical benefits. Larger clinical studies are needed to further test this method of treatment for patients with SCI who otherwise have limited meaningful treatment options. This study was reviewed and approved by the OhioHealth Institutional Review Board (IRB No. 1204946) on May 16, 2018.

Key Words: bone marrow aspirate concentrate; cell-based therapy; neural regeneration; Oswestry Disability Index; platelet rich plasma; spinal cord injury; stem cells

Chinese Library Classification No. R456; R471; R605

Introduction

Spinal cord injury (SCI) is associated with long-term, permanent disability as a direct result of damage to the nervous structures as well as by complex inflammatory and scar-forming events that reduce regenerative capacity (Kjell and Olson, 2016; Shende and Subedi, 2017). Unlike the peripheral nervous system, the central nervous system (CNS) shows little inherent ability to regenerate due to: 1) the presence of inhibitory factors present in myelin and scar tissue; 2) the intrinsic state of CNS neurons, which show limited upregulation of regeneration-associated genes; and 3) the physical barrier incurred by the presence of scar tissue (Huebner and Strittmatter, 2009). Altogether, the CNS has limited intrinsic ability to regenerate that is further exacerbated by complex post-injury sequelae. Due to these limitations, treatment for SCI has traditionally sought to minimize progressive damage through rapid administration of medications such as corticosteroids to reduce swelling and early surgical decompression of neural elements via fixation and stabilization of the bony spine.

The more recent discovery that CNS neurons may be prompted to regenerate through alteration of the local environment (Benfey and Aguayo, 1982; Huebner and Strittmatter, 2009) has resulted in interest and enthusiasm in regenerative therapies that promote structural and functional recovery through cell and tissue replacement (Abbaszadeh et al., 2018). Cell transplantation in SCI has been explored with a variety of cell types that may minimize tissue loss and support axonal regrowth, most commonly Schwann cells, olfactory ensheathing cells, and progenitor and stem cells (Tsintou et al., 2015; Gabel et al., 2017). These cell transplantation therapies have shown promise in a number of *in vitro* and animal studies; however, there has been only minor observed functional benefit in patients with SCI, and growing evidence suggests that functional recovery following SCI will not be possible with a single therapeutic strategy.

[1]Section of Neurosurgery at OhioHealth Grant Medical Center, Cedar Stem Cell Institute, Columbus, OH, USA; [2]The Ohio State University College of Medicine, Columbus, OH, USA; [3]Division of Trauma and Acute Care Surgery, OhioHealth Grant Medical Center, Columbus, OH, USA; [4]OhioHealth Research Institute, Columbus, OH, USA

***Correspondence to:** Joseph A. Shehadi, MD, joseph@drshehadi.com.

https://orcid.org/0000-0002-9692-371X (Joseph A. Shehadi)

Funding: *This study was funded by Alliance Spine, San Antonio, TX, USA.*

How to cite this article: *Shehadi JA, Elzein SM, Beery P, Spalding MC, Pershing M (2021) Combined administration of platelet rich plasma and autologous bone marrow aspirate concentrate for spinal cord injury: a descriptive case series. Neural Regen Res 16(0):000-000.*

Compared to other cell-based therapies, bone marrow aspirate concentrate (BMAC) may be preferable based on its lower immunogenicity, wide availability, and absence of ethical concerns (Li et al., 2015). BMAC can be a rich source of stem cells (e.g., hematopoietic and mesenchymal stromal cells), other progenitor cells, white blood cells, platelets and a variety of growth factors (Chahla et al., 2016; Sugaya et al., 2018). Precise mechanisms of action for BMAC as a regenerative therapy have not been fully elucidated, but may include the ability of mesenchymal stromal cells (MSCs) within the aspirate to secrete trophic factors and cytokines (Joyce et al., 2010; Dasari et al., 2014). Few studies have been conducted in humans; although intrathecal administration of autologous bone marrow-derived stem cells (BMDCs) every 4 weeks for 12 weeks (Bansal et al., 2016) and administration of BMAC once intrathecally or intralesion (Chhabra et al., 2016) corresponded to improved functional outcomes in small cohorts of patients.

While there is evidence of the effectiveness of bone marrow mesenchymal cells and/or aspirate concentrate for use in SCI (Park et al., 2010), there are limitations associated with cell delivery and integration when BMAC is delivered alone, potentially because of variable ability for the transplanted cells to integrate with tissue in the areas of interest (Kador and Goldberg, 2012; Lee et al., 2015; Zhang et al., 2015; Kim et al., 2018). Recent evidence suggests that regenerative capacity is improved when stem or stromal cells are co-administered with growth and differentiation factors (Steinert et al., 2012) and/or tissue scaffolds. One promising avenue of current research is the co-administration of stem cells with PRP. PRP contains high concentrations of growth factors, which have been shown to promote axonal growth in spinal cord tissues (Takeuchi et al., 2012; Salarinia et al., 2017) and act as a tissue scaffold (Shen et al., 2009; Lubkowska et al., 2012). In fact, co-administration of PRP and BMAC yielded positive healing effects in a rat model of SCI, as evidenced by astrocyte migration and axonal remyelination (Zhao et al., 2013).

Given the evidence that cell-based therapies such as mesenchymal stem cells and BMDCs show better results when combined with PRP in various animal models (Cho et al., 2010; Lian et al., 2014; Hosni Ahmed et al., 2017), we propose that PRP in combination with BMAC may be a viable treatment option for patients with SCI. However, there is a relative paucity in the literature of studies utilizing both PRP and BMAC to treat SCI, and further exploration is warranted. The purpose of this case series is to describe the characteristics of patients that have received PRP combined with BMAC for SCI and to describe the clinical outcomes of these patients, including change in Oswestry Disability Index (ODI) and the occurrence of post-procedure complications.

Subjects and Methods

Study population

This retrospective case series included all patients (n = 7) who received PRP plus BMAC for SCI. All procedures were performed by a single physician (JAS) at Cedar Stem Cell Institute, Columbus, OH, USA, between January 2015 and August 2017. Follow-up data, when available, was obtained through 1 year following the procedure. There are no exclusion criteria; all patients who received PRP plus BMAC for any type of SCI are included in this case series. This study was reviewed and approved by the OhioHealth Institutional Review Board (IRB No. 1204946) on May 16, 2018 with a waiver of the informed consent requirement.

PRP and BMAC preparation

Patients were placed in a lateral position on a clinic table. A large bore intravenous line was started using normal saline at 150 mL/h rate. Then, 60 mL of peripheral blood was drawn from the upper extremity to collect PRP. This blood was then mixed with 10 mL of anticoagulant citrate dextrose solution and processed and centrifuged using the double spin technique and the Cyclone® Concentrating System (Alliance Spine, San Antonio, TX, USA). In brief, this technique consists of a first spin at 2237 × g for 1.5 minutes, followed by aspiration of the plasma supernatant and subsequent second spin of the supernatant at 2237 × g for 5 minutes. This yielded on average approximately 7–8 mL of PRP.

To obtain BMAC, the patient's right posterior iliac crest region was prepared and draped using sterile technique. The skin was anesthetized with an average of 5–10 mL of 2% lidocaine without epinpherine. Next, a Jamshidi™ bone marrow biopsy needle (Ranfac Corporation, Avon, Massachusetts, USA) was introduced through the skin and past subcutaneous tissues into the right posterior iliac crest. A 60-mL locking syringe was used to slowly aspirate bone marrow, turning the needle 90 degrees following every 10 mL of aspirate. This bone marrow aspirate was then processed using the EmCyte® bone marrow concentrating system (EmCyte Corporation, Fort Myers, FL, USA). In brief, this consisted of evenly dividing approximately 50 mL of bone marrow into two 30 mL syringes along with 1000 units/mL of heparin per syringe. This mixture was then filtered and centrifuged at 2008 × g for 10 minutes to yield an average of 17 mL of BMAC. The PRP was mixed with BMACs in a larger sterile syringe, resulting in a ratio of approximately 1:2 (PRP:BMACs).

PRP and BMAC infusion

First, a standard lumbar puncture was performed using sterile technique. Approximately 8 mL of cerebrospinal fluid was removed and discarded. Next, between 7 and 9 mL of the combination PRP and BMAC mixture were slowly injected intrathecally. Then, all of the remaining PRP + BMAC volume was given back to the patient intravenously via the proximal sideport of the intravenous line. Lastly, we allowed for a gentle normal saline bolus of approximately 500 mL given slowly. Patients remained supine for 30–45 minutes following treatment and were monitored in the office for 90 minutes prior to discharge to home. Patients were instructed to call at any time with complications and six of seven patients returned to the treating physician's outpatient office 2 months post-treatment for routine follow-up. One patient was lost to in-person follow-up but did not report any complications to the treating physician. On average, patients received 8–9 mL intrathecally and 12–18 mL intravenously (IV), except for case #2, for whom the IV dose was discarded due to lack of IV access in an office setting.

Study variable collection and outcome assessment

Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at OhioHealth (Harris et al., 2009). REDCap is a secure, web-based application designed and provided by Vanderbilt University, Nashville, Tennessee, USA to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data were copied from Cedar Stem Cell Institute medical records to REDCap by an independent clinical research coordinator from the OhioHealth Research Institute.

Data collected included patient demographics, injury information, types of therapies (surgical and non-surgical) prior to receiving PRP plus BMAC treatment, procedure-related complications at 90 minutes post-treatment and 2 month routine follow-up, and functional outcomes (ODI) for up to 1 year following the procedure when available. ODI is a measure of functional disability, on a scale of 0% to 100%, where higher scores represent higher disability (Fairbank and Pynsent, 2000; Davidson and Keating, 2002). ODI scores were tabulated utilizing a standard survey covering the following ten categories: pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling. Patient responses to each category are assigned a point value from 0 (no disability due to injury) to 5 (maximum disability due to injury), and aggregate scores are divided by the total possible score of 50 to yield a percentage of functional disability. Data were summarized using descriptive statistics (mean, standard deviation, median, range for continuous data and frequency/percentage for categorical data).

Results

Table 1 summarizes demographics and characteristics for the seven SCI patients who underwent PRP plus BMAC treatment, including functional outcomes when available and post-procedure complications.

Table 1 | **Patient demographics, injury characteristics, functional outcomes, and complications**

Demographics			Injury information			
Patient	Age (yr)	Sex	Highest level	Complete (C) or incomplete (I)	Years post-injury	Complications or adverse events
1	46	F	C3	I	6.2	Self-limiting headache; patient-reported memory impairment
2	22	F	C4	C	0.7	No intravenous dose administered due to lack of intravenous access
3	65	M	T11	C	0.5	None
4	33	M	C7	C	2.1	None
5	55	M	C7	I	3.2	None
6	59	M	T4	I	4.9	None
7	26	M	C6	I	0.2	None

Patient 5: Oswestry Disability Index (ODI) scores improved from 60 at time of treatment to 20 at 12 months post-treatment. Patient 7: ODI scores improved from 48 at time of treatment to 20 at 2 months post-treatment. F: Female; M: male.

Patient demographics and injury characteristics

The mean age of patients treated was 43.7 ± 16.9 years (median 46 years; range 22–65 years) and the majority (n = 5) were male. Five patients suffered cervical injuries (C3 to C7) while the remaining two patients had thoracic injuries (T4 or T11). Patients received the PRP plus BMAC treatment between 2.4 months and 6.2 years following the initial injury (mean: 2.5 ± 2.33 years; median: 2.1 years), and all patients had at least two interventions (surgery and physical therapy) prior to undergoing PRP plus BMAC therapy. Prior surgery types included laminectomy, corpectomy, fusion, anterior cervical discectomy and fusion and/or spinal cord stimulator placement. In addition to the above, two patients also engaged in occupational therapy prior to undergoing PRP plus BMAC injections.

Procedure-related side effects and complications

Aside from a single patient who could not receive the IV dose due to lack of venous access, procedure-related complications were limited to a single patient who had a self-limiting headache (1–3 days) and self-reported difficulty with recall.

Clinical outcomes

ODI assessment results showed that with the exception of a single patient with minimal disability, remaining patients had significant functional disability (range: 48% to 68%) prior to PRP plus BMAC treatment.

Two patients (28.6%) provided baseline ODI scores with one or more follow-up evaluations. Both patients improved from "severe disability", where activities of daily living were affected to "minimal disability", where the patient can cope with most daily living activities (**Table 1**). Patient 5, who had a chronic phase C7 injury level, exhibited a 40% improvement in disability score at the 12-month follow-up. Patient 7, who had an acute-phase C6 injury, exhibited a 28% improvement in disability score at 2-month follow-up.

Discussion

In this study, we assessed the safety and effectiveness of a combined mixture of adult autologous PRP and autologous BMAC uniquely administered via both intrathecal and intravenous routes in SCI patients. Our patient population consisted primarily of individuals with chronic SCI who had undergone at least two prior interventions including surgery and physical therapy. In our cohort, one patient could not receive intravenous treatment due to lack of venous access in the office setting. Only one patient reported procedure-related complications, namely a self-limiting headache and subjective recall difficulty. Longitudinal ODI scores were obtained from two of the seven patients and demonstrated improved scores from "severe disability" to "minimal disability" for both.

Traumatic damage to the spinal cord is highly complex at the cellular level. It consists of hypoxia, ischemia, necrosis, excess production of pathological inflammatory factors, the accumulation of excitatory amino acids, the influx of large amounts of calcium ions, and significant amounts of oxygen free radicals and nitric oxide which induce apoptosis of neurons and neuroglia and disturb neurological function. Considering this cascade of events, the challenge of interventional therapies for SCI is to intervene at one or more of these levels to avoid further cellular apoptosis and to promote axonal regeneration and improve patient functionality.

One therapy that has shown promise for SCI rehabilitation in pre-clinical studies is PRP (Takeuchi et al., 2012; Salarinia et al., 2017; Chen et al., 2018). The enhancing effect of PRP is based on the premise that a large number of platelets in PRP release significant quantities of growth factors that aid the healing process. These factors include platelet-derived growth factor, transforming growth-factor beta, insulin-like growth factor, vascular endothelial growth factor, epidermal growth factor, fibroblast growth factor, keratinocyte growth factor, connective tissue growth factor, and interleukin-8 (Fernandes and Yang, 2016). Salarinia et al. (2017) demonstrated benefits of PRP using a rat SCI model simulating blunt trauma and cord contusion. They demonstrated functional motor recovery as well as axonal regeneration following intrathecal PRP injection 24 hours post-lesion. Chen et al. (2018) directly injected PRP into rat spinal cords and examined the effect of PRP on normal and injured spinal cord. In normal spinal cords, PRP induced microglia and astrocyte activation. In the SCI rats, PRP enhanced locomotor recovery and spared white matter, promoted angiogenesis and neuronal regeneration, and modulated blood vessel size. While the exact mechanisms remain elusive, Takeuchi et al. (2012) showed that human PRP promoted axon growth in neonatal rat cerebral cortex and spinal cord co-culture in an insulin-like growth factor-1- and vascular endothelial growth factor-dependent manner.

Another therapy that has gained traction for SCI treatment is transplantation of BMDCs obtained from BMAC. BMDCs have been associated with functional locomotor recovery, preserved axons, increased myelin sparing, reduced scar tissue formation (Nakajima et al., 2012), preserved spinal ultrastructure and hind limb motor recovery (Karaoz et al., 2012), and reduced inflammatory reaction (Park et al., 2005) in rat models of spinal cord contusion. In clinical trials, both the safety of autologous BMDC treatment (Callera and do Nascimento, 2006; Yoon et al., 2007) and capacity for functional improvement (Park et al., 2005; Dai et al., 2013) in SCI patients have been demonstrated. While it is known that bone marrow-derived MSCs possess tropism for damaged tissue sites, including in chronic SCI patients (Callera and de Melo, 2007), the exact mechanisms by ~~with~~ BMDC promote healing from SCI is unknown and may lie within spinal cord neuroneogenesis

(Corti et al., 2002).

One unique aspect of the present study is the combination treatment of both PRP and autologous BMAC for SCI patients. While PRP and BMAC have been proven safe and in many cases effective in treating SCI in preclinical and clinical models, their synergistic effects are much less studied. Positive synergistic effects of PRP combined with BMAC treatment have been demonstrated via improved bone healing in distraction osteogenesis of the tibia (Lee et al., 2014), rehabilitation of rotator cuff injury (Liu et al., 2019), and facial nerve repair in an acute nerve injury model (Cho et al., 2010). In a rat model of spinal cord hemisection, Zhao et al. (2013) demonstrated that a combination of PRP scaffolds with brain derived neurotrophic factor- overexpressing BMDCs resulted in a synergistic effect promoting astrocyte migration and axonal remyelination. Ammar et al. (2017) utilized a combination of hematopoietic stem cells and PRP along with a fibrin coating in SCI patients. This study demonstrated motor and objective sensory improvement in one patient, subjective sensory improvement in two other patients, and no improvement in one patient who received combination treatment. Of note, none of the patients demonstrated adverse effects and MRI studies proved non-migration of the inserted scaffolds 2–3 years following treatment. While interesting, this study drew BMDCs from peripheral blood rather than bone marrow itself, likely resulting in a substantial proportion of hematopoietic stem cells with controversial neuronal differentiation capability as opposed to mesenchymal stem cells with the proven capability to mature into neurons (Ullah et al., 2015). Additionally, this study involved heavily invasive treatment methods including laminectomy and dural- and spinal cord- dissection under general anesthesia.

Another unique aspect of the current study is the multi-focal administration of PRP plus BMAC therapy to SCI patients. In our study, PRP plus BMAC combination treatment was administered both intrathecally via lumbar puncture and intravenously for all patients except one who lacked optimal intravenous access. In addition to avoiding injection directly into the SCI site, which may potentiate previous damage, this unique multi-focal treatment method allows for multiple avenues of regeneration and potentially bypasses obstacles associated with either intrathecal or intravenous administration in any one particular patient. Syková et al. (2006) compared intra-arterial versus intravenous administration of bone marrow cells in subacute- and chronic-SCI patients, noting partial improvement in sensory and motor impairment scores and evoked potentials in all four subacute SCI patients who received intra-arterial injection and in one out of four who received intravenous injection. While their group concluded that implantation of bone marrow cells intra-arterially or intravenously was safe and without complications, conclusions on functional improvement as a result of the treatment were unable to be drawn. Geffner et al. (2008) demonstrated that administration of bone marrow stem cells into acute and chronic SCI patients via multiple routes, including simultaneous administration directly into the spinal cord, directly into the spinal canal, and intravenously was safe, feasible, and had the capability to improve quality of life scores for SCI patients. In their cohort of 25 SCI patients with 3-month comprehensive follow-up, while most patients avoided adverse events, they do note transient lack of erection or ejaculation in four patients, sweating on one half of the body in two patients, and spinal cord canal fistula in one patient.

One potential limitation of the current study lies in the number of patients enrolled. Seven total SCI patients, ranging from 2 months to 6.2 years post-injury, were treated under our unique treatment protocol. This study is also limited due to loss of regular patient follow-up post-treatment, which limits our ability to make inferences about long-term changes in sensory or motor impairment and overall functional recovery. Of the seven patients treated, immediate adverse events were noted in only one patient and were mild – a self-limiting headache and patient-reported memory impairment. Patients were monitored for an average of 90 minutes post-treatment, during which time the other six reported no complications. Although not significant enough to draw conclusions, one patient's ODI score improved from 60 at time of treatment to 20 at 12 months post-treatment, while another patient's improved from 48 at time of treatment to 20 at 2 months post-treatment. Future studies involving more patients and regular, uninterrupted follow-up will be necessary in order to further determine the safety, feasibility, and efficacy of combined intrathecal and intravenous PRP plus BMAC treatment for SCI.

Conclusions

While PRP and BMAC are commercially available and considered safe and effective for numerous medical conditions, they are not yet United States Food and Drug Administration approved for SCI. Through our preliminary investigations, a combination treatment of PRP and BMAC appears to be safe and has the potential additive benefit of stem cells from bone marrow combined with the more ideal milieu of PRP, which is known to have potent growth hormones and cytokines. This therapeutic combination shows great potential for recovery from SCI and further studies are warranted to evaluate this cutting-edge treatment modality.

Author contributions: *Study design: JAS, PB, MCS, MP; data analysis: MP, SME. All authors approved the final version of this study and contributed to the preparation of the manuscript.*

Conflicts of interest: *Dr. Shehadi's work has been funded by Alliance Spine, the manufacturer of the kits utilized for the patients described in this case series. He has also consulted for Alliance Spine and received compensation. These conflicts of interest were minimized by OhioHealth Research Institute, which provided independent personnel for data collection and analysis. Dr. Beery, Dr. Spalding, Dr. Pershing, and Mr. Elzein declare no potential conflict of interest.*

Financial support: *This study was funded by Alliance Spine, San Antonio, TX, USA. The funding body played no role in the study design, in the collection, analysis and interpretation of data, in the writing of the paper, and in the decision to submit the paper for publication.*

Institutional review board statement: *The study was approved by the OhioHealth Institutional Review Board (IRB No. 1204946) on May 16, 2018 with a waiver of the informed consent requirement.*

Declaration of patient consent: *This study is a retrospective case series, for which the informed consent requirement is waived by the institutional review board.*

Reporting statement: *This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.*

Biostatistics statement: *The statistical methods of this study were reviewed by the biostatistician of OhioHealth Research Institute, USA.*

Copyright license agreement: *The Copyright License Agreement has been signed by all authors before publication.*

Data sharing statement: *De-identified individual participant data that underlie the results reported in this article will be available immediately after study publication through 3 years to anyone who wishes to access the data. De-identified data will be stored by the OhioHealth Research Institute for 3 years following publication, then it will be destroyed per institutional policy. If requested, study protocols and outputs of statistical analysis will be available. All data sharing will occur following execution of data sharing agreements as required by OhioHealth Research Institute.*

Plagiarism check: *Checked twice by iThenticate.*

Peer review: *Externally peer reviewed.*

References

Abbaszadeh HA, Niknazar S, Darabi S, Ahmady Roozbahany N, Noori-Zadeh A, Ghoreishi SK, Khoramgah MS, Sadeghi Y (2018) Stem cell transplantation and functional recovery after spinal cord injury: a systematic review and meta-analysis. Anat Cell Biol 51:180-88.

Ammar AS, Osman Y, Hendam AT, Hasen MA, Al Fubaish FA, Al Nujaidi DY, Al Abbas FM (2017) A method for reconstruction of severely damaged spinal cord using autologous hematopoietic stem cells and platelet-rich protein as a biological scaffold. Asian J Neurosurg 12:681-690

Bansal H, Verma P, Agrawal A, Leon J, Sundell IB, Koka PS (2016) Autologous bone marrow-derived stem cells in spinal cord injury. J Stem Cells 11:51-61.

Benfey M, Aguayo AJ (1982) Extensive elongation of axons from rat brain into peripheral nerve grafts. Nature 296:150-152.

Callera F, de Melo CM (2007) Magnetic resonance tracking of magnetically labeled autologous bone marrow CD34+ cells transplanted into the spinal cord via lumbar puncture technique in patients with chronic spinal cord injury: CD34+ cells' migration into the injured site. Stem Cells Dev 16:461-466.

Callera F, do Nascimento RX (2006) Delivery of autologous bone marrow precursor cells into the spinal cord via lumbar puncture technique in patients with spinal cord injury: a preliminary safety study. Exp Hematol 34:130-131.

Chahla J, Dean CS, Moatshe G, Pascual-Garrido C, Serra Cruz R, LaPrade RF (2016) Concentrated bone marrow aspirate for the treatment of chondral injuries and osteoarthritis of the knee: a systematic review of outcomes. Orthop J Sports Med 13:2325967115625481.

Chen NF, Sung CS, Wen ZH, Chen CH, Feng CW, Hung HC, Yang SN, Tsui KH, Chen WF (2018) Therapeutic effect of platelet-rich plasma in rat spinal cord injuries. Front Neurosci 12:252

Chhabra HS, Sarda K, Arora M, Sharawat R, Singh V, Nanda A, Sangodimath GM, Tandon V (2016) Autologous bone marrow cell transplantaion in acute spinal cord injury- an Indian pilot study. Spinal Cord 54:57-64.

Cho HH, Jang S, Lee SC, Jeong HS, Park JS, Han JY, Lee KH, Cho YB (2010) Effect of neural-induced mesenchymal stem cells and platelet-rich plasma on facial nerve regeneration in an acute nerve injury model. Laryngoscope 120:907-913.

Corti S, Locatelli F, Donadoni C, Strazzer S, Salani S, Del Bo R, Caccialanza M, Bresnolin N, Scarlato G, Comi GP (2002) Neuroectodermal and microglial differentiation of bone marrow cells in the mouse spinal cord and sensory ganglia. J Neurosci Res 15:721-733.

Dai G, Liu X, Zhang Z, Yang Z, Dai Y, Xu R (2013) Transplantation of autologous bone marrow mesenchymal stem cells in the treatment of complete and chronic cervical spinal cord injury. Brain Res 1533:73-79.

Dasari VR, Veeravalli KK, Kinh DH (2014) Mesenchymal stem cells in the treatment of spinal cord injuries: A review. World J Stem Cells 6:120-133.

Davidson M, Keating JL (2002) A comparison of five low back disability questionnaires: reliability and responsiveness. Phys Ther 82:8-24.

Fairbank JC, Pynsent PB (2000) The Oswestry Disability Index. Spine 15:2940-2952.

Fernandes G, Yang S (2016) Application of platelet-rich plasma with stem cells in bone and periodontal tissue engineering. Bone Res 13:16036

Gabel BC, Curtis EI, Marsala M, Ciacci JD (2017) A review of stem cell therapy for spinal cord injury: Large animal models and the frontier in humans. World Neurosurg 98:438-443.

Geffner LF, Santacruz P, Iurieta M, Flor L, Maldonado B, Auad AH, Montenegro X, Gonzalez R, Silva F (2008) Administration of autologous bone marrow stem cells into spinal cord injury patients via multiple routes is safe and improves their quality of life: comprehensive case studies. Cell Transplant 17:1277-1293.

Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG (2009) Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42:377-381.

Hosni Ahmed H, Rashed LA, Mahfouz S, Elsayed Hussein R, Alkaffas M, Mostafa S, Abusree A (2017) Can mesenchymal stem cells pretreated with platelet-rich plasma modulate tissue remodeling in a rat with burned skin? Biochem Cell Biol 95:537-548.

Huebner EA, Strittmatter SM (2009) Axon regeneration in the peripheral and central nervous systems. Results Probl Cell Differ 48:339-351.

Joyce N, Annett G, Wirthlin L, Olson S, Bauer G, Nolta JA (2010) mesenchymal stem cells for the treatment of neurodegenerative disease. Regen Med 5:933-946.

Kador KE, Goldberg JL (2012) Scaffolds and stem cells: delivery of cell transplants for retinal degenerations. Expert Rev Ophthalmol 7:459-470.

Karaoz E, Kabatas S, Suruksu G, Okcu A, Subasi C, Ay B, Msluman M, Civelek E (2012) Reduction of lesion in injured rat spinal cord and partial functional recovery of motility after bone marrow derived mesenchymal stem cell transplantation. Turk Neurosurg 22:207-217.

Kim SJ, Kim EK, Kim SJ, Song DH (2018) Effects of bone marrow aspirate concentrate and platelet-rich plasma on patients with partial tear of the rotator cuff tendon. J Orthop Surg Res 13:1. Kjell J, Olson L (2016) Rat models of spinal cord injury: from pathology to potential therapies. Dis Model Mech 1:1125-1137.

Lee DH, Ryu KJ, Kim JW, Kang KC, Choi YR (2014) bone marrow aspirate concentrate and platelet-rich plasma enhanced bone healing in distraction osteogenesis of the tibia. Clin Orthop Relat Res 472:3789-3797.

Lee S, Choi E, Cha MJ, Hwang KC (2015) Cell adhesion and long-term survival of transplanted mesenchymal stem cells: a prerequisite for cell therapy. Oxid Med Cell Longev 2015:632902.

Li XC, Zhong CF, Deng GB, Liang RW, Huang CM (2015) efficacy and safety of bone marrow-derived cell transplantation for spinal cord injury: a systematic review and meta-analysis of clinical trials. Clin Transplant 29:786-795.

Lian Z, Yin X, Li H, Jia L, He X, Yan Y, Liu N, Wan K, Li X, Lin S (2014) Synergistic effect of bone marrow-derived mesenchymal stem cells and platelet-rich plasma in streptozotocin-induced diabetic rats. Ann Dermatol 26:1-10.

Liu F, Meng Q, Yin H, Yan Z (2019) Stem cells in rotator cuff injuries and reconstructions: A systematic review and meta-analysis. Curr Stem Cell Res Ther 14:683-697.

Lubkowska A, Dolegowska B, Banfi G (2012) Growth factor content in PRP and their applicability in medicine. J Biol Regul Homeost Agents 26:3S-22S.

Nakajima H, Uchida K, Guerrero AR, Watanabe S, Sugita D, Takeura N, Yoshida A, Long G, Wright KT, Johnson We, Baba H (2012) Transplantation of mesenchymal stem cells promotes an alternative pathway of macrophage activation and functional recovery after spinal cord injury. J Neurotrauma 29:1614-1625.

Park HC, Shim YS, Ha Y, Yoon SH, Park SR, Choi BH, Park HS (2005) Treatment of complete spinal cord injury patients by autologous bone marrow cell transplantation and administration of granulocyte-macrophage colony stimulating factor. Tissue Eng 11:913-922.

Park WB, Kim SY, Lee SH, Kim HW, Park JS, Hyun JK (2010) The effect of mesenchymal stem cell transplantation on the recovery of bladder and hindlimb function after spinal cord contusion in rats. BMC Neurosci 11:119.

Salarinia R, Sadeghnia HR, Alamdari DH, Hoseini SJ, Mafinezhad A, Hosseini M (2017) Platelet rich plasma: Effective treatment for repairing of spinal cord injury in rat. Acta Orthop Traumatol Turc 51:254-257.

Shen YX, Fan ZH, Zhao JG, Zhang P (2009) The application of platelet-rich plasma may be a novel treatment for central nervous system diseases. Med Hypotheses 73:1038-1040.

Shende P, Subedi M (2017) Pathophysiology, mechanisms and applications of mesenchymal stem cells for the treatment of spinal cord injury. Biomed Pharmacother 91:693-706.

Steinert AF, Rackwitz L, Gilbert F, Nöth U, Tuan RS (2012) Concise review: the clinical application of mesenchymal stem cells for musculoskeletal regeneration: current status and perspectives. Stem Cells Transl Med 1:237-247.

Sugaya H, Yoshioka T, Kato T, Taniguchi Y, Kumagai H, Hyodo K, Ohneda O, Yamazaki M, Mishima H (2018) Comparative analysis of cellular and growth factor composition in bone marrow aspirate concentrate and platelet-rich plasma. Bone Marrow Res 2018:1549826.

Syková E, Jendelová P, Urdziková L, Lesný P, Hejcl A (2006) Bone marrow stem cells and polymer hydrogels--two strategies for spinal cord injury repair. Cell Mol Neurobiol 26:1113-1129.

Takeuchi M, Kamei N, Shinomiya R, Sunagawa T, Suzuki O, Kamoda H, Ohtori S, Ochi M (2012) Human platelet-rich plasma promotes axon growth in brain-spinal cord coculture. Neuroreport 23:712-716.

Tsintou M, Dalamagkas K, Seifalian AM (2015) Advances in regenerative therapies for spinal cord injury: A biomaterials approach. Neural Regen Res 10:726-742.

Ullah I, Subbarao RB, Rho GJ (2015) Human mesenchymal stem cells- current trends and future prospective. Biosci Rep 35:e00191.

Yoon SH, Shim YS, Park YH, Chung JK, Nam JH, Kim MO, Park HC, Park SR, Min B-H, Kim EY, Choi BH, Park H, Ha Y (2017) Complete spinal cord injury treatment using autologous bone marrow cell transplantation and bone marrow stimulation with granulocyte macrophage-colony stimulating factor: Phase I/II clinical trial. Stem Cells 25:2066-2073.

Zhang J, Huang X, Wang H, Liu X, Zhang T, Want Y, Hu D (2015) The challenges and promises of allogeneic mesenchymal stem cells for use as a cell-based therapy. Stem Cell Res Ther 6:234.

Zhao T, Yan W, Xu K, Qi Y, Dai X, Shi Z (2013) Combined treatment with platelet-rich plasma and brain-derived neurotrophic factor-overexpressing bone marrow stromal cells supports axonal remyelination in a rat spinal cord hemi-section model. Cytotherapy 15:792-804.

C-Editors: Zhao M, Li CH; T-Editor: Jia Y