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# Stem Cell Therapy As A Regenerative Approach In Veterinary Medicine

Duygu DALĞIN Yücel MERAL

*Ondokuz Mayıs University, Faculty of Veterinary Medicine, Department of Internal Medicine, Samsun, Turkey*

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**SUMMARY**

Stem cells are promising alternatives in chronic diseases of animals as well as humans. Stem cells has two differentiating characteristics; First, they are unspecilized cells with the self renewing capacity by cell division, even after long periods of inactivity. Second, they differentiate to tissue or organ spesific cells with speciliazed functions, under physiologic or culture conditions. Stem cells provide the potential for many outstanding subjects such as gene targeting, cloning, chimera production and transgenic animal formation. The ability of stem cells to differentiate to 200 different cell types in the organism places them to a major step among theraupetic agents. Literature establishes that stem cell therapy is a feasible regenerative alternative. Several companies in Turkey supplies safe and licensed products. Among the stem cells, those with the best chance of therapeutic success are the mesentheric stem cells (isolated from bone marrow or adipose tissue), due to their ability to promote tissue repair, activation of paracrine factors, immunomodulation, and perception of the cell homing signaling. These cells are predominantly preferred in pets for bone diseases, tendons and cartilage, muscles, and other tissues. Stem cell therapy must be more prevalantly used in companion animal medicine, certainly by the skilled practitioners and standartized and licenced material. This review summarizes the current literature and endications of stem cell therapy in veterinary medicine.

***Key Words:*** *Veterinary medicine, Regenerative Therapy, Stem cell*

**ÖZET**

**Veteriner Hekimlikte Rejeneratif Tedavi Yaklaşımı Olarak Kök Hücre Tedavisi**

Kök hücreler beşeri hekimlikte olduğu kadar veteriner hekimlikte de kronik hastalıkların tedavisi açısından umut verici bir alternatifir. Kök hücrelerin iki önemli özelliği bulunur; ilki uzun inaktivite dönemlerinden sonra bile hücre bölünmesi yoluyla öz yenileme kapasitesine sahip özelleşmemiş hücrelerdir ve ikincisi fizyolojik veya kültür şartlarında farklı organ ve doku sistemlerine ait hücre dizilerine dönüşebilirler. Kök hücreler, gen hedefleme, klonlama, kimera üretimi ve transgenik hayvan üretimi gibi pek çok ilgi çekici konu açısından potansiyel oluştururlar. Kök hücrelerin organizmada 200'den fazla hücreye dönüşebilme kabiliyeti, terapötik ajanlar arasında önemli bir yer almasını sağlar. Literatür kök hücre tedavinsin uygulanabilir bir rejeneratif alternatif olduğunu ortaya koymaktadır. Türkiye'de birkaç şirket güvenli ve ruhsatlı ürünler arz etmektedir. Kök hücre tipleri arasında doku tamiri kapasitesi, parakrin faktör aktivasyonu, immunmodülasyon gibi faktörler baz alınarak terapötik başarı şansı en yüksek olanı mezenterik kök hücreler (kemik iliği veya yağ doku kökenli) olarak belirlenmiştir. Bu hücreler petlerin kemik, tendon ve kıkırdak hasarları ve diğer doku hastalıklarında en sık tercih edilen tiptir. Kök hücre tedavisi, elbette eğitimli personel ve ruhsatlı ürünler kullanılarak küçük hayvan hekimliğinde daha yaygın olarak yer almalıdır. Bu derlemede güncel literatür ve veteriner hekimlikte kök hücre tedavi endikasyonları özetlenmiştir.

***Anahtar Kelimeler:*** *Veteriner hekimlik, Rejeneratij Tedavi, Kök hücre*

## INTRODUCTION

Stem cells are promising alternatives in chronic diseases of animals as well as humans. Stem cells has two differentiating characteristics (Teshager et al. 2014); First, they are unspecilized cells with the self renewing capacity by cell division, even after long periods of inactivity. Second, they differentiate to tissue or organ spesific cells with speciliazed functions, under physiologic or culture conditions. Stem cells mainly characterized as adult and embriyonic derived cells, one originate from adult cells and the other embriyonic cells (Stoltz et al. 2015). Adult derived stem cells constitues system repair by tissue regeneration while, embriyonic stem cells differentiate to the cells of the organ they localize (Boiani and Scholer 2005).

Stem cells provide the potential for many outstanding subjects such as gene targeting, cloning, chimera production and transgenic animal formation (Saito et al.

Corresponding author: Duygu DALĞIN
*Ondokuz Mayıs Univ., Veteriner Fak., Ic Hastalıkları AD, Samsun, Turkey* *e-mail: duyguc@omu.edu.tr*

2001). The ability of stem cells to differentiate to 200 different cell types in the organism places them to a major step among theraupetic agents (Zubko and Frishman 2009; Stoltz et al. 2015). Currently, stem cell research is the most widespread performed preclinic study area for the therapy of cell based disorders. Many researchers report about the basic and general characteristics of mesenchimal stem cells (Ribitsch et al. 2010; Spencer et al. 2011). These studies are not only limited by laboratory, but also performed routinely by many practitioners. The most popular of them, despite the controversies by some researchers, is stem cell therapy in orthopedic disorders of horses. Latest studies report that basic data on the subject are satisfactory and many studies on laboratory, pet and farm animals based on the present data are available in MEDLINE ve Google scholar web (Choi et al. 2009; Koch et al. 2009; Frisbie and Smith 2010). This review summarizes the current status of stem cell therapies in veterinary medicine.

### Stem Cell Sources

Stem cells are classified as embriyonic stem cells and adult stem cells, based on the tissue they are derived. The non-rigid and form changing characteristics of differentiated stem cells may result from one cell type as well as many cell types (Ramakrishna et al. 2011).

Totipotent stem cells may differentiate from 3 germ layers (ectoderm, mesoderm, endoderm) with placenta (Ramakrishna et al. 2011; Spencer et al. 2011). Similarly, pluripotent stem celly may differentiate from 3 germ layers, but except placenta. Multipotent stem cells differentiate from many cell types in a spesific tissue, while unipotent cells may only differentiate from a single cell type. First successfull stem cell isolation was derived from mouse as mouse embriyonic stem cell (ESCs) and following satisfactory results were obtained with hamster, minc, rabbit, rat, monkey, marmoset, chicken, human, baboon, dog, cat, horse, pig, cattle, sheep, goat and buffalo (Ribitsch et al. 2010). Adult stem cells has various types such as haemopoetic stem cells, mesenchimal stem cells, neural stem cells, skin stem cells, retinal stem cells (Markoski 2016). Mesenchimal stem cells (MSCs), may be isolated from bone marrow, adipose tissue, umbilical cord blood (UCB), amniotic liquid, placenta, dental pulpa, tendons, sinovial membranes and skeletal muscle (Jiang et al. 2002; Markoski 2016). Stem cells has the ability to differentiate to fibroblasts, muscle, bone, tendon, ligament and adipose tissue cells (Appasani and Raghu 2011). First Friedenstein et al. (1970), had succeeded to isolate these stem cells from murine bone marrow in colonies. Later, Caplan (1991) iniatially named these cells as mesenchimal stem cells (MSCs). MSC's were isolated from human, rat, mouse, dog, cat, pig, horse, sheep, goat and cattle, and are the most challenging instruments in regenerative therapy with their high ex-vivo development and colonizing ability.

## STEM CELLS IN VETERINARY REGENERATIVE MEDICINE

Stem cell therapy application is preferred locally, as systemic administrations will almost certainly will result with accumulations in capillary beds and emboli (Deak et al. 2010; Orabi et al., 2014). Source of stem cells for transplantation may be the same animal (autologous), same species (allogenic) or a different species (xenogenic) (Gade et al. 2012). Latest studies reveal that mesenchimal and embriyonic stem cell therapies has a wide endication spectrum such as spinal cord damages, bone-cartilage and cardiovascular repairs Deak et al. 2010; Garbern and Lee 2013). First allogenic stem cell greft in humans was performed in 1968 in USA using donor bone marrow (Bach et al. 1968). From those days, many invitro stem cell studies were done and clinical utilization of stem cells became prevalent. Today stem cells are standartized and are subject to the standarts of International Stem Cell Therapy Organization (ISCT) (Dominici et al. 2006). Mesenchimal stem cells used in routin clinical cases or in experimental manner are obtained from bone marrow or adipose tissue. In veterinary medicine we have limited knowledge on stem cell therapy in chronic disorders, except few studies in dog, horse, goat and cattle. Some companies such as Vetstem, Medistem and Histostem produce autologous, allogenic or xenogenic stem cells on order to use in orthopedic and other injuries.

### Cartilage Defects

Mouse embriyonic stem cells (AB2.2 or CCE cells), completely repaired the damage in mouses with experimentally induced cartilage defects in patellar sulcus in 8 weeks (Wakitani et al. 2004). Cartilization of the growing cells for repair reveals that chondrogenic origined embriyonic stem cells (ESC's) in osteochondral defects repair and in complete layer osteochondural defects repair as in SD rats patellar sulcus, ESC's embedded in collagen gel must be used. In a study, 35 stem cell reminiscent colony derived from 40 stage spesific antigen (SSEAs) positive sheep embryo were divided into two groups, embedded in fibrin and were transplanted in 14 sheeps' osteochondral defekts in medial femoral chondilus (Dattena et al. 2009). Same cells were applied to cartilage defected sheep and reported a better tissue regeneration and organization and concluded that cartilage repair with MSC's in adult animals delay the recovery. Repair of articular cartilage defects with polimerised (Solchaga et al. 1999), Tip I collagene (Wakitani et al. 1994) and polilactic asid mezenchimal stem cells gives better results. A rabbit model was used in the therapy of infrapatellar adipose pad osteoarthritis with mezenchimal stem cells (Toghraie et al. 2011). Goat osteoarthritis model demonstrated the regenerative effect in maniscal tissue and delay of progressive damage with MSC's (Murphy et al. 2003). Another study reported the therapy of chronic osteoarthritis in 21 dogs with autologous adipose derived (Black et al. 2007). Cartilage defects in knee joint in 10 dogs were repaired with canine MSC's embedded in Type I glycosamino glycan (Xiang et al. 2006). Polymers used in cartilage repair delays the recovery. The major obstacle in MSC therapy in cartilage repair is the integration of neocartilago matrix around natural cartilago matrix. Other clinical benefits of MSC therapy of cartilage damages are the convenience of arthroscopic intervention and the facility of cartilage regeneration.

### Wound Repair

In a study on 110 diabetic rats with early stage diabetic wounds, local injection of ESC's around the wound resulted with satisfactory recovery in very short (Lee et al., 2011). Similarly, bone marrow derived MSCs in pressure sores of rats resulted with a fast and successfull recovery (Wu et al. 2007). In addition, favorable results were obtained with autologous bone marrow derived nucleated cells in rabbits burn wounds and corneal alkali wounds (Ye et al. 2006; Oloumi et al. 2008), and with Warton's gel stem cells in goat dermal wounds (Azari et al. 2011).

MSC's also were used experimentally in brain infarcts (Jeong et al. 2005), myocardial infarcts (Garbern and Lee 2013) and aoutoimmune diseases.

### Spinal Damages

Self copying and potential ability of human embriyonic stem cells emerge 8 weeks after implantation with the help of neural precursors immunsupressive neonatal mouse brain (Zhang et al. 2001). Similarly, successfull therapy cases are present in Parkinson rat model without terratoma in 12 weeks (Ben hur et al. 2004). Neuron derived human embriyonic stem cells (hESC) are used in primate and rodent models for the therapy of neuronal damages without tumor formation. Frequently encountered acute spinal damages of cats and dogs results with the loss of myeline sheets responsible for the transmission neural impuls. Limited regeneration capacity of neural tissues requires discovery of advanced therapeutics. Therefore, differentation of stem cells to neurons and acceleration of tissue recovery abilities promise significant clinical success (Dasari et al. 2007). Potential differentiaton ability of stem cells and its ability to integrate to axon pathways nearby neuronal differentation makes it a valuable therapy component. In another study, human umbilical cord (UBC) derived MSC's were transplanted to rats (xenogenic transplantation) and reported that reversion of locomotor functions due to spinal cord injury took only 14 days (Dasari et al. 2007). Similarly, it was reported that allogenic umbilical cord blood derived MSC (UCB-MSC) transplanted dogs walked in two weeks, and also pressure sores because of the bedridden period recovered in a short time (Deng et al. 2006). Clinical efficiency of bone marrow derived MSC's and autologous MSC's were compared in dogs with experimentally induced spinal cord damages and satisfactory results were reported for both (Jung et al. 2009). Acceleration of neuronal transmission and neuronal regeneration were observed in therapy with MSC's. Another result of these studies is the similar success observed with adipose tissue derived stem cells (ADSCs) (Ryu et al. 2009).

### Tendon and Ligament Therapies

Conventional tendon and ligament therapies results with less functional tissues. Therefore stem cell therapy was evaluated for such conditions. Favorable results were reported with the application of collagen gel embedded MSC's to patellar tendons of adult New Zealand rabbits within a month (Awad et al. 1999). The tendons recovered with MSC's were compared with the control groups, and previous characteristics including strength, stress and flexor energy intensity were observed to be regained. In horses, autologous bone derived MSC's are successfully used in superficial tendon therapies (Smith et al. 2003). In 8 horses, tendinitis of superficial digital tendons due to collegenase were treated with ADNC injections (Nixon et al. 2008). Also in race horses, tendinitis are successfully treated with MSC's. In a study with rats (Watanabe et al. 2002) MSC's were applied to ligament wound areas and were differentiated ro fibroblast like cells in 28 days. Research reveal that MSC's treatment in horse ligament damages gives favorable results (Koch et al. 2009; Frisbie and Smith 2010).

### Bone Recovery

MSC's has significant osteogenic differenciations. Autologous stem cell transplantations accelerate bone recovery and regeneration. MSC's provide new bone formation in the transplantation area, nearby new bone formation in the actual bone. In multi fragment bone fractures, MSC's forms powerful connections between onto porous cermic cylinders and thus accelerate the recovery (Kraus and Kirker 2006). Comparisions with the control groups after recovery revealed satisfactory strength. In dogs further studies on combination of hydroxyapatit or chitosan scaffolds with adipose tissue derived autologous MSC's are performed (Lee et al. 2009). Another study reports recovery in critical dimensioned bone defects with allogenic MSC's (Arinzeh et al. 2003).

In large animals, sheep autologous bone marrow MSC's (BMSC) application with hydroxyapatit ceramic (HAC) was reported to be more successfull than HAC alone (Kon et al. 2000). Goat bone marrow derived MSC's resulted in recovery within 8 weeks in multi fragment tibia fracture (Liu et al. 2010). All these studies suggest that MSC's accelerate bone recovery period and the bone forms with previous strength.

### Cardiac Defects

Laflamme et al. (2005), injected differentiated cardiac enriched human embriyonic stem cells (hESC) to atimic rats left ventricular wall and observed cardiomyosit formation in 4 weeks. In this way, hESC formed human myocardial cells in the rat heart. These formed cells were started to be used in permitted studies for human myocardial damages. In another study, injection of mouse embriyonic stem cell (mESC) derived cardiomyosits presented angiogenic effects for 32 weeks (Min et al. 2003). Menard et al. (2005), observed that cardiac derived mouse embriyonic stem cell injection to 18 sheep with experimentally induced miyocardial infact resulted with scar tissue and stem cell colonization in the miyocardial tissue. Similar results were obtained with the large animals supporting the favorable effects on heart regeneration (Garbern and Lee 2013).

### Reproductive Medicine

Although it is not widespread yet, reproductive medicine is another endication area of stem cell therapies (Pukazhenti et al. 2006). Testis xenografting is one relevance and the primary clinical application for testis xenografting would be as a means to preserve the breeding potential of a genetically valuable pre-pubertal male animal (Pukazhenti et al. 2006). Use of stem cell-based approaches in attempts to preserve the germ plasm of threatened species could begin on an opportunistic basis in the form of xenografting of testis tissue obtained quickly after the death of pre-pubertal individuals. Another relevance is spermatogonial stem cell transplantation and the primary clinical uses of SSCT would be to preserve or manipulate the male germline or both (Dobrinski and Travis 2007). This aspect seems to be a focused research area in the future.

## CONCLUSION

In conclusion, literature establishes that stem cell therapy is a feasible regenerative alternative and several companies in Turkey supplies safe and licensed products. Among the stem cells, those with the best chance of therapeutic success are the MSC (isolated from bone marrow or adipose tissue), due to their ability to promote tissue repair, activation of paracrine factors, immunomodulation, and perception of the cell homing signaling (Markoski 2016). These cells are predominantly preferred in pets for bone diseases, tendons and cartilage, muscles, and other tissues. Stem cell therapy must be more prevalantly used in companion animal medicine, certainly by the skilled practitioners and standartized and licenced material.

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