Short Communication

Intra-Articular Injections with Allogeneic Dental Pulp Stem Cells for Chronic Osteoarthritis

Ratikorn Bootcha[1] Jedee Temwichitr[2] Soontaree Petchdee[3*]

Abstract

Stem cell therapies are rapidly gaining attention as a promising tool for tissue regeneration. A variety of stem cell types have been studied as potential candidates to restore the structure and function of damaged organs or tissues. Recent studies have demonstrated the use of stem cells isolated from dental pulp in dentistry and tissue engineering. In our previous studies we have shown the applications of puppy deciduous teeth stem cells (pDSCs) to restore infarcted myocardium and ulceration of the cornea. For this study, our aim was to provide a novel therapeutic application of allogeneic pDSCs in dogs with chronic osteoarthritis of the coxofemoral joints. The method to isolate mesenchymal stem cells derived from dental pulp of dogs and the use of allogeneic puppy deciduous teeth stem cells in osteosrthritis problems were evaluated. Clinical effects of multiple intra-articular injections of pDSCs were investigated on 8 dogs with lameness associated with osteoarthritis (OA). Clinical assessments were collected by interviews and questionnaires. Immediate improvements in clinical scoring in all dogs were seen in 14 days after pDSC injection with no complications. The findings indicated that pDSC treatment considerably helped reduce pain and lameness, improve the quality of life activities and prevent osteoarthritis progression. Multiple Intra-articular injections of pDSCs might be a novel strategy for the treatment of OA in dogs.

Keywords: Osteoarthritis (OA), puppy deciduous teeth stem cells (pDSCs), Intra-articular injection

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Introduction

Osteoarthritis (OA) is one of the most common causes of chronic pain in dogs and is estimated to occur in one out of five adult dogs. OA can occur at any age and in any breed, however large breeds are at risk of developing OA (Noel, 2009). OA is a chronic degenerative joint disease caused by inflammation of articular cartilage, subchondral bone, synovium and fluid of joints (Schulz, 2007; Garvincan et al., 2012). Clinical appearances of OA include pain, lameness, limited mobility of joint, functional loss, and disability. Factors such as mechanical, biochemical, and genetic are all participated in pathogenesis of OA (Chevalier, 1998; Wearing et al., 2006). Osteoarthritis of hip joint and stifle joint are generally seen and are the common causes of joint inflammation in dogs. Diagnosing OA can be done through several different procedures such as orthopedic examinations, radiographic imaging (X-ray), anthrocentesis, and magnetic resonance imaging (MRI). X-ray is the common effective method for diagnosing OA in dogs, but some soft tissues such as tendon cannot be seen on X-rays. MRI established better pictures of soft tissue and cartilage, however it is more expensive than the other tests. Unfortunately, osteoarthritis of stifle joint requires special diagnostic procedures such as joint aspiration and MRI to identify OA.

Non-steroidal anti-inflammatory drugs (NSAIDs) provide the basis of pharmacological treatment of pain from OA in dogs. However, NSAIDs can cause adverse effects such as gastric ulcers, bleeding and abdominal pain (Lamont et al., 2000; Luna et al., 2007; Mansa et al., 2007).

Stem cell therapies, alternatives to other therapeutic strategies, are rapidly emerging as a new treatment for tissue reparation and regeneration in several fields of medicine. A recent study has shown that autologous or allogeneic stem cells including mesenchymal stem cells (MSCs) have the ability to modify and regenerate in several disease processes of the musculoskeletal system (Peeters et al., 2013). MSCs have been used and generally provided good to excellent results without significant adverse consequence for intra-articular transplantation (Moseley et al., 2010). MSCs exist in several tissues such as bone marrow, adipose tissue, umbilical cord and dental tissues. Clinical usage of cell-based therapy can be characterized by their multi-lineage ability and gene expression profile. A previous study reported that MSCs were derived from 4 sources; bone marrow, adipose, umbilical cord and dental tissue. Dental tissue derived MSCs have high proliferative potentials for self-renewal, whereas adipose tissue derived stem cells have the lowest proliferative capacity (Stanko et al., 2013). However, there is a study which showed that bone marrow and adipose tissue derived stem cells had the same capacity for regeneration of the bone (Han et al., 2014). Recent studies have demonstrated several populations of stem cells isolated from dental tissue including pulp of adult teeth, periodontal ligament, and dental follicle. Dental pulp stem cells (DPSCs) and stem cells from human exfoliated deciduous teeth (SHED) represented common mesenchymal stem cell-like properties such as self-renewal and multilineage differentiation. DPSCs and SHED have demonstrated the ability to generate not only dental tissue but also bone tissue (Miura et al., 2003; Nagamura et al., 2009; Lee et al., 2014; Gronthos et al., 2000). Cell-based therapies using SHED have extended to a large number of tissues due to their lineage ability, high degree of plasticity, and stemness (Yamada et al., 2011). A recent study has shown that transplantation of autologous adipose tissue mesenchymal stem cells (AD-MSCs) using force platform analysis showed significant potential in the treatment of lameness associated with severe OA in dogs (Vilar et al., 2013). However, DPSCs have not been studied in veterinary patients with osteoarthritis. In our previous studies, we have reported the uses of canine DPSCs in the infarcted myocardium and the ulceration of the cornea (Petchdee et al., 2014; Pattanapol et al., 2014). The purpose of this study was to determine the efficacy of allogeneic intra-articular puppy deciduous teeth stem cell (pDSC) injection in dogs with chronic OA by means of a clinical trial.

Materials and Methods

Animals: In this study, the clinical effects of intra-articular injection of pDSCs in dogs were characterized by lameness and dogs with painful OA of the coxofemoral joint were evaluated using orthopedic examinations and radiographic imaging. Eight dogs with bilateral coxofemoral joints OA with a minimum duration of 3 months were recruited based on orthopedic examinations to rule out other lameness from neurologic signs. The breeds included Thai Bangkeaw, Golden Retriever, Rottweiler, Siberian husky, Chow Chow, Poodle, Shih Tzu, and cross-breed. Their body weights ranged from 8 to 47 kg. Database of the animals is shown in Table 3.

All dogs were required to have normal or unremarkable hematology and chemistries prior to enrollment. Analgesics, nutraceuticals and alternative treatments, if used, were discontinued for 14 days before enrollment. The dogs were required to be on NSAIDs for at least 14 days before enrollment to keep the same level of drug throughout the study. Each dog demonstrated gait change characteristic of OA, including persistent lameness at walk and trot, pain on manipulation of the affected joint, limited range of motion with pain at less than full range of passive motion, and functional disabilities, including level of stiffness as measured by willingness to walk and run. Clients provided advised consent form prior to enrollment and completed take home questionnaires with pain scores and quality of life questions during the study period. Each dog demonstrated the pretreatment radiographic evidence of degenerative joint disease of grade 2 or higher on the following radiographic (X-ray) scoring.

Radiographic scoring for assessing dogs with osteoarthritis (Takahashi et al., 2004):

0 = Normal
1 = Radiographic evidence of instability, no degenerative change (no osteophytes)
2 = Mild degenerative change (Definite

osteophytes and possible narrowing of joint space)

3 = Moderate degenerative change (Moderate multiple osteophytes, definite narrowing joint space, subchondral sclerosis and possible definition of bone contour)

4 = Severe degenerative change (Large osteophytes, marked narrowing of joint space, severe subchondral sclerosis and definite deformity of bone contour)

Puppy deciduous teeth stem cell (pDSC) preparation: Puppy deciduous teeth from dogs were collected. Teeth surfaces were cleaned and the root was cut to reveal the pulp chamber. Dental pulp tissue was separated using a 18G needle and was digested in collagenase. The cells were removed and suspended in 5 ml Dulbecco's PBS (Gibco, Invitrogen, New York). After centrifugation, the cells were placed onto T25 culture flask and incubated for 4 days in a carbon dioxide incubator maintained at 37°C and 5% CO_2 until cell adhesion as shown in Figure 2. The cells were replaced with fresh DMEM (Gibco, Invitrogen New York) media and were carried until 80% confluency. pDSCs were freshly prepared and stored in sterile tubes, each tube contained $5x10^6$ cells in 1.0 ml of phosphate buffered saline (PBS). pDSCs at passages 3-5 were characterized by fluorescence activated cell sorting analysis (Petchdee et al., 2014) and all injection techniques were performed under sedation and aseptic conditions.

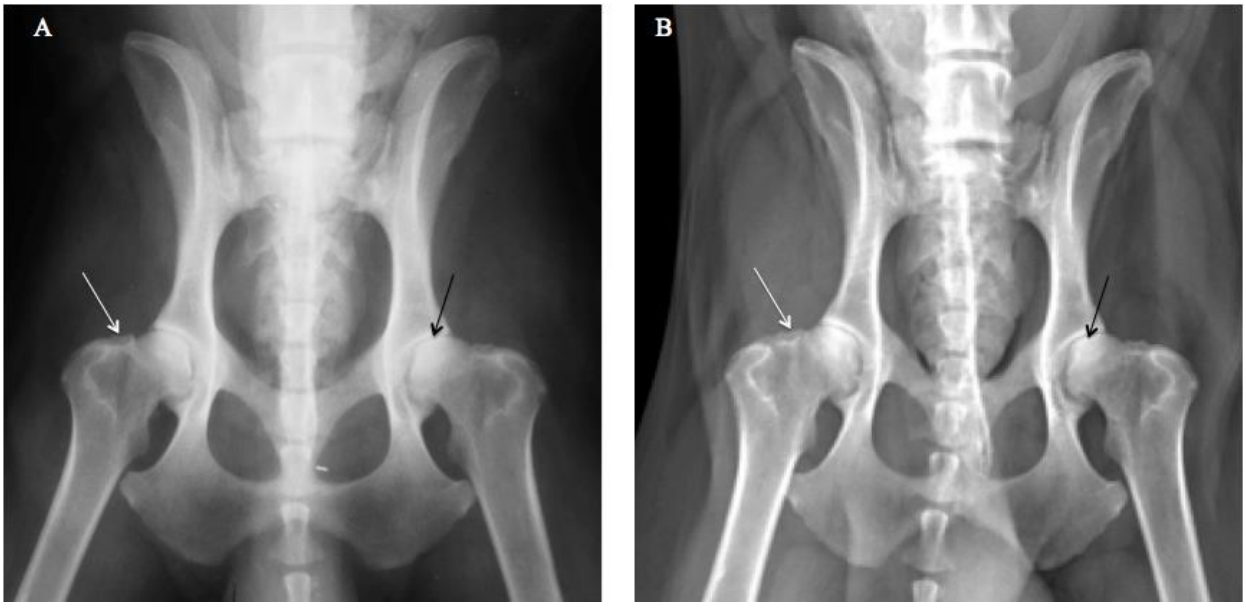

Figure 1 Radiographic findings before pDSC injection in A and after pDSC injection in B presenting subchondral sclerosis (black arrow) and osteophyte formation on distal femur (white arrow)

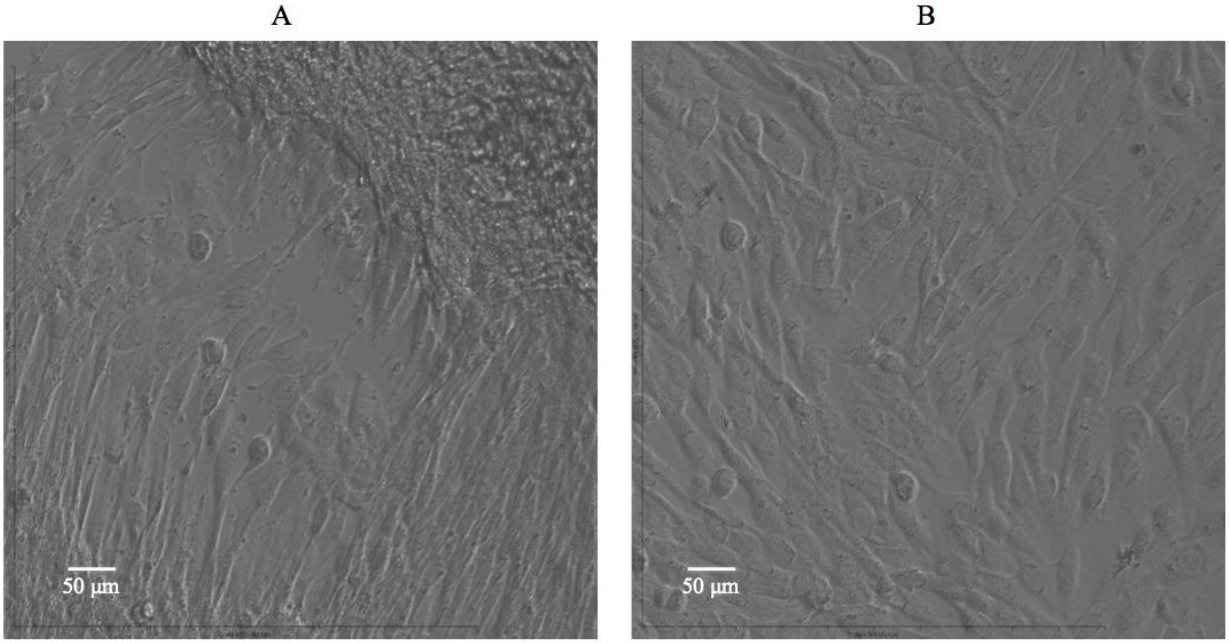

Figure 2 Photomicrograph of puppy deciduous teeth stem cells (pDSCs) isolated from pulp tissue of dog teeth. Cells aligning close to the pulp tissue were shown in primary culture (A) and became semi-confluent in 25 cm^2 flasks in 4-6 days (B).

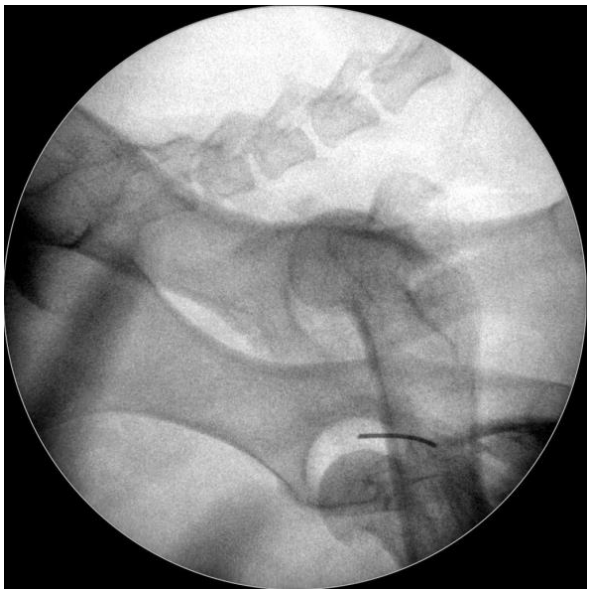

Figure 3 Contrast fluoroscopy showing needle placement that indicates the accuracy of intra-articular injection

***Treatments*:** Each dog received 5x10^6 cells per joint. Intra-articular injection was performed aseptically through conventional arthrocentesis (Taylor, 2007). Dog should be positioned in lateral recumbence with the pelvis parallel to table and procedure was performed under sedation using intravenous Propofol (3-6 mg/kg). All dogs underwent the intra-articular injection with Fluoroscopy guidance to confirm the position of the needle as shown in Figure 3. The hip should be slightly abducted and the femur rotated medially. The greater trochanter served as landmark. The needle was inserted in the dorsal to greater trochanter and direct medio-ventrally towards the femoral head. The second injection of pDSCs was given within 14 days after the first injection.

Evaluation: Clinical outcome measurements were based on veterinary orthopedic examination evaluation using a numerical rating scale based on a standardized questionnaire. Veterinary evaluation included history, physical examination, lameness examination, consisted of joint mobility and notation of pain on manipulation, a modified version of published criteria (Table 2). Owners were also asked to complete a questionnaire translated from Helsinki Chronic Pain Index (HCPI). Baseline results were documented before the dogs received the intra-articular injection. Intra-articular injection of pDSCs was administered at 2-week interval. Follow-up visits were at 14, 30, 60, 90 and 120 days after the injection. The sequence of the study appears in Table 1. All dogs were evaluated by one veterinarian throughout the study.

Statistical analysis: All results were expressed as mean±standard error of the mean (SEM). Statistical analysis was performed with Instat3 (GraphPad Software Inc., USA). Difference between 2 groups was analyzed by a paired *t*-test. A value of $p<0.01$ was considered statistically significant.

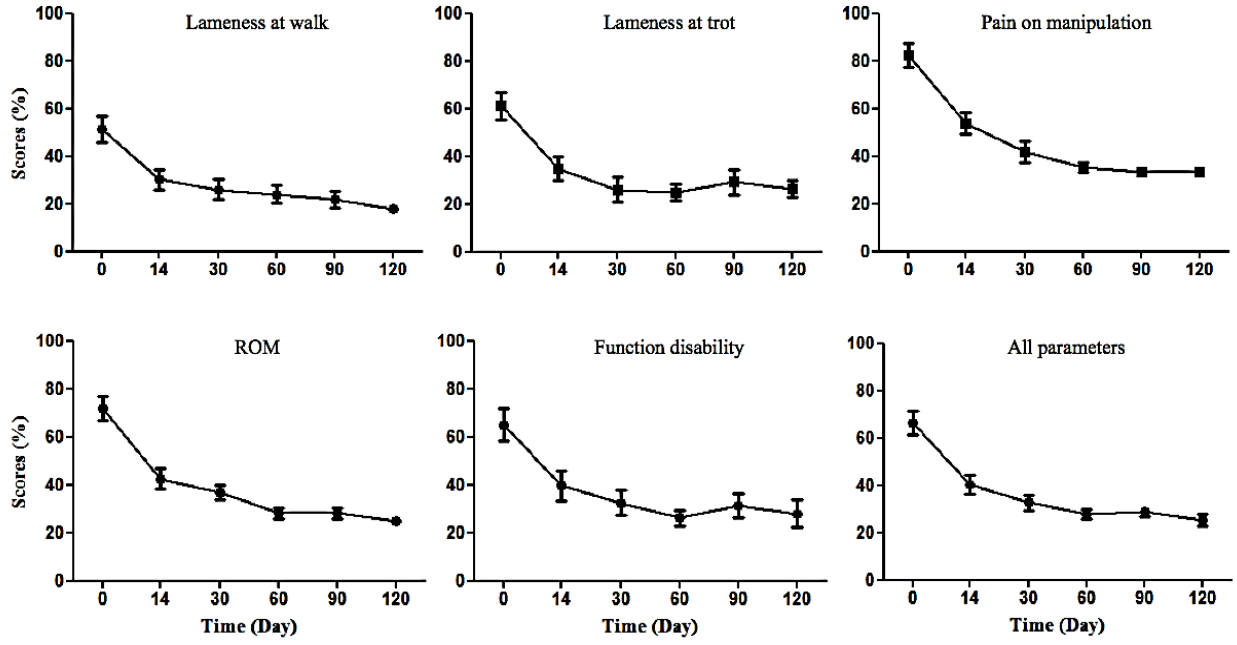

Figure 4 Analysis of percentage (mean±SEM) of lameness at walk, lameness at trot, pain on manipulation, Range of motion (ROM), function disability and all parameters in dogs at pre- and post-injections. Dogs that received multiple intra-articular injections showed improvement of orthopedic scores compared to the baseline

Results and Discussion

Overall dogs with OA of the coxofemoral joint that were treated with multiple intra-articular injections of allogeneic pDSCs demonstrated statistically significant improvement in lameness and functional ability. Our study is the first successful clinical application of allogeneic pDSC therapy in dogs with chronic osteoarthritis. This study provides initial evidences that multiple intra-articular administrations

of allogeneic pDSCs are safe and have the potential to reduce pain, increase affected joint range of motion and improve quality of life. Five dogs completed the study of 120 days. One dog received NSAIDs because of other medical issues. For two dogs, their owners could not continue with the follow-up. There was no other adverse event reported. However, two dogs demonstrated limping and biting at the injection site, but it was resolved within 24-48 hours. X-rays were performed before and after treatment as shown in Figure 1. Radiographic findings of coxofemoral joint osteoarthritis showed changes in subchondral bone and osteophyte formation. Although the radiographic findings did not confirm the positive outcome from the joint morphology, significant reduction in pain without progression was observed after treatment. The results suggest that multiple injections of pDSCs can reduce pain and might prevent the progression of OA. After treatment, the veterinary orthopedic examination scores decreased overtime. Improvement in functions and quality of life were documented. The dogs with OA of the coxofemoral joint expressed a favorable clinical outcome at 120 days after treatment (Table 4). Veterinary assessment showed improvement from baseline of lameness at walk, lameness at trot, pain on manipulation, range of motion and the combined scores for all parameters by 14 days after pDSC injection (Figure 4). Results showed significantly better clinical outcomes such as decreased patient discomfort, increased functional ability, improved aggressive behavior, and improved quality of life. We were not able to include the force plate analysis in our study. However, subjective scoring systems correlated well and can be used as a good tool to assess chronic joint problems and total hip replacement for OA in dogs (Quinn et al., 2007).). Even though the optimal dose has not been confirmed, pain was reduced and the quality of life was improved immediately in 14 days after $5x10^6$ pDSC injection and clinically significant effects were observed for 120 days. In this study, the number of patients was low and included only 8 dogs. Further studies with a control group are needed to confirm these results. In recent studies performed in animal models of OA, a single injection of AD-MSCs into rabbit knee joints with OA showed protection against the development of cartilaginous and meniscal damage. AD-MSC administration inhibited ligament damage and also inhibited the progression of joint destruction (ter Huurne et al., 2012; van Lent, 2013). The immunosuppressive phenotype of AD-MSCs may be motivated by pro-inflammatory cytokines such as prostaglandin E2 (PGE2) released by the synnovium (van Lent, 2013). In our study, multiple of pDSC injections were effective in reducing pain associated with OA and in the treatment of inflammation. pDSCs provide longer-lasting pain relief for dogs with OA (120 days). The results of this study indicate that allogeneic pDSC injection offers profound benefits in dogs suffering from chronic osteoarthritis. The use of pDSCs showed clinical outcomes such as increased functional ability and improved quality of life. Secretions of paracrine and autocrine factors are possibly a mechanism that enhances therapeutic effects. Anti-inflammation effects can be activated through the secretion of tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1) receptor antagonist and prostaglandin E2 (PGE2), which create the negative feedback loop of inflammation (Prockop et al., 2011). Another action of pDSCs is to inhibit the macrophage to produce TGFβ-regulate factors that are important for mediating the formation of osteophyte (Van der Kraan, 2007; Van Lent et al., 2004; Spaggiari, 2013). Our findings suggest that pDSCs can be used as a potential treatment of osteoarthritis and chronic pain in dogs. However, understanding the therapeutic mechanisms of pDSCs requires further studies to support our findings.

Table 1 Clinical trial sequence

	Day 0	Day 14	Day 30	Day 60	Day 90	Day 120
Baseline Examination, Physical Examination	✓					
On-site Evaluation of Veterinarian	✓	✓				
Blood Sample	✓					✓
1st Transplantation	✓					
2nd Transplantation		✓				
Follow-up		✓	✓	✓	✓	✓
Evaluation of Veterinarian		✓	✓	✓	✓	✓

Table 2 Veterinary orthopedic examination assessment scores

	Undetectable	Intermittent	Persistent	Persistent non-weight-bearing	Ambulatory only with assistance	Non-ambulatory
Lameness-walk	1	2	3	4	5	6
Lameness-trot	1	2	3	4	5	6

	No pain	Mild pain (Attempt to withdraw limb)	Severe pain (Immediate limb withdrawal)
Pain on manipulation	1	2	3

	No limitation	Pain only at full range of motion	Pain at less than full range of motion	Pain at any attempt to manipulate joint
Range of motion	1	2	3	4

	Normal activity	Slightly stiff gait, only noticeable on running	Stiff, dog has noticeable difficulty walking or running	Very stiff, dog does not want to walk or run unless coaxed	Dog does not want to walk, must be helped up, and will not run
Functional disability	1	2	3	4	5

Table 3 Database before pDSC injection

Parameters	No.1	No. 2	No.3	No.4
Gender	Male	Female	Female	Female
Age	9	11	6	11
Breed	Thai Bangkaew	Cross Breed	Chow Chow	Golden Retriever
Weight	18.	20	38	32
Lameness at walk	2.5	3	3	3.6
Lameness at trot	3.5	4	3	3.6
Pain on manipulation	2.25	2.25	2.75	3
Range of motion	2.5	2.5	3.25	3
Functional disability	2.75	3.25	3.75	4
Crepitus	+	-	+	+
Radiographic finding score	3	2	4	4
Parameters	No.5	No.6	No.7	No.8
Gender	Female	Male	Female	Female
Age	6	4	6	1
Breed	Poodle	Rottweiler	Shih Tzu	Siberian Husky
Weight	8	47	7	20
Lameness at walk	2	3	5	2.5
Lameness at trot	3	3.25	6	3
Pain on manipulation	2	2.5	3	2
Range of motion	2.5	2.25	4	3
Function disability	2	2.5	5	3
Crepitus	+	+	+	+
Radiographic finding score	3	3	4	3

Table 4 Orthopedic examination scores in dogs with bilateral hip osteoarthritis. Values are mean±SEM, $^{**}p < 0.01$, $^{***}p < 0.001$ compared with baseline.

Parameters	Baseline Mean ± SEM (days)	14	30	60	90	120
Lameness at walk	3.08 ± 0.32	1.81 ± 0.25***	1.56 ± 0.26**	1.44 ± 0.22***	1.31 ± 0.20***	1.08 ± 0.07***
Lameness at trot	3.67 ± 0.36	2.08 ± 0.29***	1.56 ± 0.32**	1.5 ± 0.21***	1.75 ± 0.31***	1.58 ± 0.17**
Pain on manipulation	2.47 ± 0.15	1.61 ± 0.14**	1.25 ± 0.13***	1.06 ± 0.06***	1***	1***
Range of motion (ROM)	2.88 ± 0.20	1.7 ± 0.17**	1.47 ± 0.12**	1.12 ± 0.08***	1.12 ± 0.08***	1**
Functional disability	3.25 ± 0.34	1.98 ± 0.31***	1.63 ± 0.26**	1.31 ± 0.16***	1.56 ± 0.25**	1.4 ± 0.23**

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บทคัดย่อ

การฉีดเซลล์ต้นกำเนิดจากโพรงประสาทฟันเข้าภายในข้อต่อของสุนัขเพื่อรักษาโรคข้อเสื่อมเรื้อรัง

รติกร บุตรชา[1] เจดีย์ เต็มวิจิตร[2] และสุนทรี เพ็ชรดี[3*]

การบำบัดรักษาโรคด้วยเซลล์ต้นกำเนิดได้รับความสนใจเป็นอย่างมากในเวชศาสตร์การฟื้นฟู มีการศึกษาเซลล์ต้นกำเนิดหลายชนิด เนื่องจากการมีคุณสมบัติในการฟื้นฟูโครงสร้างและหน้าที่ของอวัยวะหรือเนื้อเยื่อที่ได้รับความเสียหาย การศึกษาที่ผ่านมากล่าวถึงการใช้เซลล์ต้นกำเนิดที่มีอยู่ในเนื้อเยื่อโพรงประสาทฟันในงานด้านทันตกรรมและวิศวกรรมเนื้อเยื่อ สำหรับการศึกษาของผู้วิจัยก่อนหน้านี้ ผู้วิจัยได้แสดงการใช้เซลล์ต้นกำเนิดจากฟันน้ำนมลูกสุนัข (pDSCs) ในการฟื้นฟูกล้ามเนื้อหัวใจตายและการรักษาแผลที่กระจกตา จุดประสงค์ของการศึกษาในครั้งนี้เพื่อศึกษาการรักษาโรคข้อเสื่อมเรื้อรังของข้อต่อ coxofemoral ในสุนัขด้วยวิธีใหม่ โดยได้ทำการประเมินการ แยกเซลล์ต้นกำเนิดมีเซนไคมอลจากเนื้อเยื่อโพรงประสาทฟันสุนัข และการใช้เซลล์ต้นกำเนิดจากโพรงประสาทฟันน้ำนมของลูกสุนัขแก้ไขปัญหาการเกิดข้อเสื่อม ทำการรักษาโดยการฉีดเซลล์ต้นกำเนิด pDSCs เข้าภายในข้อต่อของสุนัข 8 ตัวที่มีความบกพร่องทางการเดินซึ่งมีสาเหตุมาจากการเกิดภาวะข้อเสื่อม (OA) ผลการรักษาประเมินจากคะแนนจากการสัมภาษณ์และแบบสอบถาม ซึ่งพบว่า การฉีด pDSCs เข้าภายในข้อต่อของสุนัขได้ผลดี และสามารถเห็นผลการรักษาได้ทันทีภายหลังการฉีด 14 วันโดยไม่เกิดภาวะแทรกซ้อน ผลการวิจัยแสดงให้เห็นว่า pDSCs สามารถลดอาการปวด ช่วยให้สุนัขที่มีภาวะข้อเสื่อมเรื้อรังมีคุณภาพชีวิตที่ดีขึ้น และป้องกันการลุกลามของการเกิดข้อเสื่อม ดังนั้น pDSCs น่าจะเป็นกลยุทธ์ใหม่ในการบำบัดรักษาโรคข้อเสื่อมในสุนัขได้

คำสำคัญ: โรคข้อเสื่อม เซลล์ต้นกำเนิดจากฟันน้ำนมลูกสุนัข การฉีดยาเข้าข้อ

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