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ORIGINAL ARTICLE

Autologous point-of-care stromal vascular fraction transplantation in dogs with advanced osteoarthritis of the knee and hip joints

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Objective The aim of the study was to assess lameness in dogs with advanced osteoarthritis of the hip and knee joints after a single autologous point-of-care transplantation of the Stromal Vascular Fraction (SVF) into the affected joint.

Materials and methods During a minilaparotomy, 10 g of falciform fat was removed from each patient for each joint to be treated. A modern and time-saving procedure (ARC TM System, InGeneron GmbH, Houston, USA) was used for the in-house preparation of the SVF, so that the isolated cells could be applied to the respective joint within 2 h after fat removal. In total, five knee joints of five patients and seven hip joints of four patients were treated.

Results Improvement in lameness according to owner questionnaires was seen in 3 of 5 patients with knee joint arthritis and 2 of 4 patients with hip joint arthritis. Based on gait analysis, only one dog with gonarthrosis and one dog with coxarthrosis showed improvement up to a maximum of 3 months after surgery.

Conclusion This is the first case series on the treatment of osteoarthrosis of the knee or hip joint using point-of-care transplantation of the SVF. In individual cases, this method may represent a therapeutic approach for the treatment in dogs with advanced cox- or gonarthrosis, although only a short-term effect can be expected, which calls into question the effort and costs involved.

Keywords centrifuge; coxarthrosis; dogs; gonarthrosis; point of care; regenerative cells

Abbreviations ADRC, adipose tissue derived regenerative cells; CBPI, Canine Brief Pain Inventory; IEWG, International Elbow Working Group; LOAD, HVAS, Hudson Visual Analogue Scale; PVF, peak vertical force; SI, symmetry index; VI, vertical impulse

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In veterinary medicine, therapy with stem cells and other regenerative cells is becoming increasingly important not only for horses, but also for dogs with osteoarthritis.[1–3] The principle of stem cell therapy is based on the pluripotent properties of these cells, which are usually obtained from adipose tissue or bone marrow. Various studies have shown that after autologous transplantation, they can develop into osteoblasts, chondroblasts and myoblasts, depending on the site of injection.[4–7] In addition, immunomodulatory properties of regenerative cells have also been demonstrated, which could explain a possible anti-inflammatory and analgesic effect.[8–10] Some veterinary studies have already investigated stem and other regenerative cell therapy in dogs with osteoarthritis of various, large joints.[1,3,11–13] Various clinical studies have also shown that the stromal vascular fraction (SVF) of fat cells in particular provides a micro-environment for the regenerative cells contained therein.[14–16]

Allotransplantation of abdominal adipose-derived stem cells in 203 dogs with osteoarthritis and various other joint defects showed improvement in lameness, although gait analysis was not performed. The stem cells were administered partly intravenously and partly intraarticularly.[17]

In a previously published work, the effect of joint injection with mesenchymal stem cells autologously isolated from the patient's subcutaneous and inguinal fat tissue was investigated in 10 dogs with coxarthritis. This was previously obtained from the patient during an operation and prepared in an external laboratory. The isolated stem cells were applied intra-articularly alone or in combination with platelet-rich plasma. Although an initial improvement in lameness was noted in the gait analysis, this did not extend beyond the 3-month follow-up. The results of the owner questionnaires, on the other hand, reflected an improvement in lameness even at the 6-month check.[3]

The effect of neonatal mesenchymal stem cells in 16 dogs with cruciate ligament rupture and Tibial Plateau Leveling Osteotomy (TPLO) was investigated by Taroni et al.[12] Allogeneic stem cells derived from neonatal tissue were injected postoperatively into the affected stifle joint. Success was assessed by clinical and radiographic examination and gait analysis, with no difference between the examination and control groups.[12]

In some studies on the therapy of osteoarthritis with regenerative cells, the cells taken from the patient must first be transported to a laboratory, incubated for multiplication and finally the regenerative cells isolated.[1,3,11,13] From studies on equine mesenchymal stem cells, it is known that transport and storage can have a negative impact on cell viability.[18] The present study focused on autologous transplantation of SVF from fat cells, which are known from various studies to provide a micro-environment for the regenerative cells they

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contain.[14–16] SVF from canine fat cells can be generated using a fast and modern processing system (ARC™ System InGeneron GmbH, Houston, USA).[14] The aim of the present case series was to examine whether this near-patient "point-of-care" method, which has not yet been described in small animal medicine, represents a possible therapeutic approach for dogs with osteoarthritis of the hip or knee joint.

Material and methods

Patients

The study included dogs that showed lameness due to advanced unilateral or bilateral osteoarthritis of the hip or knee joint (low, medium or high grade) and, therefore, presented to the Clinic for Small Animal Surgery and Reproduction, Ludwig Maximilian University, Munich. Owners of the patients could voluntarily apply to participate in the study for this purpose. A prerequisite for the study was also that the other joints of the affected limb as well as the joints of the remaining limbs were without specific findings during orthopedic examination. The remaining joints of the affected limb were also radiographed and were found to be without any particular findings. If it was a bilateral lameness due to bilateral osteoarthritis of one joint, both sides were treated at the same time. Another prerequisite for the study was that the patients showed significant mild or worse lameness and that the patients did not respond to conservative therapy. All other diseases that are often associated with arthrosis were also ruled out before inclusion in the study by means of adequate imaging procedures. Surgery for the causative disease or joint injection had to have been performed at least 6 months previously. This ensured that the patient's lameness was due to osteoarthritis and not to other orthopaedic diseases, such as cruciate ligament rupture or patellar luxation of the knee joint.

Preliminary examination

The preliminary examination included taking a history, a clinical examination of the patient, an orthopaedic examination of all four limbs, a radiographic examination of the affected limbs, a gait analysis examination and answering owner questionnaires (Hudson Visual Analogue Scale, HVAS and Canine Brief Pain Inventory, CBPI). Both had proven valid in past studies to assess the painfulness and quality of life of dogs with osteoarthritis in everyday life.[19–21] Gait analysis had also proven to be an objective method of assessing lameness in dogs in past studies.[19,20] The gait laboratory in which the gait analysis was performed included eight high-speed infrared cameras (Vicon Motion System Ltd, Oxford, UK) and a treadmill (size 180 × 80 cm) consisting of four modified piezoelectric force plates. In all investigations, the speed of the treadmill was 1.2 m/s at walk and 2 m/s at trot. At least 20 steps/limb and examination were collected to determine the kinetics, Vertical Impulse (VI), Vertical Peak Force (PVF) and Symmetry Index.

Surgery to obtain the stromal vascular fraction

Induction of anaesthesia was by means of a benzodiazepine (diazepam 0.5 mg/kg bw i.v.) and a narcotic (propofol 2–4 mg/kg bw, i.v.) before continuing as inhalation anaesthesia with isoflurane (1.2–1.4 vo% in expired air) after endotracheal intubation. Methadone (Comfortan 0.2 mg/kg i.v.) was given perioperatively for pain management followed by the opioid buprenorphine (Buprenodale 0.02 mg/kg i.v.) post-surgery. During anaesthesia, the patient was infused with electrolyte-containing infusion solution (10 mL/kg/h i.v.) and the usual vital signs were monitored by pulse oximetry, ECG, blood pressure measurement and temperature probe. For fat collection, a minimally invasive laparotomy (3–4 cm) was performed in the linea alba with collection of 10 g falciform fat per joint to be treated in the umbilical region and the wound was closed. This form of cell extraction was described as a simple method with good yield of regenerative cells, incl. stem cells, according to the study by Sullivan et al.[22]

The mesenchymal stem cells were isolated from the extracted adipose tissue according to the instructions of the kit (ARC™ system, InGeneron, Houston, Texas, US). The fat was first minced, Ringer's lactate solution was added, Matrase™ was added as an enzymatically reacting component, and the fat was isolated, filtered and washed in a defined sequence of steps. Under brief sedation using propofol (2–4 mg/kg bw), the joint to be treated was cleaned, disinfected and the stem cell suspension (1.5 mL) was injected into the joint. Time between collection and injection of the SVF was all in all 2 h. 0.1 mL of the suspension was run for live-death staining using a fluorescent dye (SYTO™ 13, Invitrogen, (Waltham, Massachusetts, USA) and trypan blue.

An NSAID (Caprofen 4 mg/kg bw oral) was administered once a day by the owner for the following 7 days and stitches were removed at the clinic after 10 days. After that, no more painkillers were administered.

Follow-up examinations

After 10 days, the clinical and orthopaedic examination and the evaluation by owner questionnaires were repeated. Further follow-up examinations, including gait analysis, were performed at 1, 2, 3 and 6 months post-injection. Radiographs of the treated joints were taken again at 3 and 6 months. If patients developed further orthopaedic conditions during the follow-up period, they were excluded for further follow-up. If the lameness did not improve after 3 months and the owners opted for a different therapeutic approach, they were also excluded from the study.

Statistical analysis

The total number of points awarded (0–10) was assessed during the owner questionnaires in which the owners awarded points accordingly for each question. Afterwards, the average points are calculated; results were considered an improvement if patients improved by at least two points on average, as is common in these already validated questionnaires.[19–21] Both questionnaires were evaluated independently of each other and handled equally. VI, PVF and Symmetry Index were determined to assess lameness. Gait analysis was performed using Vicon Nexus 1.7.1 (Vicon Motion System Ltd, Oxford, UK), QuadruPedLocomotion (internal software). An improvement in PVF and VI of the affected limb of at least 10% was considered an improvement in lameness.

The radiographs were either assessed according to the Mager scheme (knee joint) (29, 30) or classified according to the Fédération Cynologique Internationale (FCI) guidelines (hip joint) (31).

Excel (Microsoft 2016) was used for descriptive statistics in order to outline a possible effect of the SVF transplantation on the lameness of the dogs based on the owner questionnaire score, gait analysis and the radiographic score.

Results

In total, five knee joints of five patients and seven hip joints of four patients were treated. The dogs were four males and five females. The mean age was 7.5 (range 4.9–10.0), and the mean weight was 32.4 (range 11–50) (Table 1). In one patient with gonarthritis, both knees were treated with stem cell therapy 1 year apart after surgical treatment of patellar luxation. In the other four patients with gonarthritis, a cruciate ligament tear in the affected knee was surgically treated and a meniscectomy was performed previously. The cause of the coxarthritis was hip joint dysplasia in all cases.

Overall, 3 out of 5 patients with gonarthritis showed an improvement in quality of life using both questionnaires. Two out of 4 of the patients with bilateral coxarthritis also showed an improvement in lameness using both owner questionnaires (Tables 2, 3, and Figure 1). In the gait analysis, one dog with gonarthritis (dog 4) showed an improvement in lameness up to and including the 3-month check, but without becoming lameness-free. Further, one dog with coxarthritis (dog 7) showed a reduction in lameness up to and including the 2-month check, but also without becoming lameness-free. In addition, the dog showed neurological symptoms at the 3-month follow-up and could not be followed up. None of the patients had complications after the surgery.

The patient with coxarthritis (dog 9), who had also improved on the treadmill up to 2 months after surgery, developed spinal canal disease after 3 months, so that he also had to be excluded for the follow-up examinations.

One patient with gonarthritis (dog 5) had to be excluded from the study after only 1 month, as the patient did not put any weight on the limb at all, as was the case before the therapy, and the owners decided on a different therapy approach.

One patient with bilateral coxarthritis (dog 8), who did not improve both during gait analysis and according to the owner, required additional painkillers intermittently after therapy, which the owner gave especially after peak loads.

Table 1. Breed, age and weight of the dogs included in the study

Dog	Breed	Age (years)	Weight (kg bw)
1	Great Dane	5.4	50
2	Border collie	7.2	11
3	Doberman	7.9	39
4	Mixed breed	9.9	42.5
5	Mixed breed	7.5	38.3
6	German shorthair	6.2	30
7	German shepherd	8.7	31
8	Border collie	10	16.5
9	Epagneul Breton	4.9	33
Mean		7.5	32.4

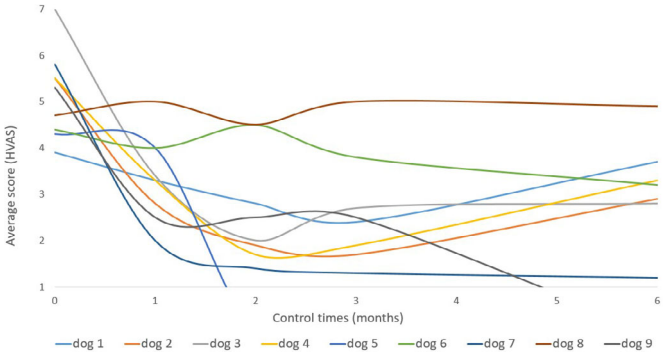

Figure 1. Average score of the dogs in the Hudson Visual Analogue Scale (HVAS) at the corresponding control dates (months); 10 = poor, 1 = good.

The degree of gonarthritis according to Mager was grade 2/4 in one knee joint and 4/4 in four knee joints. With regard to the hip joints, six hips were found to be grade E and one hip grade D preoperatively.

Up to the respective final checks, only one patient (dog 3) showed a progression of osteoarthritis compared to the already existing bony proliferations before therapy. However, as the patient's knee was already assessed with the highest grade (grade 4) before therapy, there was no difference in terms of grading (Table 4).

The average number of injected cells was 10.16×10^6 cells ($6.1–18.56 \times 10^6$) (Table 4). In the two patients who improved on both the questionnaires and the gait analysis, the number of cells injected was not higher than the average number of cells injected.

Discussion

Taking into account the available literature, the present study is the first case series in which osteoarthritis of the knee or hip joint in dogs was treated by means of point-of-care transplantation of regenerative cells. Overall, the majority of patients showed an improvement in quality of life according to the owner questionnaires. However, only one patient with gonarthritis and one patient with coxarthritis showed an improvement in lameness over a period of 3 months. This corresponds with the study by Vilar et al.,[3] in which after stem cell therapy in dogs with osteoarthritis, an improvement in lameness was only detectable at the 3-month follow-up using gait analysis.

With regard to the placebo effect, it has to be considered that the present study was not a blinded study, which is also a limitation of the study. Especially the results of the owner questionnaires could, therefore, have been influenced due to the lack of blinding. The placebo effect was proven in a study on dogs with osteoarthritis. Here, the owner's subjective assessment of lameness was compared with the results of an objective gait analysis. The authors, therefore, point out that a placebo effect must always be taken into account when the owner assesses lameness.[23]

Table 2. Causative disease of patients, treated joints and time points after surgery (in months) at which patients' lameness improved using gait analysis and owner questionnaires CBPI (Canine Brief Pain Inventory) and HVAS (Hudson Visual Analog Scale)

Dog	Causative disease	Treated joints	Gait analysis	CBPI	HVAS
1	Cruciate ligament rupture	Left knee joint			
2	Patellaluxation	Left knee joint		1,2,3,6	1,2,3,6
3	Cruciate ligament rupture	Rightknee joint		1,2,3,6	1,2,3,6
4	Cruciate ligament rupture	Right knee joint	1,2,3	1,2,3,6	1,2,3,6
5	Cruciate ligament rupture	Left knee joint			
6	Hip dysplasia	Right hip joint			
7	Hip dysplasia	Both hip joints		1,2,3,6	1,2,3,6
8	Hip dysplasia	Both hip joints			
9	Hip dysplasia	Both hip joints	1,2,3	1,2,3	1,2,3

Table 3. Score of HVAS at time points before and after treatment

Dogs	Pre tretment	1 months	2 months	3 months	6 months
Dog 1	3,9	3,3	2,8	2,4	3,7
Dog 2	5,5	2,8	1,9	1,7	2,9
Dog 3	7	3,4	2	2,7	2,8
Dog 4	5,5	3,3	1,7	1,9	3,3
Dog 5	4,3	4			
Dog 6	4,4	4	4,5	3,8	3,2
Dog 7	5,8	2	1,4	1,3	1,2
Dog 8	4,7	5	4,5	5	4,9
Dog 9	5,3	2,5	2,5	2,5	

Table 4. Osteoarthritis score of the treated joints and number of injected cells

Dog	Treated joint	Osteoarthritis score before/ after treatment	Number of injected cells ($\times 10^6$)
1	Knee joint unilateral	4/4	6.71
2	Knee joint unilateral	2/2	10.16
3	Knee joint unilateral	4/4	6.1
4	Knee joint unilateral	4/4	11.86
5	Knee joint unilateral	4/4	10.34
6	Knee joint unilateral	E/E	18.56
7	Hip joint bilateral	E/E	9.3/12.5
8	Hip joint bilateral	E/D	8.7/8.8
9	Hip joint bilateral	E/E	10.35/9.15

All patients in this study had other orthopaedic conditions of the affected and remaining joints excluded prior to therapy to rule out any other contributing factors to the lameness. It was also ensured that no other surgical procedures or cortisone injections were performed in any of the dogs for at least 6 months before and after stem cell therapy. Pain medication was only administered perioperatively and in the first 7 days postoperatively, so that this had no influence on the gait analysis. All pain medication was also discontinued before the preoperative gait analysis. Different modalities were chosen to monitor the success of the therapy and re-evaluate the lameness, and follow-up appointments were scheduled at several, uniformly defined times. Therefore, it can be assumed that patients whose lameness improved in the follow-up examinations may represent a therapy success.

As in the present case series, several other studies in which regenerative cells for the therapy of osteoarthritis in dogs were first cultivated in external laboratories and finally injected into the affected joint

demonstrated a short-term therapeutic success based on owner questionnaires.[3,13]

It is striking that the results of the objective gait analysis and those of the owner questionnaires do not coincide in part. The present study shows that lameness improved in 2 out of 9 patients on the basis of gait analysis and owner questionnaires and in 6 out of 9 patients only on the basis of owner questionnaires. This could be explained by the fact that the gait analysis assesses the lameness and the owner questionnaire assesses the general quality of life, that is, different aspects. Whether the quality of life of the animals actually improved or whether it was a placebo effect was not further investigated in the study. As these were painful patients with advanced osteoarthritis, no placebo group was included in the study for ethical reasons. However, a low correlation between gait analysis and owner questionnaires is already a known phenomenon. In their study on the treatment of coxarthritis in 10 dogs, Vilar et al.[13] were also able to show that the results of the gait analysis and the owner questionnaires correlate only slightly.[13]

All patients suffered from osteoarthritis at the time of treatment according to the Mager scheme or FCI grading, which was accompanied by lameness. How successful the therapy is when the osteoarthritis is already at an early stage, for example, when joint defects do not yet lead to lameness or are not clearly visible radiographically, would have to be clarified in further clinical studies.

In order to adequately assess the condition and development in the joint during therapy, arthroscopy before and 3 and 6 months after surgery might have been helpful. For example, in a study on stem cell therapy in dogs, the condition of the cartilage and the osteoarthritis in the elbow was assessed by arthoscopy. After the therapy, a regeneration of the cartilage could be determined[24]; this has not been done in the present case.

In the present study, dogs of all ages were included. In the aforementioned study on stem cell allotransplantation in dogs (24), the age of the donor animals was <5 years.[17] Vilar et al.[13] recruited animals between 4 and 8 years of age and Black et al.[1] also included animals up to 11 years of age.[1,13] A maximum age of patients from whom stem cells are harvested for transplantation does not yet exist and would need to be further investigated in follow-up studies.

Medium and large breeds were particularly represented among the patients. The minimum weight was 11 kg. As in the study by Shah et al.,[17] 10 g of abdominal fat per joint was removed for treatment. Overall, enough fat was obtained from all patients in the present study.

Due to the alio loco pre-treatment and surgery of the dogs, the heterogeneous morphometry and heterogeneous history, the patients reflect a realistic picture of a group of osteoarthritis patients, but also represent a limitation of the case series. Follow-up studies with larger patient groups and uniform histories would be useful to better assess the success of therapy. However, as this therapy approach in the present study largely caused no improvement or only a short-term improvement in lameness, the further use of this therapy in patients suffering from advanced osteoarthritis seems questionable. Furthermore, as many osteoarthritis patients may suffer from orthopaedic comorbidities, such as osteoarthritis in other joints, the recruitment of suitable and comparable study candidates is more difficult.

In the present study, only the number of vital cells was determined. Black et al.[11] reported the injection of 3–5 $\times$ 10^6 live cells to treat dogs with cubarthritis. In contrast, Vilar et al.[13] reported 15 $\times$ 10^6 cells, with regenerative cells cultured for a fortnight in an external laboratory, also to treat canine coxarthritis. This is comparable to the cell count in the present study. However, the laboratory techniques used to prepare the cells are often difficult to compare. For example, Pavarotti et al.[25] recently published a study in which pure fat fragmented but without isolation of regenerative cells was injected into the affected joint in dogs with osteoarthritis. In contrast to the treated elbow joints, the study did not find any improvement in PVF in the hip joints in gait analysis.[25] It remains to be clarified in further follow-up studies whether this or a procedure with isolation of the regenerative cells represent a practically relevant therapeutic approach. Ultimately, the question remains open as to whether the technique used, the location of the osteoarthritis or the progression of the osteoarthritis is decisive for the success of the therapy. It seems questionable whether larger follow-up studies on point-of-care transplantation of SVF in dogs with osteoarthritis would be useful, as no long-term therapeutic success in the treatment of knee and hip joints could be demonstrated on the basis of the present study.

Conclusion

The time-saving autologous point-of-care transplantation of regenerative cells using an in-house centrifuge may represent a possible therapeutic approach for patients with cox- and gonarthritis, although the therapeutic success may only be short-term which again calls into question the effort and costs involved.

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Ethics statement

The procedure was conducted in accordance with the guidelines of the Protection of Animal Act. All investigations and treatments were approved by the Ethics Committee of the Center of the Faculty of Veterinary Medicine, Ludwig-Maximilians-University Munich (application 31-20-06-2014).

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Conflicts of interest and sources of funding

The authors declare no conflict of interest. The funding sponsors had no role in the collection, the analyses or interpretation of data.

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