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UNIVERSIDADE ESTADUAL PAULISTA

"JÚLIO DE MESQUITA FILHO"

Campus de Botucatu

Faculdade de Medicina Veterinária e Zootecnia

EFEITO ANALGÉSICO DO PLASMA RICO EM PLAQUETAS E CÉLULAS-TRONCO NA DOR CRÔNICA DE CÃES COM DISPLASIA COXOFEMORAL

CELINA EMIKO OKAMOTO OKUBO

BOTUCATU – SP

Maio 2016

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CELINA EMIKO OKAMOTO OKUBO

Tese apresentada à Faculdade de Medicina Veterinária e Zootecnia, Universidade Estadual Paulista "Júlio de Mesquita Filho", Campus de Botucatu, para obtenção do título de mestre na área de Biotecnologia animal.

Orientador: Prof. Titular Stelio Pacca Loureiro Luna

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EFEITO ANALGÉSICO DO PLASMA RICO EM PLAQUETAS E CÉLULAS-TRONCO NA DOR CRÔNICA DE CÃES COM DISPLASIA COXOFEMORAL

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EFEITO ANALGÉSICO DO PLASMA RICO EM PLAQUETAS E CÉLULAS-TRONCO NA DOR CRÔNICA DE CÃES COM DISPLASIA COXOFEMORAL

Dissertação apresentada à Faculdade de Medicina Veterinária e Zootecnia, Universidade Estadual Paulista "Júlio de Mesquita Filho", Campus de Botucatu, para obtenção do título de Mestre.

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Botucatu, 23 de Maio de 2016.

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Carl Jung

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LISTA DE ABREVIATURAS, SIGLAS E SÍMBOLOS

p	Nível de significância
σ	Desvio padrão
BIDC	Breve Inventário de Dor Canina
BVS	Biblioteca Virtual em Saúde
CEUA	Comissão de Ética no Uso de Animais
CT	Célula-tronco
CTM-TAs	Células-tronco mesenquimais derivadas de tecido adiposo
DAD	Doença articular degenerativa
DCF	Displasia coxofemoral
DMSO	Dimetilsulfóxido
DP	Distribuição do Peso
EAV	Escala Analógica Visual
EAVdor	Escala Analógica Visual para dor
EAVloc	Escala Analógica Visual para claudicação
END	Escala Numérica Descritiva
FMVZ	Faculdade de Medicina Veterinária e Zootecnia
Kg	Quilogramas
IDCH	Indicador de Dor Crônica da Universidade de Helsink
IGP	Impressão Geral do Proprietário sobre a qualidade de vida do cão
µM	Micrômetros
mL	Mililitros
µL	Microlitros
n	Número de animais
PBS	Solução Tampão Fosfato-salino
PCR	Reação em Cadeia pela Polimerase
PDGF	Fator de Crescimento Derivado de Plaquetas
PRP	Plasma Rico em Plaquetas
SFB	Soro Fetal Bovino
TGF-beta	Fator de Crescimento Transformador beta
VEGF	Fator de Crescimento Vascular Endotelial

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RESUMO

OKAMOTO-OKUBO, C.E. Efeito analgésico do plasma rico em plaquetas e células-tronco na dor crônica de cães com displasia coxofemoral. 2016. 66p. Dissertação (Mestrado) - Faculdade de Medicina Veterinária e Zootecnia, Universidade Estadual Paulista "Júlio de Mesquita Filho", Botucatu, 2016.

Este estudo clínico, controlado, aleatório, duplo cego, investigou o efeito intra-articular do plasma rico em plaquetas (PRP) (n = 8) ou de células-tronco alogênicas (CT) (n = 8) na dor crônica de cães com displasia coxofemoral (DCF) bilateral. Os proprietários avaliaram o Breve Inventário de Dor Canina (BIDC), o Índice de Dor Crônica de Helsink (IDCH), a Escala Analógica Visual para dor (EAVdor) e claudicação (EAVloc), e a Qualidade de Vida (QV). Uma médica veterinária avaliou a Escala Visual Analógica da dor à palpação (EAVpalp), a Escala Numérica Descritiva para dor (END) e a porcentagem de distribuição de peso corporal. As avaliações foram realizadas antes, aos 30 e 60 dias após o tratamento. Depois de CT, IDCH, EAVdor e EAVpalp foram reduzidos, QV aumentou aos 60 dias e BIDC reduziu aos 30 e 60 dias. Após PRP, EAVloc e END reduziram em 60 dias e BIDC aos 30 e 60 dias. Não houve diferença entre os grupos. Ambos CT e PRP foram aparentemente benéficos para reduzir a dor crônica em cães que sofrem de DCF bilateral por 60 dias, mas CT foi superior nas variáveis de dor crônica em comparação com PRP. O benefício clínico de ambos os tratamentos é que eles produzem um alívio da dor a longo prazo em cães com DCF sem efeitos adversos aparentes.

Palavras chave: Células-tronco, injeções, intra-articular, coxofemoral, cães

ABSTRACT

Analgesic effect of platelet-rich plasma and stem cells in chronic pain in dogs with hip dysplasia. 2016. 66p. Faculdade de Medicina Veterinária e Zootecnia, Universidade Estadual Paulista “Júlio de Mesquita Filho”, Botucatu, 2015.

This randomized, controlled, double-blind clinical study investigated the effect of intra-articular platelet-rich plasma (PRP) (n=8) or allogeneic stem cells (SC) (n=8) in chronic pain of dogs with bilateral hip dysplasia (HD). The owners evaluated the Canine Brief Pain Inventory (CBPI), the Helsinki Chronic Pain Index (HCPI), a Visual Analogue Scale for pain (VASpain) and lamness (VASloc) and the quality of life (QL). A veterinarian evaluated the Visual Analogue Scale of pain in response to palpation (VASpalp), the descriptive numerical scale for pain (DNS) and the percentage of body weight distribution. All evaluations were performed before, at 30 and 60 days after treatment. After SC, HCPI, VASpain and VASpalp reduced and QL increased at 60 days and CBPI reduced at 30 and 60 days. After PRP, VASloc and DNS reduced at 60 days and CBPI at 30 and 60 days. There was no difference between groups. Both SCs and PRP were apparently beneficial to reduce chronic pain in dogs suffering from bilateral hip dysplasia for 60 days, but SCs improved more chronic pain variables compared to PRP. The clinical benefit of both treatments is that they produce a long term pain relief in dogs with hip dysplasia with no apparent adverse effects.

Key words: Stem cells, injections, intra-articular, hip joint, dogs

CAPÍTULO I

1. INTRODUÇÃO

A medicina regenerativa é uma nova área das medicinas humana e veterinária e é foco de estudos recentes, principalmente voltados para o uso da terapia de células-tronco mesenquimais derivadas de tecido adiposo (CTM-TAs), com o objetivo de tratar osteoartroses [1-20]. Com esse mesmo foco, a aplicação de Plasma Rico em Plaquetas (PRP) também é amplamente utilizada para tratar problemas osteoarticulares não apenas no homem, mas também em diversas espécies como nos cães [7,8,21-33].

A dispasia coxofemoral (DCF) é uma alteração não infecciosa e progressiva que ocorre na cartilagem das articulações acometidas[34]. Caracteriza-se por uma sinovite e degeneração da cartilagem articular com perda da matriz, e que pode resultar na completa perda da superfície cartilaginosa[35].

A hipótese deste estudo é que as terapias com CTM-TAs alogênicas ou PRP são alternativas terapêuticas eficazes e similares para controlar a dor e melhorar a qualidade de vida em cães com DCF bilateral [3,4].

2. REVISÃO DE LITERATURA

2.1- Displasia coxofemoral (DCF) bilateral em cães

A displasia coxofemoral (DCF) é uma enfermidade crônica, conhecida também como doença articular degenerativa (DAD)[36]. Estudos mostram a alta prevalência da DAD em cães, com 20% da população canina acima de 1 ano de idade apresentando esta enfermidade em diferentes graus[37]. A DCF está relacionada com dor crônica, claudicação, incapacidade funcional e redução da

3- REFERÊNCIAS BIBLIOGRÁFICAS

(Segundo normas Vancouver)

1. Guercio A, Marco PD, Casella S, et al. Production of canine mesenchymal stem cells from adipose tissue and their application in dogs with chronic osteoarthritis of the humeroradial joints. Cell Bio Int. 2012;36:189–194.
2. Black LL, Gaynor J, Gahring D, et al. Effect of adipose-derived mesenchymal stem and regenerative cells on lameness in dogs with chronic osteoarthritis of the coxofemoral joints: a randomized, double-blinded, multicenter, controlled trial. Vet Ther. 2007;4:272-284.
3. Black LL, Gaynor J, Adams C, et al. Effect of intraarticular injection of autologous adipose-derived mesenchymal stem and regenerative cells on clinical signs of chronic osteoarthritis of the elbow joint in dogs. Vet Ther. 2008;9:192-200.
4. Cuervo B, Rubio M, Sopena J, et al. Hip Osteoarthritis in Dogs: A Randomized Study Using Mesenchymal Stem Cells from Adipose Tissue and Plasma Rich in Growth Factors. Int J Mol Sci. 2014;15:13437-13460.
5. Vilar JM, Batista M, Morales M, et al. Assessment of the effect of intraarticular injection of autologous adipose-derived mesenchymal stem cells in osteoarthritic dogs using a double blinded force platform analysis. BMC Vet Res. 2014;10.
6. Vilar JM, Morales M, Santana A, et al. Controlled, blinded force platform analysis of the effect of intraarticular injection of autologous adipose-derived mesenchymal stem cells associated to PRGF-Endoret in osteoarthritic dogs. BMC Vet Res. 2013;9.

7. Upchurch DA. Administration of adipose-derived stromal vascular fraction and platelet rich plasma in dogs with coxofemoral osteoarthritis. Department of Clinical Sciences. 2015.

8. Yun S, Ku SK, Kwon YS. Adipose-derived mesenchymal stem cells and platelet-rich plasma synergistically ameliorate the surgical-induced osteoarthritis in Beagle dogs. J Orthop Surg Res. 2016;11:9.

9. Uth K, Trifonov D. Stem cell application for osteoarthritis in the knee joint: A minireview. World J Stem Cells. 2014;6:629-636.

10. Tsai S-Y, Huang Y-C, Chueh L-L, et al. Intra-articular transplantation of porcine adipose-derived stem cells for the treatment of canine osteoarthritis: A pilot study. World J Transplant. 2014;4:196-205.

11. Bornes TD, Adesida AB, Jomha NM. Mesenchymal stem cells in the treatment of traumatic articular cartilage defects: a comprehensive review. Arthritis Res Ther. 2014;16.

12. Lee JK, Responte DJ, Cissell DD, et al. Clinical translation of stem cells: insight for cartilage therapies. Crit Rev Biotechnol 2014;34:89–100.

13. Wood JA, Chung D-J, Park SA, et al. Periocular and Intra-Articular Injection of Canine Adipose-Derived Mesenchymal Stem Cells: An In Vivo Imaging and Migration Study. J Ocul Pharmacol Ther. 2012;28.

14. Kim I, Bang SI, Lee SK, et al. Clinical implication of allogenic implantation of adipogenic differentiated adipose-derived stem cells. Stem Cells Transl Med. 2014;3:1312-1321.

15. Shen W, Chen J, Zhu I, et al. Intra-Articular Injection of Human Meniscus Stem/Progenitor Cells Promotes Meniscus Regeneration and Ameliorates

Osteoarthritis Through Stromal Cell-Derived Factor-1/CXCR4- Mediated Homing. Stem Cells Transl Med. 2014;3:387–394.

16. Qi Y, Feng G, Yan W. Mesenchymal stem cell-based treatment for cartilage defects in osteoarthritis. Mol Biol Rep. 2012;39:5683–5689.

17. Whitworth DJ, Banks TA. Stem cell therapies for treating osteoarthritis: Prescient or premature? Vet J. 2014;202:416–424.

18. Shenaq DS, Rastegar F, Petkovic D, et al. Mesenchymal progenitor cells and their orthopedic applications: Forging a Path towards Clinical Trials. Stem Cells Int. 2010.

19. Chen FH, Tuan RS. Mesenchymal stem cells in arthritic diseases. Arthritis Res Ther. 2008;10.

20. Carrade DD, Owens SD, Galuppo LD, et al. Clinicopathologic findings following intra-articular injection of autologous and allogeneic placentally derived equine mesenchymal stem cells in horses. Cytotherapy. 2011;13:419-430.

21. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. Curr Rev Musculoskeletal Med. 2008;1:165-174.

22. Drengk A, Zapf A, Sturmer EK, et al. Influence of platelet-rich plasma on chondrogenic differentiation and proliferation of chondrocytes and mesenchymal stem cells. Cells Tissues Organs. 2009;189:317-326.

23. Aziz Aly LA, El-Menoufy H, Hassan A, et al. Influence of autologus adipose derived stem cells and PRP on regeneration of dehiscence-type defects in alveolar bone: A Comparative Histochemical and Histomorphometric Study in Dogs. Int J Stem Cells. 2011;4:61-69.

24. Filardo G, Kon E, Buda R, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2011;19:528-535.

25. Ahmad Z, Howard D, Brooks RA, et al. The role of platelet rich plasma in musculoskeletal science. JRSM Short Rep. 2012;3:40.

26. Mishra A, Harmon K, Woodall J, et al. Sports medicine applications of platelet rich plasma. Curr Pharm Biotechnol. 2012;13:1185-1195.

27. Mishra A, Randelli P, Barr C, et al. Platelet-rich plasma and the upper extremity. Hand Clin. 2012;28:481-491.

28. Zarins B. Platelet-rich plasma (PRP) – Potential orthopaedic applications of autologous preparations rich in growth factors (PRGF). Massachusetts General Hospital, 2013.

29. Hoareau GL, Jandrey KE, Burges J, et al. Comparison of the platelet-rich plasma and buffy coat protocols for preparation of canine platelet concentrates. Vet Clin Pathol. 2014;43:513-518.

30. Sundman EA, Cole BJ, Karas V, et al. The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. Am J Sports Med. 2014;42:35-41.

31. Cook JL, Smith PA, Bozynski CC, et al. Multiple injections of leukoreduced platelet rich plasma reduce pain and functional impairment in a canine model of ACL and meniscal deficiency. J Orthop Res. 2015; 34:607-6015.

32. Kazemi D, Fakhrjou A. Leukocyte and Platelet Rich Plasma (L-PRP) Versus Leukocyte and Platelet Rich Fibrin (L-PRF) For Articular Cartilage

Repair of the Knee: A Comparative Evaluation in an Animal Model. Iran Red Crescent Med J. 2015;17:e19594.

33. Xie X, Ulici V, Alexander PG, et al. Platelet-Rich Plasma Inhibits Mechanically Induced Injury in Chondrocytes. Arthroscopy. 2015;31:1142-1150.

34. Wiegant K, Intema F, van Roermund PM, et al. Evidence of cartilage repair by joint distraction in a canine model of osteoarthritis. Arthritis Rheumatol. 2015;67:465-474.

35. Lust G, Summers BA. Early, asymptomatic stage of degenerative joint disease in canine hip joints. Am J Vet Res. 1981;42:1849-1855.

36. Boal S, Miguel Carreira L. Serum and synovial fluid C-reactive protein level variations in dogs with degenerative joint disease and their relationships with physiological parameters. Vet Res Commun. 2015;39:163-169.

37. Paster ER, LaFond E, Biery DN, et al. Estimates of prevalence of hip dysplasia in Golden Retrievers and Rottweilers and the influence of bias on published prevalence figures. J Am Vet Med Assoc. 2005;226:387-392.

38. Henrotin Y, Sanchez C, Balligand M. Pharmaceutical and nutraceutical management of canine osteoarthritis: present and future perspectives. Vet J. 2005;170:113-123.

39. Flückiger M. Scoring radiographs for canine Hip Dysplasia - The big three organisations in the world. European Journal Compagnion Animal Practice. 2007;17:135-140.

40. Brandt KD, Dieppe P, Radin E. Etiopathogenesis of osteoarthritis. Med Clin North Am. 2009;93:1-24, xv.

41. Man GS, Mologhianu G. Osteoarthritis pathogenesis - a complex process that involves the entire joint. J Med Life. 2014;7:37-41.

42. Brown DC, Boston RC, Coyne JC, et al. Ability of the canine brief pain inventory to detect response to treatment in dogs with osteoarthritis. J Am Vet Med Assoc. 2008;233:1278-1283.

43. Alexander JW. The pathogenesis of canine hip dysplasia. Vet Clin North Am: Small Anim Pract. 1992;22:503-511.

44. Malek S, Sample SJ, Schwartz Z, et al. Effect of analgesic therapy on clinical outcome measures in a randomized controlled trial using client-owned dogs with hip osteoarthritis. BMC Vet Res. 2012;8:185.

45. Perea S. Nutritional management of osteoarthritis. Compendium on Continuing Education for the Practising Veterinarian. 2012;34:E4.

46. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice.The Lancet. 2011;377:2115-2126.

47. Teixeira LR. Owner assessment of chronic pain and gait analysis of dogs with hip dysplasia treated with acupuncture. Botucatu Medical School. Botucatu -SP: São Paulo State University, 2015.

48. Holton LL, Scott EM, Nolan AM, et al. Comparison of three methods used for assessment of pain in dogs. J Am Vet Med Assoc. 1998;212:61-66.

49. Brown DC, Boston RC, Coyne JC, et al. Development and psychometric testing of an instrument designed to measure chronic pain in dogs with osteoarthritis. Am J Vet Res. 2007;68:631-637.

50. Anderson AF, Smith M. Progress in cartilage restoration. Am J Sports Med. 2009;37 Suppl 1:7S-9S.

51. Smyth NA, Murawski CD, Haleem AM, et al. Establishing proof of concept: Platelet-rich plasma and bone marrow aspirate concentrate may

improve cartilage repair following surgical treatment for osteochondral lesions of the talus. World J Orthop. 2012;3:101-108.

52. Aragon CL, Hofmeister EH, Budsberg SC. Systematic review of clinical trials of treatments for osteoarthritis in dogs. J Am Vet Med Assoc. 2007;230:514-521.

53. Innes J. Diet and disease: exploring the link through nutrigenomics. Can Vet J. 2006;47:68-70.

54. Pereira LdV. A importância do uso das células tronco para a saúde pública. Ciência & Saúde Coletiva. 2008;13:7-14.

55. Haas S, Weidner N, Winkler Jr. Adult stem cell therapy in stroke. Curr Opin Neurol. 2005;18:59-64.

56. Carrade DD, Borjesson DL. Immunomodulation by Mesenchymal Stem Cells in Veterinary Species. Comp Med. 2013;63:207–217.

57. Raghunath J, Salacinski HJ, Sales KM, et al. Advancing cartilage tissue engineering: the application of stem cell technology. Curr Opin Biotechnol. 2005;16:503-509.

58. Oldershaw RA. Cell sources for the regeneration of articular cartilage: the past, the horizon and the future. Int J Exp Pathol. 2012;93:389-400.

59. Fraser JK, Wulur I, Alfonso Z, et al. Fat tissue: an underappreciated source of stem cells for biotechnology. Trends Biotechnol. 2006;24:150-154.

60. Grasys J, Kim BS, Pallua N. Content of Soluble Factors and Characteristics of Stromal Vascular Fraction Cells in Lipoaspirates from Different Subcutaneous Adipose Tissue Depots. Aesthet Surg J. 2016.

61. Church CD, Berry R, Rodeheffer MS. Isolation and study of adipocyte precursors. Methods Enzymol. 2014;537:31-46.

62. Singer NG, Caplan AI. Mesenchymal stem cells: mechanisms of inflammation. Annu Rev Pathol. 2011;6:457-478.

63. Zhang J, Huang X, Wang H, et al. The challenges and promises of allogeneic mesenchymal stem cells for use as a cell-based therapy. Stem Cell Res Ther. 2015;6:234.

64. Mrugala D, Bony C, Neves N, et al. Phenotypic and functional characterisation of ovine mesenchymal stem cells: application to a cartilage defect model. Ann Rheum Dis. 2008;67:288-295.

65. Carrade DD, Lame MW, Kent MS, et al. Comparative Analysis of the Immunomodulatory Properties of Equine Adult-Derived Mesenchymal Stem Cells. Cell Med. 2012;4:1-11.

66. Poncelet AJ, Vercruysse J, Saliez A, et al. Although pig allogeneic mesenchymal stem cells are not immunogenic in vitro, intracardiac injection elicits an immune response in vivo. Transplant Res. 2007;83:783-790.

67. Zhang J, Bai X, Zhao B, et al. Allogeneic adipose-derived stem cells promote survival of fat grafts in immunocompetent diabetic rats. Cell Tissue Res. 2015.

68. Bartholomew A, Sturgeon C, Siatskas M, et al. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp Hematol. 2002;30:42-48.

69. Berman DM, Willman MA, Han D, et al. Mesenchymal stem cells enhance allogeneic islet engraftment in nonhuman primates. Diabetes. 2010;59:2558-2568.

70. Kang JW, Kang KS, Koo HC, et al. Soluble factors-mediated immunomodulatory effects of canine adipose tissue-derived mesenchymal stem cells. Stem Cells Dev. 2008;17:681-693.

71. Kim HS, Kim KH, Kim SH, et al. Immunomodulatory effect of canine periodontal ligament stem cells on allogenic and xenogenic peripheral blood mononuclear cells. J Periodontal Implant Sci. 2010;40:265-270.

72. Lee WS, Suzuki Y, Graves SS, et al. Canine bone marrow-derived mesenchymal stromal cells suppress alloreactive lymphocyte proliferation in vitro but fail to enhance engraftment in canine bone marrow transplantation. Biol Blood Marrow Transplant. 2011;17:465-475.

73. Khatri M, O'Brien TD, Sharma JM. Isolation and differentiation of chicken mesenchymal stem cells from bone marrow. Stem Cells Dev. 2009;18:1485-1492.

74. Moreno R, Martinez-Gonzalez I, Rosal M, et al. Characterization of mesenchymal stem cells isolated from the rabbit fetal liver. Stem Cells Dev. 2010;19:1579-1588.

75. Liu H, Kemeny DM, Heng BC, et al. The immunogenicity and immunomodulatory function of osteogenic cells differentiated from mesenchymal stem cells. J Immunol. 2006;176:2864-2871.

76. Cho PS, Messina DJ, Hirsh EL, et al. Immunogenicity of umbilical cord tissue derived cells. Blood. 2008;111:430-438.

77. Peroni JF, Borjesson DL. Anti-inflammatory and immunomodulatory activities of stem cells. Vet Clin North Am: Equine Pract. 2011;27:351-362.

78. Le Blanc K, Rasmusson I, Gotherstrom C, et al. Mesenchymal stem cells inhibit the expression of CD25 (interleukin-2 receptor) and CD38 on

phytohaemagglutinin-activated lymphocytes. Scand J Immunol. 2004;60:307-315.

79. Bernardo ME, Locatelli F, Fibbe WE. Mesenchymal Stromal Cells. Ann N Y Acad Sci. 2009;1176:101–117.

80. Ahmad Z, Howard D, Brooks RA, et al. The role of platelet rich plasma in musculoskeletal science. JRSM Short Rep. 2012;3.

81. Carneiro MO, Barbieri CuH, Neto JB. Platelet-Rich Plasma gel promotes regeneration of articular cartilage in knees of sheeps. Acta Ortop Bras. 2013;21.

82. Perazzi A, Busetto R, Martinello T, et al. Description of a double centrifugation tube method for concentrating canine platelets. BMC Vet Res. 2013;9.

83. Aleixo GAS, Coelho MCOC, Teixeira MN, et al. Comparação entre dois protocolos para obtenção de plasma rico em plaquetas, em cães. Arq Bras Med Vet Zootec. 2011;63:567-573.

84. Thoesen MS, Berg-Foels WS, Stokol T, et al. Use of a centrifugation-based, point-of-care device for production of canine autologous bone marrow and platelet concentrates. Am J Vet Res. 2006;67:1655-1661.

85. Trichler SA, Bulla SC, Thomason J, et al. Ultra-pure platelet isolation from canine whole blood. BMC Vet Res. 2013;9:144.

86. Dohan Ehrenfest DM, Bielecki T, Mishra A, et al. In search of a consensus terminology in the field of platelet concentrates for surgical use: platelet-rich plasma (PRP), platelet-rich fibrin (PRF), fibrin gel polymerization and leukocytes. Curr Pharm Biotechnol. 2012;13:1131-1137.

87. Anitua E, Sanchez M, Nurden AT, et al. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor

production by synovial fibroblasts from arthritic patients In: M S, ed: Rheumatology. 2007;1769–1772.

88. Brossi PM, Moreira JJ, Machado TsS, et al. Platelet-rich plasma in orthopedic therapy: a comparative systematic review of clinical and experimental data in equine and human musculoskeletal lesions. BMC Vet Res. 2015;11.

89. Anitua E, Andia I, Ardanza B, et al. Autologous platelets as a source of proteins for healing and tissue regeneration. J Thromb Haemostasis. 2004;91:4-15.

90. Akeda K, An HS, Okuma M, et al. Platelet-rich plasma stimulates porcine articular chondrocyte proliferation and matrix biosynthesis. Osteoarthritis Cartilage. 2006;14:1272-1280.

91. Van Buul GM, Koevoet WL, Kops N, et al. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. Am J Sports Med. 2011;39:2362-2370.

92. Wei L-C, Gao S-G, Xu M, et al. A novel hypothesis: The application of platelet-rich plasma can promote the clinical healing of white-white meniscal tears. Med Sci Monit. 2012;8:HY47-50.

93. Bozynski CC, Stannard JP, Smith P, et al. Acute Management of Anterior Cruciate Ligament Injuries Using Novel Canine Models. J Knee Surg. 2015.

5. CONCLUSION

Both SCs and PRP were apparently beneficial to reduce chronic pain in dogs suffering from bilateral hip dysplasia for 60 days, but SCs improved most of chronic pain variables compared to PRP. The clinical benefit of both treatments is that they produce a long term pain relief in dogs with hip dysplasia, with no apparent adverse effects.

6. REFERENCES

(Vancouver Citation Style)

1. Mortellaro CM. Pathophysiology of osteoarthritis. Vet Res Comm. 2003;27 Suppl 1:75-78.

2. Carneiro MO, Barbieri CuH, Neto JB. Platelet-Rich Plasma gel promotes regeneration of articular cartilage in knees of sheeps. Acta Ortop Bras. 2013;21.

3. Vilar JM, Morales M, Santana A, et al. Controlled, blinded force platform analysis of the effect of intraarticular injection of autologous adipose-derived mesenchymal stem cells associated to PRGF-Endoret in osteoarthritic dogs. BMC Vet Res. 2013;9.

4. Black LL, Gaynor J, Adams C, et al. Effect of intraarticular injection of autologous adipose-derived mesenchymal stem and regenerative cells on clinical signs of chronic osteoarthritis of the elbow joint in dogs. Vet Ther. 2008;9:192-200.

5. Yun S, Ku SK, Kwon YS. Adipose-derived mesenchymal stem cells and platelet-rich plasma synergistically ameliorate the surgical-induced osteoarthritis in Beagle dogs. J Orthop Surg Res. 2016;11:9.

6. Upchurch DA. Administration of adipose-derived stromal vascular fraction and platelet rich plasma in dogs with coxofemoral osteoarthritis. Department of Clinical Sciences, 2015.

7. Anitua E, Sanchez M, Nurden AT, et al. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. Rheumatology. 2007;46:1769-1772.

8. Cuervo B, Rubio M, Sopena J, et al. Hip Osteoarthritis in Dogs: A Randomized Study Using Mesenchymal Stem Cells from Adipose Tissue and Plasma Rich in Growth Factors. Int J Mol Sci. 2014;15:13437-13460.

9. Guercio A, Marco PD, Casella S, et al. Production of canine mesenchymal stem cells from adipose tissue and their application in dogs with chronic osteoarthritis of the humeroradial joints. Cell Biol Int. 2012;36:189–194.

10. Black LL, Gaynor J, Gahring D, et al. Effect of adipose-derived mesenchymal stem and regenerative cells on lameness in dogs with chronic osteoarthritis of the coxofemoral joints: a randomized, double-blinded, multicenter, controlled trial. Vet Ther. 2007;4:272-284.

11. Vilar JM, Batista M, Morales M, et al. Assessment of the effect of intraarticular injection of autologous adipose-derived mesenchymal stem cells in osteoarthritic dogs using a double blinded force platform analysis. BMC Vet Res. 2014;10.

12. Ahmad Z, Howard D, Brooks RA, et al. The role of platelet rich plasma in musculoskeletal science.JRSM Short Rep. 2012;3.

13. Hoareau GL, Jandrey KE, Burges J, et al. Comparison of the platelet-rich plasma and buffy coat protocols for preparation of canine platelet concentrates. Vet Clin Pathol. 2014;43:513-518.

14. Aleixo GAS, Coelho MCOC, Teixeira MN, et al. Comparação entre dois protocolos para obtenção de plasma rico em plaquetas, em cães. Arq Bras Med Vet Zootec. 2011;63:567-573.

15. Dohan Ehrenfest DM, Bielecki T, Mishra A, et al. In search of a consensus terminology in the field of platelet concentrates for surgical use:

platelet-rich plasma (PRP), platelet-rich fibrin (PRF), fibrin gel polymerization and leukocytes. Curr Pharm Biotechnol. 2012;13:1131-1137.

16. Brossi PM, Moreira JJ, Machado TsS, et al. Platelet-rich plasma in orthopedic therapy: a comparative systematic review of clinical and experimental data in equine and human musculoskeletal lesions. BMC Vet Res. 2015;11.

17. Perazzi A, Busetto R, Martinello T, et al. Description of a double centrifugation tube method for concentrating canine platelets. BMC Vet Res. 2013;9.

18. Anitua E, Andia I, Ardanza B, et al. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemostasis. 2004;91:4-15.

19. Flückiger M. Scoring radiographs for canine Hip Dysplasia - The big three organisations in the world. EJCAP. 2007;17.

20. Brown DC, Boston RC, Coyne JC, et al. Development and psychometric testing of an instrument designed to measure chronic pain in dogs with osteoarthritis. Am J Vet Res. 2007;68:631-637.

21. Hielm-Björkman AK, Rita H, Tulamo R-M. Psychometric testing of the Helsinki chronic pain index by completion of a questionnaire in Finnish by owners of dogs with chronic signs of pain caused by osteoarthritis. Am J Vet Res. 2009;70:727-734.

22. Holton LL, Scott EM, Nolan AM, et al. Comparison of three methods used for assessment of pain in dogs. J Am Vet Med Assoc. 1998;212:61-66.

23. Teixeira LR. Owner assessment of chronic pain and gait analysis of dogs with hip dysplasia treated with acupuncture. Botucatu Medical School. Botucatu -SP: São Paulo State University, 2015.

24. Mokbel AN, Tookhy OSE, Shamaa AA, et al. Homing and reparative effect of intra-articular injection of autologus mesenchymal stem cells in osteoarthritic animal model. BMC Musculoskelet Disord. 2011;12.

25. Kazemi D, Fakhrjou A. Leukocyte and Platelet Rich Plasma (L-PRP) Versus Leukocyte and Platelet Rich Fibrin (L-PRF) For Articular Cartilage Repair of the Knee: A Comparative Evaluation in an Animal Model. Iran Red Crescent Med J. 2015;17:e19594.

26. Sundman EA, Cole BJ, Karas V, et al. The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. Am J Sports Med. 2014;42:35-41.

27. Arnoczky SP, Torzilli PA. Biomechanical analysis of forces acting about the canine hip. Am J Vet Res. 1981;42:1581-1981.

28. Luna SP, Basilio AC, Steagall PV, et al. Evaluation of adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs. Am J Vet Res. 2007;68:258-264.

29. Malek S, Sample SJ, Schwartz Z, et al. Effect of analgesic therapy on clinical outcome measures in a randomized controlled trial using client-owned dogs with hip osteoarthritis. BMC Vet Res. 2012;8:185.

30. KuKanich B. Outpatient oral analgesics in dogs and cats beyond nonsteroidal antiinflammatory drugs: an evidence-based approach. Vet Clin North Am Small Anim Pract. 2013;43:1109-1125.

31. Lascelles BD, Gaynor JS, Smith ES, et al. Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs. J Vet Intern Med. 2008;22:53-59.

32. Bernardo ME, Locatelli F, Fibbe WE. Mesenchymal Stromal Cells. Ann N Y Acad Sci. 2009;1176:101–117.

33. Anitua E, Sanchez M, Nurden AT, et al. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. Rheumatology. 2007;1769–1772.

34. Jaeger GT, Larsen S, Soli N, et al. Two years follow-up study of the pain-relieving effect of gold bead implantation in dogs with hip-joint arthritis. Acta Vet Scand. 2007;49:9.

35. Mills K, Hettinga BA, Pohl MB, et al. Between-limb kinematic asymmetry during gait in unilateral and bilateral mild to moderate knee osteoarthritis. Arch Phys Med Rehabil. 2013;94:2241-2247.

36. Genevois JP, Chanoit G, Carozzo C, et al. Influence of anaesthesia on canine hip dysplasia score. J Vet Med Physiol Pathol Clin Med. 2006;53:415-417.