Stem cells and platelet-rich plasma for the treatment of naturally occurring equine tendon and ligament injuries: a systematic review and meta-analysis

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OBJECTIVE
Platelet-rich plasma (PRP) and mesenchymal stromal or stem cells (MSCs) have been investigated as treatments for equine tendon and ligament injuries, but little consensus exists on the efficacy of these treatments. The study sought to evaluate the efficacy of PRP and MSC treatments by systematic review and meta-analysis.

METHODS
A systematic review was performed using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Inclusion criteria required an original, peer-reviewed study where horses were administered MSCs or PRP (or both), and a comparator group was described. Studies were assessed for risk of bias and study quality. Random effects meta-analysis with inverse variance weighting was used to calculate pooled estimates of the ORs for the primary outcomes of return to performance and reinjury.

RESULTS
The search criteria identified 764 unique studies, and 21 studies met the inclusion criteria for the systematic review. Seventeen studies were further assessed for the primary outcomes of return to performance and reinjury rate within a meta-analysis. Meta-analyses revealed no increase in the likelihood of a return to performance with any of the biologic treatments. However, MSCs and MSCs administered concurrently with PRP provide a reduced risk of reinjury.

CLINICAL RELEVANCE
The current study identified a decrease in reinjury rate in horses administered MSCs or a combination of MSCs and PRP for tendinopathy and desmopathy. However, results should be interpreted with consideration of the heterogeneity of findings, poor study quality, and high risk of bias in the majority of studies.

Keywords: platelet-rich plasma, mesenchymal stem cells, horse, tendon, ligament
comparisons exist between different biologic treatments. Therefore, clinical decision-making is often based on personal preference, clinical experience, and differences in cost, accessibility, and ease of processing of different biologic therapies.

Although a large, blinded, placebo-controlled, randomized clinical trial directly comparing the use of PRP and MSCs would be ideal for determining if PRP or MSCs are beneficial for the treatment of clinical desmopathy or tendinopathy in the horse, efficacy information is already available for individual treatments in multiple previously performed clinical trials. A meta-analysis is a systematic assessment of previous literature to derive conclusions on treatment effects and outcomes. This study sought to compile and analyze prior clinical trials to provide a summary measure of the effect of PRP and MSCs for tendinopathy and desmopathy while simultaneously assessing the quality of the available literature. Only clinical studies involving naturally occurring injuries were included to provide outcome measures immediately relevant to clinical practice. Primary outcomes (return to performance and rate of reinjury) were chosen based on their clinical relevance and their relationship to the economic impact of these injuries. We hypothesized administration of PRP or MSCs would result in higher odds of returning to performance and decreased risk of reinjury compared to the comparator group.

Methods

Criteria for consideration and inclusion

The Population, Intervention, Comparison, Outcome (PICO) tool was used to formulate search criteria and inclusion criteria. The selected “Population” consisted of horses of any age, breed, or sex diagnosed with naturally occurring desmopathy or tendinopathy. The “Intervention” required the selected studies to have used PRP and MSCs for the treatment of tendinopathy or desmopathy. A “Comparator” group must have been present. The comparator group could be an additional biologic or therapeutic, a placebo such as saline, or rest and rehabilitation without administration of an intervention. A historical comparator was considered acceptable if the population was appropriately matched in level of performance, follow-up, and appropriately reported. All studies had to include the “Outcome” of return to athletic performance and reinjury rate. All selected studies were either clinical trials (randomized or nonrandomized) or cohort studies of naturally occurring diseases in peer-reviewed articles; conference proceedings and abstracts were excluded from the study.

Search methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines were followed when completing this systematic review. Studies were selected using the Web of Science Core Collection (including CAB Abstracts, BIOSIS Citation Index, MEDLINE, etc), PubMed, and Scopus from January 1, 2000, to January 1, 2023. Search criteria included ((equine* OR equid* OR horse*) AND (stem cell* OR stromal cell* OR PRP* OR PRP OR platelet concentrate*) AND (tendon* OR tendonitis* OR tendinopathy* OR ligament* OR desmitis* OR desmopathy*)). Language was not limited. Citations were imported in Covidence systematic review software (Veritas Health Innovation) for review by 2 independent researchers (WM, AC). All studies were assessed for the first-level and second-level screening using Covidence, allowing for duplicates to be automatically removed. First-level screening included screening titles and abstracts for primary research that described a clinical trial or cohort study using MSCs or PRP (or both) to treat ligament or tendon disease in horses. Second-level screening included a more in-depth screening to determine if the full text was available in English, if the study described horses with naturally occurring tendon or ligament disease, whether MSCs or PRP (or both) was used, and if the study provided a comparison of at least 2 treatments. Third-level screening was comprehensive and included data extraction as described below.

Data extraction and management

Data were extracted independently by 2 researchers (WM, AC) into a customized data extraction form. Details of the study recorded included country of study, study period, and year of publication; study population details recorded included the primary use of the horses enrolled and age. The lesion type, ultrasound findings, and lameness findings were recorded. The length of follow-up, loss to follow-up, intervention type, intervention dose, route of administration, number of treatments, follow-up examinations, and additional treatments administered were recorded. Disagreements in all screening processes were resolved by discussion among authors. The primary outcomes of return to performance and reinjury were recorded when available.

Methods of review

Study quality was assessed using the Jadad Scoring/Oxford quality scoring system by 2 independent researchers (WM, AC). Risk of bias was assessed as low risk, high risk, or unclear risk for each of 8 categories, including random sequence generation, group similarity at baseline; concealed allocation of groups, blinding of caregivers and personnel, blinding of outcome assessment; incomplete outcome data, selective outcome reporting, and other sources of bias. Studies were assigned an unclear risk of bias if there was insufficient information available to assess the category. No effort was made to contact study authors to gain additional information.

Data analysis

Random effects meta-analysis with inverse variance weighting was used to calculate pooled estimates of the ORs comparing treated versus control
groups for the primary outcomes of return to performance and reinjury. A 3-level model with a random effect of study was used when the analysis involved multiple effect sizes from the same study. A continuity correction of 0.5 was applied to studies with a zero cell count. Heterogeneity was assessed using $I^2$, and the Cochrane Q test. Subgroup analyses were performed for the treatment groups PRP, MSC, and both MSC and PRP. All analysis was performed using the meta package (v6.5.0) for the R statistical software program (v4.3.2; The R Foundation).

**Results**

**Search results**

A total of 1,256 citations were identified from the literature search; 492 duplicate citations were removed (Figure 1). A total of 21 studies were selected for full-text review (Supplementary Table S1).

The studies selected included 7 studies classified as randomized controlled trials and 6 retrospective studies. The remaining studies included prospective uncontrolled clinical trials, nonrandomized prospective controlled trials, and a single observational case-control study. All studies involved clinical investigations with naturally occurring or spontaneous tendinopathy or desmopathy and had at least 2 groups.

A variety of control groups were reported, including saline controls, conservative management (rest or rehabilitation alone or with anti-inflammatory), and conservative management with additional therapies (pin-firing and ESWT). Additionally, 5 studies used a historical control.

Most studies reported a selection of horses from a population of client-owned animals. However, a single study included only animals with severe injury that were donated to the hospital for the study and subsequent euthanization.

The ages, breeds, sexes, and uses of the horses varied greatly between studies. Ten studies evaluated racehorses, 8 studies evaluated English sport horses, 1 study included a mix of racing and sport horses and 1 study included Western performance horses. A single study did not report horse use. Studies with PRP administration included horses 1 to 22 years old. Studies with MSC administration included horses from 2 to 20 years old. Horses treated with a combination of PRP and MSCs ranged from 2 to 19 years old.

**Clinical studies using PRP**

Six studies evaluated the efficacy of PRP for desmopathy or tendinopathy. Within this group, 5 studies compared the use of PRP to either saline control, or rest, while 1 study compared the use of PRP to the use of PRP combined with a collagen hydrogel.

Three studies evaluated PRP administration for suspensory ligament (SL) desmopathy. Of these studies, 2 studies focused on the treatment of proximal SL desmitis and the remaining study evaluated the use of PRP in SL branch desmitis in yearlings. Proximal suspensory desmitis cases were chronic or a mix of acute and chronic. Duration was not defined in cases of suspensory branch desmopathy as authors identified these lesions during yearling screening in animals without lameness. The remaining 3 studies evaluated PRP as a treatment for superficial digital flexor tendon (SDFT) and deep digital flexor tendon (DDFT) tendinopathy.

Six studies assessing treatment with PRP included a wide range of breeds, disciplines, ages, and sexes. A single study focused on suspensory branch desmitis included only Thoroughbred yearlings. The primary disciplines of horses included in PRP studies were sport, racing, and western performance, or were not reported.

The majority of studies utilized ultrasound-guided intralesional injection of PRP. A single study used either intralesional injection or direct infiltration of the proximal SL, and 1 study did not use ultrasound guidance. All of the included studies involved a single injection of PRP, except for 1 study where 3 PRP administrations were recommended at 1-week intervals. However, only approximately half of the horses received the 3 treatments. The second and third treatments were not paid for by the study, so the authors hypothesized that there was less incentive to continue with the treatments.

Platelet concentration and dose were inconsistent among the 6 studies. Reported treatment volumes ranged from 2 to 6 mL, and
4 studies\textsuperscript{16,17,23,32} reported the mean or median concentration. A single study\textsuperscript{18} reported only the volume administered but not the concentration, and a single study\textsuperscript{14} reported neither the volume nor the concentration. Additionally, the methods and devices used to prepare the PRP varied between studies. All studies followed the manufacturer protocols or a modified version of the protocol. One study\textsuperscript{16} reported buffering of the PRP with sodium bicarbonate following preparation, and a single study\textsuperscript{14} reported activation of the PRP product with calcium chloride before injection.

Comparator groups varied by study but always included rest and rehabilitation. Two studies\textsuperscript{16,17} utilized a saline control group, 2 studies\textsuperscript{22,34} compared the treatment group to rest and controlled exercise alone or with NSAIDs, and a single study\textsuperscript{18} compared PRP treatment effects to rest with shock-wave therapy. The remaining study,\textsuperscript{32} which was not included in the meta-analysis, compared PRP to PRP in collagen hydrogel.

Adverse effects were reported in 2 of the 6 studies\textsuperscript{18,21} and included mild, transient local heat and swelling. In 1 of the studies,\textsuperscript{18} the anticoagulant used in the PRP processing was suspected to be causing the reported adverse effects. No adverse effects were reported in the remaining 3 studies.\textsuperscript{16,17,32} The final study\textsuperscript{32} did not report the presence or absence of adverse effects. Of the 6 PRP studies, 5 studies\textsuperscript{16–18,23,34} reported the number of horses that returned to performance, while only 1 reported the rate of reinjury.\textsuperscript{17} A single study\textsuperscript{32} did not report either outcome and was excluded from the meta-analysis (Supplementary Table S2).

Reporting of ultrasound findings was inconsistent between studies. Ultrasound findings were described before and after treatment in 3 studies,\textsuperscript{17–19,32} while the remaining studies\textsuperscript{16,18,34} reported ultrasound findings before treatment only. Of the 3 studies\textsuperscript{17,18,32} that compared ultrasound findings before and after treatment, all reported improvement from treatment to the end of the follow-up period.

Lameness findings were reported in 4 out of 6 studies.\textsuperscript{17–19,23,32} Only 1 study\textsuperscript{23} reported lameness using a described grading scheme (American Association of Equine Practitioners). Lameness was noted to improve in all 4 studies\textsuperscript{17–19,23,32} over the course of the follow-up period. The rest and rehabilitation plan was described in 4 of the 6 studies.\textsuperscript{17–19,23,32}

Clinical studies using MSCs

Ten studies\textsuperscript{12,19,20,22–24,26,29,30,33} evaluated the efficacy of MSCs for treatment of desmopathy or tendinopathy. Comparator groups varied between studies. Four studies\textsuperscript{20,24,29,30} compared MSC treatment to rest and controlled exercise alone or a historical control\textsuperscript{32} of rest and controlled exercise alone. Two studies\textsuperscript{18,19} used a placebo control administered intrasessionally. Finally, a single study\textsuperscript{22} compared allogeneic amnion–derived MSCs to autologous bone marrow–derived MSCs.

Seven out of the 10 studies\textsuperscript{12,19,20,25,26,29,30} focused on cases of SDFT or DDFT tendinopathy. The remaining 3 studies\textsuperscript{22,24,33} examined a mix of injuries, including SDFT and DDFT tendinopathy, SL desmopathy, and rare cases of inferior check ligament, oblique sesamoidean ligament, and distal interphalangeal joint collateral ligament (DIPJCL) desmopathy. Six studies\textsuperscript{12,22,25,29,30,33} did not report on chronicity of the lesions, 3 studies\textsuperscript{18,24,26} reported the lesions to be acute, with 1 study\textsuperscript{20} indicating the treatment of recurrent tendinitis but providing no information on the previous episodes of tendinitis.

Four studies\textsuperscript{21,24,29,30} reported mean or median ages of less than 10 years old for the horses included, and the remainder of the studies\textsuperscript{12,19,20,25,27,29,30} did not report the ages of the participants. Horses were used for racing in the majority of studies, while 2 studies\textsuperscript{24,33} focused on horses used for various sport disciplines. The final study\textsuperscript{22} involved a mix of horses, including sport horses and horses used for flat and harness racing.

There was a wide variety of different MSC types investigated in the identified papers. Five studies\textsuperscript{12,19,25,26,29} employed the use of autologous bone marrow–derived MSCs, and 1 study\textsuperscript{22} used autologous bone–marrow–derived MSCs as a comparator group for allogeneic amnion–derived MSCs. The remaining studies investigated allogeneic umbilical cord blood–derived MSCs,\textsuperscript{24} autologous blood–derived MSCs,\textsuperscript{30} autologous adipose–derived MSCs,\textsuperscript{20} and conditioned medium from allogeneic amniotic membrane–derived MSCs.\textsuperscript{13} All studies utilized ultrasound-guided intrasional injection of stem cells, and a single study\textsuperscript{30} used both local and systemic intravenous injection of MSCs for each treated horse.

A majority of the studies (7/10)\textsuperscript{12,19,22,24–26,33} used MSCs reported the mean concentration or dose range administered. The single study\textsuperscript{32} using conditioned media reported the volume used (2 mL). One study\textsuperscript{20} indicated in excess of 10 million cells were available for implantation but did not state the exact dose administered. Doses ranged from 600,000 cells to 31.2 million cells per lesion, but 6 of the studies\textsuperscript{12,18,22,24–26} reported amounts within the range of 1 to 10 million cells per dose.

A single MSC study\textsuperscript{20} reported adverse effects, which included mild local heat and swelling that was treated with daily hydrotherapy and resolved within 5 days following injection. Five studies\textsuperscript{19,22,24,29,33} indicated no adverse effects following injection during the study period. Three of the remaining studies\textsuperscript{12,25,26} did not report on the presence or absence of adverse effects in the study population but did report that no adverse effects were encountered during the initial safety and feasibility studies performed. A single study\textsuperscript{30} did not indicate whether adverse events occurred.

Four studies\textsuperscript{12,22,24,33} out of the 10 reported the number of horses that returned to performance (8, 13, 20, and 21). Two studies\textsuperscript{29,30} reported a return to performance only in the treatment group. In the final 2 studies,\textsuperscript{25,26} the number of horses that returned to performance could be calculated using the provided data. A total of 7 studies\textsuperscript{12,19,20,24,25,26,29,30} reported a rate of reinjury. Two studies\textsuperscript{19,20} did not report either.
primary outcome and were excluded from the subsequent meta-analysis (Supplementary Table S2).

Ultrasound findings were described before and after treatment in 5 out of the 10 studies. All reported significant improvement or resolution of the lesions from treatment to the end of the follow-up period.

Lameness was reported in 4 studies. Two of these reported mean and range AAEP scores before treatment, but no lameness findings were reported after treatment, while the other 2 studies mentioned absence or reduction of lameness during the rehabilitation period. Lameness was not reported in the remaining 6 studies.

The rehabilitation plan was thoroughly described in 5 studies, and it was mentioned but not described in 4 studies, and the remaining study made no mention of the rehabilitation protocol.

**Clinical studies using combined therapies**

Five studies evaluated the concurrent administration of PRP and MSCs for desmopathy or tendinopathy. Two studies included only cases of DIPJCL desmopathy, 1 study included cases of only SDFT tendinopathy, and the remaining 2 studies included a mix of SDFT and DDFT tendinopathy and SL desmopathy cases. Of these 5 studies, 3 studies focused on acute injuries of less than 30-day duration, and the remaining 2 studies were composed of horses with injuries of greater than 1-month duration.

Four of the 5 studies included sport horses of various breeds and disciplines, and the remaining study included steeplechase horses. Four studies reported the range of ages of the included horses, while the remaining study did not report the ages of the horses.

A variety of MSCs were used in the 5 studies. Two studies used autologous bone marrow-derived MSCs and autologous PRP, and 2 studies used allogeneic adipose-derived MSCs diluted in autologous PRP. A single study investigated the use of tenogenically induced adipogenic MSCs with autologous PRP for a combination of SL and SDFT injuries. The volume or concentration of PRP used was reported in 3 studies out of the 5, and the MSC dose was reported in all 5 studies. Reported doses ranged from 2 to 12 million cells per lesion.

Ultrasound guidance was used in 4 of the 5 studies, and MRI guidance was used for the study of DIPJCL desmopathy. In the majority of the studies, only a single dose was administered during the treatment protocol. In a single study, approximately a third of cases were given a second dose if there was minimal clinical and ultrasonographic improvement noted at the 3-month follow-up exam.

A variety of comparator groups were included in the 5 studies. One study compared the combination of MSCs and PRP to an injection of PRP alone. Two studies used a study by Dyson as a historical comparator of rest and controlled exercise. The remaining 2 studies compared MSC and PRP treatment to rest and pin-firing and rest and NSAID therapy (acetylsalicylic acid and phenylbutazone).

A mild transient local inflammatory response was reported to occur sporadically in 1 study, while the remaining 4 studies reported no adverse effects following injection of the combined MSCs and PRP. Four studies out of the 5 reported a return to performance and re-injury rate. Only 1 study failed to report either primary outcome and was excluded from the meta-analysis (Supplementary Table S2).

The reporting of ultrasound and lameness findings varied. Ultrasound findings were described before and after treatment in 4 studies, while the remaining study reported MRI findings. Of the 4 studies that compared ultrasound findings before and after treatment, all reported notable improvement in the treatment group by 4 to 6 months after treatment, including improved fiber alignment and structure, filling of hypoechoic defects, and decreased cross-sectional area. The study with MRI findings reported partial or complete resolution of DIPJCL lesions in 4 horses that underwent repeat MRI after treatment.

Lameness was reported to some degree in 4 of the 5 studies. Only 2 studies described lameness using a described grading scheme. Lameness was reported to improve in 3 of the studies over the course of the follow-up period. One study did not report baseline lameness but reported persistent lameness during the follow-up period in the control group. The rest and rehabilitation plan were well described in 3 studies and mentioned but not described in 2 studies.

**Study quality and bias**

Although patients would have been unaware of the treatment being administered, in all but 1 study, the clinicians or caretakers were aware of the treatment administered. Of the 23 studies included in the systematic analysis, only 2 studies obtained a Jadad score of 3 indicating a good quality study (Table 1). Three studies achieved a score of 2, 12 studies achieved a score of 1, and 4 studies received a score of 0. Although randomization is mentioned in 7 of the included studies for allocation of the treatment and control groups, only 1 study describes the method of randomization in sufficient detail to ensure adequate randomization.

All studies in the systematic review were assessed for publication bias using the 8 criteria listed above and classified as low, high, or unclear risk of bias accordingly (Figure 2). Seven of the studies avoided selection bias by randomly assigning participants to treatment or control groups. For 2 studies, race records of the treated groups were assessed, and racing data were used as the primary objective outcome. No studies effectively blinded examining veterinarians or owners.
Seventeen of the 21 studies were included in the meta-analysis. Studies that failed to report both primary outcomes were excluded from analysis. There were 5 included studies classified as randomized controlled trials and 6 studies classified as retrospective studies. The remaining studies were classified as prospective uncontrolled clinical trials, nonrandomized prospective controlled trials, and an observational case-control study.

For the purposes of the meta-analysis, the studies were separated into 3 treatment categories: PRP, MSCs (including MSC conditioned media), and the PRP/MSC combination therapy. Studies were classified as having follow-up periods of 6 months or less, 7 to 17 months, or greater than or equal to 18 months. Three studies included data from 2 different follow-up periods. Comparator groups including rest, saline administration, and additional therapies (ESWT and pin-firing) were grouped together as conservative management.
Figure 3—Forest plot demonstrating the results of selected studies using a meta-analysis to compare return to performance of the experimental (treatment) and control groups. The random effects model is shown. MSC = Mesenchymal stromal or stem cells. PRP = Platelet-rich plasma.

Figure 4—Forest plot demonstrating the results of selected studies using a meta-analysis to compare the rate of reinjury of the experimental (treatment) and control groups. The random effects model is shown. MSC = Mesenchymal stromal or stem cells. PRP = Platelet-rich plasma.
Meta-analysis of return to performance for PRP, MSCs, and PRP/MSC combination therapy compared to conservative management showed no statistical difference in the OR of the 3 groups ($\chi^2$ [df = 2] = 0.16; $P = .92$; Figure 3).

Meta-analysis of reinjury rate for PRP, MSCs, and PRP/MSC combination therapy compared to conservative management resulted in a pooled estimate of reinjury OR of 0.29 (95% CI [0.18 to 0.46]; Figure 4). There was no statistically significant difference between the 3 groups ($\chi^2$ [df = 2] = 1.06; $P = .59$); however, the OR was statistically significant in groups 2 and 3 (CI limits both < 1) indicating a protective effect against reinjury in horses treated with MSCs and MSCs combined with PRP. Only a single study reported reinjury rate following PRP administration (OR of 1.00).

Studies using 2 different biologic therapies were analyzed separately (Figure 5). No pooled estimate was made due to different therapies used and the lack of a saline or rest and rehabilitation control group.

**Discussion**

Tendon and ligament injuries are a major cause of economic loss and loss of use in the equine industry. Studies have reported the estimated prevalence of tendon and ligament injuries in performance horse populations ranging from approximately 6.2% to 14.7%. Due to the poor vascularity of tendons and ligaments in the equine distal limb, the healing process is prolonged and results in the formation of scar tissue with greater stiffness and less strength, predisposing horses to reinjury. Biologic therapies including MSCs and PRP have been studied extensively in recent years for the treatment of tendinopathy and desmopathy in horses. Both PRP and MSCs have been shown to have positive effects on outcomes in the treatment of tendinosis and desmitis in the horse.

However, published studies vary widely in design and reporting of results, and limited direct comparisons exist between these treatments. Our systematic review revealed studies with variation in the age, breed, and use of horses. Further, treatments administered had varied processing, dosage and concentrations, and timing of the treatment. Jadad scores were low for the majority of the studies, indicating poor quality clinical trials. The meta-analysis suggests that there is no increase in the likelihood of return to performance with any of the biologic treatments. However, MSCs and MSCs administered concurrently with PRP do appear to provide a reduced risk of reinjury. PRP alone could not be evaluated for risk of reinjury as only a single study reported reinjury rate.

In a systematic review and meta-analysis by Montano et al., no difference was identified in outcomes between PRP-treated horses and control-treated horses. However, study type and outcome measures were inconsistent and variable. Studies included both experimentally induced and naturally occurring injuries and were not required to have a control group, and outcome measures included degree of lameness, ultrasound appearance, return to competition, reinjury, realignment of collagen fibers, and inflammatory mediators. A systematic review completed by Brossi et al. identified the same variability in selected outcome measures and a high risk of bias. Although our study also identified a high risk of bias, it sought to investigate specific clinically relevant outcome measures for both MSC and PRP administration and required controlled studies in an effort to provide focused information for equine practitioners.

Individual studies have focused on a decrease in reinjury rate associated with the administration of MSCs. However, a meta-analysis has not been previously performed to assess whether the decrease in reinjury rate is reflected in the larger body of literature. The performed meta-analysis suggests both MSC and MSC administered concurrently with PRP are protective against reinjury. Unfortunately, the reinjury rates associated with PRP administration were only reported in a single study. No difference was detected in reinjury rate between MSCs, MSCs administered concurrently with PRP, and PRP alone. All reinjury rates for the meta-analysis were reported out of the total animals available for follow-up. The overall lack of consistent outcome reporting, lack of homogeneity between studies and lesions, and often small sample and control group size likely contribute to the high heterogeneity of the reported results and large CIs.

There are significant differences in accessibility, cost, and ease of use for different biologic products, making a better understanding of their effectiveness
crucial in clinical decision making. The prolonged rest period (6 to 12 months in most cases) required for rehabilitation of tendinopathy and desmopathy can lead to significant economic loss along with decreased return to performance following healing. Individual experimental studies investigating MSC or PRP for tendinopathy or desmopathy suggest treatment may lead to a faster repair or stronger repair. The meta-analysis results do not support an increased rate of return to performance when horses are treated with MSC, PRP, or a combination of MSC and PRP, although time to return to performance was not assessed. Rehabilitation periods were variable between studies, and compliance to rehabilitation and follow-up examinations was underreported.

There was no significant difference identified in the rate of return to performance between treatment groups. In some cases, the number of horses that returned to full work was not clearly reported but was calculated from available data. In these cases, some errors could have been introduced into the analysis. Another potential source of error is the lack of consistency in defining return to performance. Because the breeds and uses of the horses varied widely within and between the included studies, it is impossible to standardize what level of athletic activity was considered a return to performance. Despite these limitations, this study suggests that veterinarians should not be administering MSC or PRP with the sole intent of increasing the odds of an animal returning to performance. This is supported by experimental studies that indicate that although tendon tissue healing characteristics are superior in MSC- and PRP-treated animals, the resolution of lameness does not differ between groups. It is important to note that return to performance is only one factor in the economic loss due to tendinopathy and desmopathy, and the rate of reinjury is of significant concern in the industry from both economic and welfare standpoints.

The systematic review and Jadad scoring identified an overall lack of randomization in the included clinical trials. In clinical cases, randomization of horses to treatment and control groups (especially for saline placebo injection) is often difficult. Therefore, historical controls were employed in multiple studies. Historical controls are potentially problematic due to the differences in time period, rest and rehabilitation protocols employed, follow-up times, and horse populations. However, all studies that employed 1 or more historical controls utilized a comparison with Dyson. Unfortunately, 2 studies that evaluated the use of PRP and MSC concurrently were in sport horses, and historical controls included national hunt horses. It should be noted that another potential source of error is the overall variability in the control groups between included studies, specifically, those groups treated with saline placebo controls. Saline placebo controls were used in these studies to attempt to more closely replicate the conditions in the treatment group (needle placement, volume injected), but the injection of saline could also have potential unrecognized negative effects when injected into a lesion.

The authors had sought to include additional outcome measures in the systematic review and meta-analysis including degree of lameness and ultrasound findings. However, reporting of these results was extremely variable, ultrasound grading was inconsistent, and limited lameness data was available. Additionally, while most follow-up exams and lameness assessments were performed by veterinarians, some studies relied on owner or agent evaluations. In those studies that evaluated and reported lameness to some degree before and after treatment or through the follow-up period, 7 of the 8 studies indicated notable improvement or resolution of lameness within 1 to 4 months of injury in both the treatment and control group. In these studies, that reported ultrasound findings, all studies suggested improvement in ultrasound characteristics with biologic treatment, and those with comparison to control groups reported superior ultrasound appearances in the treatment groups versus controls. Control groups utilized in these studies included rest and rehabilitation alone, saline, PRP alone, and nonconditioned MSC media. However, in almost all studies, there was a lack of blinding for ultrasound examinations following treatment, resulting in a high degree of potential bias.

The systematic review identified large variability in the dose utilized for MSC and PRP. With intralesional injection, some variability in the volume administered should be expected. However, little rationalization is given for the dose. In addition, although a majority of studies used a single-dose administration, 3 studies had some horses that received more than 1 dose. This highlights some difficulties in unblinded clinical examinations where treatment administration may be altered depending on owner finances or clinical results during the study. It should be noted that the dosing of PRP in humans and small animals is highly variable as well, with little consistency between studies on the most effective doses, concentrations, or preparation methods.

Studies that used a biologic therapy as a comparator were reported separately. A single study reported allogeneic amnion-derived MSCs resulted in an improved return to performance (OR, 14.06) and a decreased risk of reinjury (OR, 0.16) compared to bone marrow-derived MSCs (BDMSCs). It is worth highlighting that MSCs from multiple different sources (amnion, bone-marrow, tenogenically induced allogeneic peripheral blood MSCs, etc) were grouped for the meta-analysis portion of this study, and this study suggests that MSCs may have large variations in efficacy depending on the source. A second study by Lange-Consiglio et al investigated conditioned medium from MSCs compared to nonconditioned medium. This study was included in the meta-analysis under the assumption that an MSC-conditioned medium would act similarly to MSCs and that a nonconditioned medium was an appropriate comparator. This study also resulted in a marked decrease in reinjury rate, suggesting
conditioned media may be an alternative to the administration of MSCs. Despite limitations including study variability and reporting, and while recognizing the high potential bias and lack of randomization and blinding in the current body of literature, our study identified a significant decrease in reinjury rate in horses that were administered MSCs or a combination of MSCs and PRP for tendinopathy and desmopathy. Improvement is clearly needed in both study design and reporting of clinical trials investigating equine biologic therapies for tendinopathy and desmopathy so unbiased and robust recommendations may be given to equine practitioners. Such improvements should include more consistent and thorough reporting of treatment characteristics (dose, preparation, etc.) and outcome data, larger treatment and control groups, standardization of rehabilitation protocols, effective randomization, and inclusion of blinding.

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