CLINICAL CONCEPTS IN PLATELET RICH PLASMA

Managing Pain and Improving Joint Health

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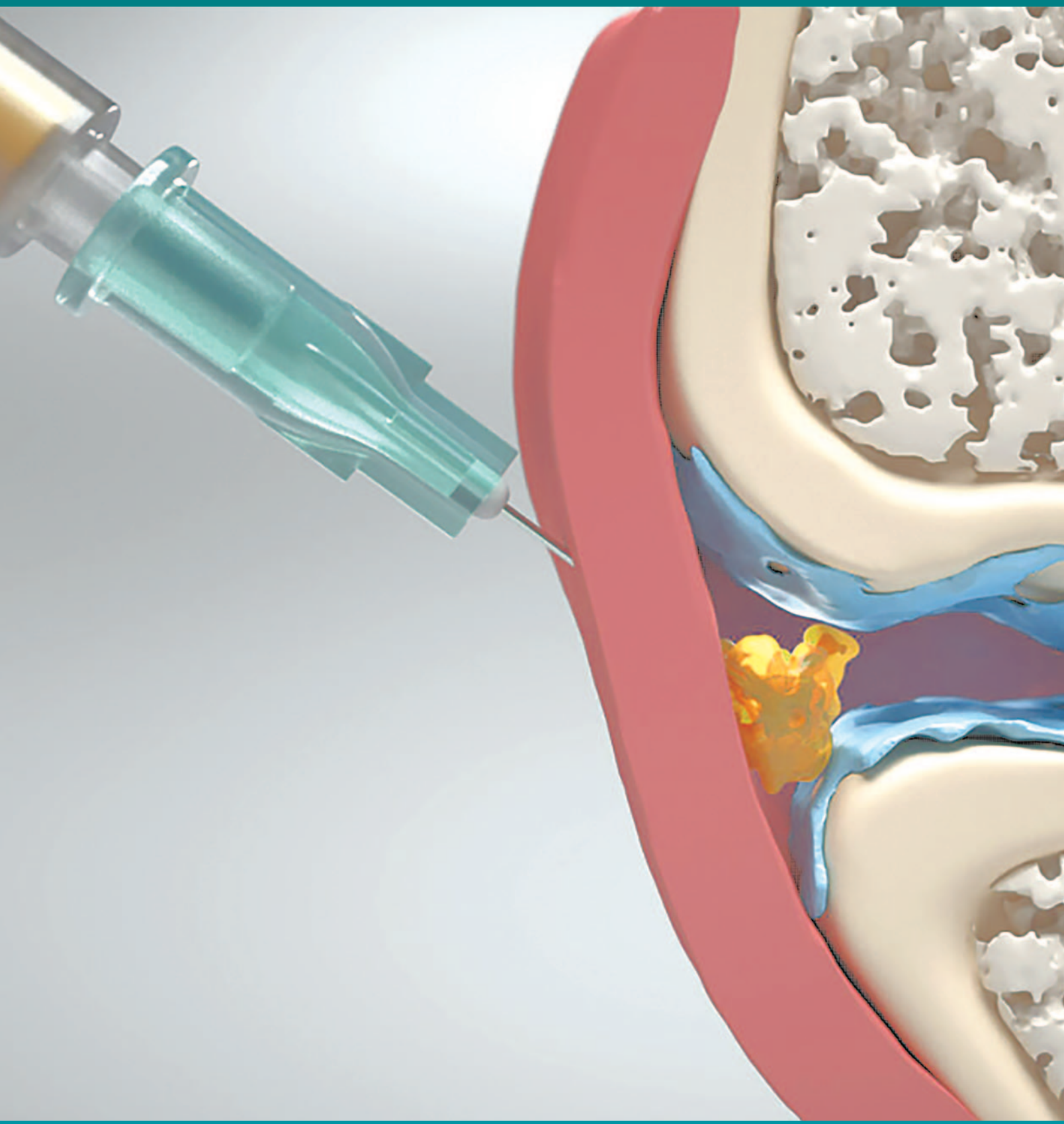


YOUR GUIDE TO ADMINISTERING PLATELET RICH PLASMA

Osteoarthritis (OA) is one of the major disabilities facing pets as they age. This condition frequently leads to pain during otherwise normal daily activities — and generally contributes to a decline in the quality of life. *(Belshaw, Dean, & Asher, 2020)*

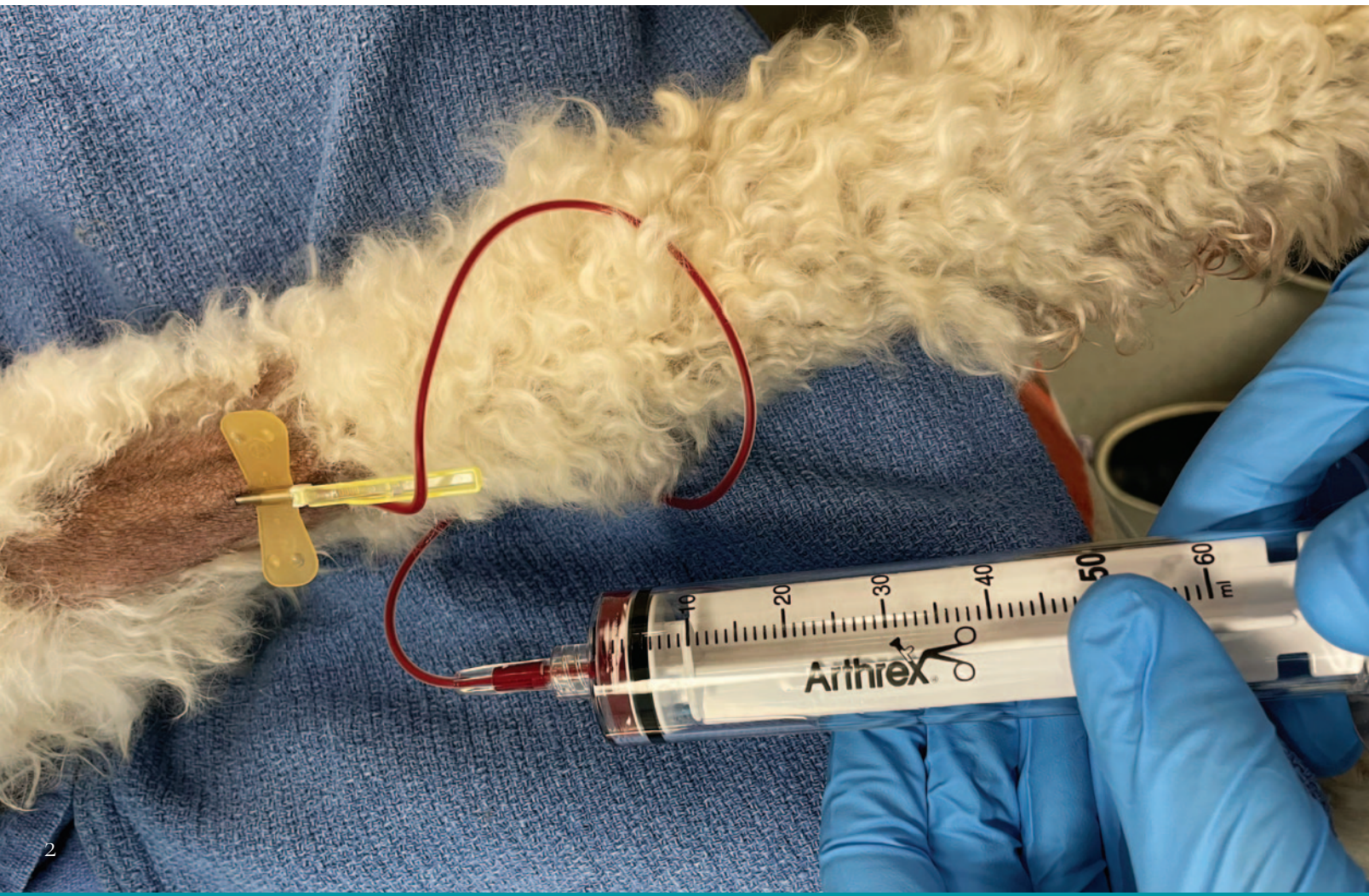
In veterinary medicine, there are a variety of intraarticular injection-based treatments for animals with specific goals for each modality to help combat OA-related changes. These goals can range from pain management to improving the joint environment closer to healthy conditions, attempting to regenerate joint tissues to return native function and structure.

There is a long list of treatment modalities that have been utilized in human orthopedic pathologies which have been hypothesized as potentially benefitting animals that suffer from similar pathologies. Of the long list of treatments, the three that historically have had the most interest in animals are corticosteroids, hyaluronic acid (HA), and platelet rich plasma (PRP) injections.

Corticosteroid injections provide anti-inflammatory and immunosuppressive effects when administered intraarticularly; however, there is significant debate surrounding their use because of concerns for subsequent degeneration of articular tissues, risks of articular infections, and potential serious systemic effects with repeated use. *(Ayhan, Kesmezacar, & Akgun, 2014)* The types of corticosteroids utilized for OA treatment include the crystalline (triamcinolone) and non-crystalline (methylprednisolone) forms. While there have not been any physical function studies completed in canines with corticosteroid injections, there have been studies completed in humans with one showing an improvement in pain by 44% in the treatment group and a 31% improvement in the placebo group. *(Jüni et al., 2015)* There is not a consensus on the safety of corticosteroid injections and its effect on articular cartilage in animals, but one study has shown that the use of triamcinolone injection is cytotoxic to canine cartilage with a reduction in cell viability during in vitro studies. *(Euppayo et al., 2016)* When a study on an equine model of OA was tested in vivo, the injection of methylprednisolone was found to have negative effects on the cartilage compared to the controls when the histopathology was analyzed, but in the same study, triamcinolone showed positive results without affecting the underlying bone. *(D D Frisbie et al., 1997)* While there is not consensus regarding corticosteroid injections and their toxicity on articular cartilage, studies showing detrimental effects of the injections on the cartilage raise serious concerns and veterinarians should look towards other potential options to treat their patients suffering from OA.

Hyaluronic acid is a native component of the synovial fluid that bathes the articular surfaces of the articulating joints. HA is a fluid with viscous properties that has been described as helping with shock absorption and lubrication during daily functions. Due to these properties, HA is considered a viscosupplement when utilized intraarticularly. *(Ayhan et al., 2014; Brockmeier & Shaffer, 2006)* Native HA has been demonstrated to decrease in concentration in the synovial fluid during the progression of OA. In addition, HA is an important component of the cartilage matrix. Subsequently, HA supplementation seems logical. *(Gupta, Lall, Srivastava, & Sinha, 2019; Marshall, Manolopoulos, Mancer, Staples, & Damyanovich, 2000)* HA is commercially available with formulations that are based on the molecular weight, or size, of the injection formulation. While there is likely a benefit with low and medium molecular weight formulations the literature favors the high molecular weight formulations of HA. *(Ayhan et al., 2014)* These high molecular weight formulations have been shown to provide similar properties to naturally occurring HA while still having the capability to be cleared from the joint through synovial capillaries. *(Kuroki, Cook, & Kreeger, 2002; Marshall et al., 2000)* HA treatment has also been described as potentially increasing the endogenous production of HA within a pathological joint, further supporting the potential efficacy of HA injections. *(Moreland, 2003; Marshall et al., 2000)*

While HA may be a reasonable treatment option under certain conditions, it is not a cure for OA nor a regenerative injection option. Studies have indicated improvement in kinetic evaluation and limb function with HA treatment with maximum benefit 4–8 weeks following the treatment. *(Pashuck et al., 2016)* Other studies have shown no improvements in cartilage degradation with HA injections when cartilage was analyzed histologically in



a cranial cruciate transection model. *(Smith et al., 1998; Marshall et al., 2000)* These results indicate that the injection of HA may provide some short-term pain relief through improved joint motion, but it is not actually providing a protective effect for the progression of cartilage damage. The routine use of intraarticular HA is hindered by the short duration of benefits and the need for multiple injections.

Combination therapy of HA and corticosteroids has been suggested as a treatment option due to the separate effects each treatment has independently on the joint to improve joint function with OA. A study of combination treatment in canines with elbow and hip OA showed improved mobility based on client questionnaires at a 6-month timepoint. *(Samuel P Franklin & Franklin, 2021; S P Franklin & Cook, 2013)* In other studies that looked at this treatment combination there were improvements in the subjective measures that were reported by the owners, but this combination did not show a significant difference when compared to autologous fluid or stem cell-based treatments. *(Samuel P Franklin & Franklin, 2021; S P Franklin & Cook, 2013)* These results indicate that these symptom-based treatment modalities may not provide any improved clinical outcomes over autologous treatments such as PRP. Additionally, they do not promote and may inhibit, the cartilage healing that the autologous fluid treatments may provide.

PRP is one of the more clinically examined injectable orthobiologics being utilized in canine OA. PRP is described as an autologous treatment that is isolated from the patient's own blood and provides potential healing effects on orthopedic pathology by providing growth factors and reducing inflammation in an affected joint. *(Arnoczky & Sheibani-Rad, 2013)* The main growth factors that are consistently found in PRP that help improve the healing capability of damaged cartilage are

transforming growth factor β (TGFβ) and platelet-derived growth factor (PDGF). *(Arnoczky & Sheibani-Rad, 2013)* To obtain PRP a venous puncture is necessary. Up to 9 mLs/kg of blood can safely be collected at one time point every 2 weeks. *(Diehl et al., 2001; Hawk, Leary, & Morris, 2005; Morton et al., 1993)* Larger volume of blood collection allows for larger volumes of plasma to be concentrated for injection into an injured joint or joints. Once whole blood is collected, it undergoes a species-specific centrifugation process to separate the whole blood into its unique content. *(Perazzi et al., 2013)* Prior to this centrifugation process an anticoagulant is added. Acid citrate dextrose-A (ACD-A) may be the best option for this application compared to citrate phosphate dextrose-A (CPD-A). *(Marx, 2001)* A slow spin centrifugation is usually performed to bring the red blood cells to the bottom with a buffy coat in the middle and plasma at the top. When double centrifugation is utilized, the plasma is manually removed, avoiding large amounts of buffy coat collection as this is where the leukocytes and immune cells reside. This fluid is then centrifuged at a faster rate to pellet all cellular components and the platelets are separated from the platelet poor plasma (PPP).

With the collection of PRP completed, the next important step is activating the platelets so the growth factors they contain can be released and are readily available to be utilized by the damaged tissue. Several activation methods have been proposed and investigated for efficacy. The easiest form of activation is through freezing and thawing the PRP. Studies have shown that freezing and thawing does create significant release of growth factors in canines while 3 cycles may maximize the total release of the growth factors. *(Samuel P Franklin, Birdwhistell, et al., 2017; Hagen et al., 2020)* This method becomes useful when the PRP needs to be stored for later use, but this option become less attractive when the PRP needs to be used at the patient bedside in a timely manner. Another activation method that has been investigated is the use of calcium chloride or calcium gluconate. *(Raul F Silva et al., 2012)* The calcium binds to the anticoagulant and will results in a gel formation 30 minutes following the activation. A final proposed method for activation without the formation of a gel like product is the use of human gamma thrombin. *(Samuel P Franklin, Birdwhistell, et al., 2017; Samuel P Franklin & Birdwhistell, 2018)* There are currently no studies on canines for xenogenic use of this protein and the manufactures of this product do not state it as an indicated use. It has also been suggested that platelets are naturally activated when they are injected into the joint. While there are no studies investigating this claim in canines, there are mixed results in equine studies. One equine study combined PRP with synovial fluid in an ex vivo setting and results suggested it did activate the platelets, but in another equine study the joints were aspirated 5 days after the initial unactivated PRP injection and the authors found intact platelets indicating that there is not full activation of the platelets in vivo. *(Textor, Willits, & Tablin, 2013; Textor & Tablin, 2013)*

When isolating the platelets and plasma for PRP it is important to consider the other components of the blood that may be collected with the process and the effects they may have on the joint which the PRP is being injected into. First, erythrocytes can be collected when removing the plasma after the initial centrifugation. It is generally agreed upon that erythrocytes have negative side effects on the synoviocytes of the joint, causing an increase in joint inflammation due to synoviocyte death. *(Braun et al., 2014; Everts et al., 2019)* The next component are the leukocytes contained within the buffy coat. This component has been shown to increase IL-1β and matrix metalloproteinase 9, which have negative side effects on the cells and matrix of the cartilage leading to increased cartilage degeneration. *(Sundman, Cole, & Fortier, 2011)* This has been further supported by an ex vivo study that showed an increase in synoviocyte cell death when there were leukocytes present in the PRP compared to the leukocytes not being present. *(Braun, Kim, Chu, & Dragoo, 2014)*

When considering PRP for a patient, it is important to factor in the time and costs associated with the treatment. The process of collecting PRP can be completed with basic laboratory equipment and clinical supplies but these processes reduce the overall quality of the product compared to commercial systems. A commercial system is a better option for private practice clinicians. While these commercial systems may be more costly to start, the overall price point is reduced when the main reoccurring cost is the disposables associated with each use. This cost may be further reduced as companies may be willing to provide the centrifuge needed while an agreed upon number of disposables are utilized per year. This option may be a beneficial one for clinicians who have a large client base and are likely to perform a significant quantity of these procedures in a given calendar year. It is important to note that not all PRP systems are created equal. A study analyzing 5 separate PRP systems showed a large amount of variability in platelet concentration, from baseline up to a 5-fold increase. *(Samuel P Franklin et al., 2015)* Another study showed there is a strong correlation between this concentration and the concentration of the growth factors. *(Samuel P Franklin et al., 2017)* This highlights the importance of selecting a system that has been proven to provide a high-quality product to maximize the potential of healing and an improvement in quality of life.

BLOOD COLLECTION TECHNIQUE

When needing to collect a significant amount of blood for processing a biologic (generally > 20mL of blood at a time), sedation of the patient is recommended. This will be needed regardless for injection after processing the blood for PRP/ACP/ACS. The patient is placed in lateral recumbency, and the jugular vein is aseptically prepared. A butterfly needle is useful so that if more than one syringe of blood is collected it is easy to do so without having to obtain venous access more than once. For large breed dogs a 19-gauge needle is used. In general, the largest gauge needle that is appropriate should be used for blood collection. If access cannot be gained via the jugular vein, the lateral saphenous vein in the pelvic limb or the cephalic vein in the thoracic limb are alternatives for access.

In general, it is safe to draw up to a maximum of 10% of the patient's total blood volume every 2 weeks for systemically healthy animals, though most recommendations suggest that only 7.5% be drawn at one sitting. A dog's total blood volume is ~7-9% of its body weight. To calculate a dog's blood volume, the following formula is used: patient body weight (kg) * 80 mL/kg. Cats have a slightly lower blood volume at ~6.5% of their body weight. This can then be used to calculate the amount of blood that can be drawn. The amount of blood needed for processing varies by the system being used. Rarely are dogs too small for the volume needed for most systems. However, this needs to be assessed on a case-by-case basis as some systems require 60mL of blood to process, and in smaller dogs this can become unsafe. In most cats, it is not safe to use a system that requires such a large volume, and a system needs to be utilized that requires less blood volume. If there is concern for a patient's systemic health, blood draws of large volumes should not be performed. In some cases, IV fluid therapy following a large blood draw can be considered, but in routine cases is usually not needed if guidelines for appropriate safe volumes of blood collection are followed.

PRP PREPARATION

Approximately 10% of a dogs blood volume may be safely acquired for PRP preparation every two weeks. This translates to approximately 9mls/kg of body weight. In a 30kg dog this would provide 270 mls of blood for processing. In many patients, significantly more blood can be safely drawn than can be processed by most PRP systems. *(Diehl et al., 2001; Hawk et al., 2005; Morton et al., 1993)*

When considering a 25 kg dog up to 225 mLs can safely be acquired. These large volumes, or greater, are commonly acquired from canine blood donors for the preparation of whole blood transfusions or packed red

blood cell and plasma transfusions. Hence, the upper limit of blood that can be safely processed likely greatly exceeds what most PRP preparation systems enable.

PRP INJECTION FREQUENCY RECOMMENDATIONS

Two protocols are often cited regarding the frequency of PRP administration. There is limited definitive clinical evidence to support one protocol over another.

Protocol 1: Administer PRP and observe for improvement. If there was improvement but lameness is returning, consider second injection.

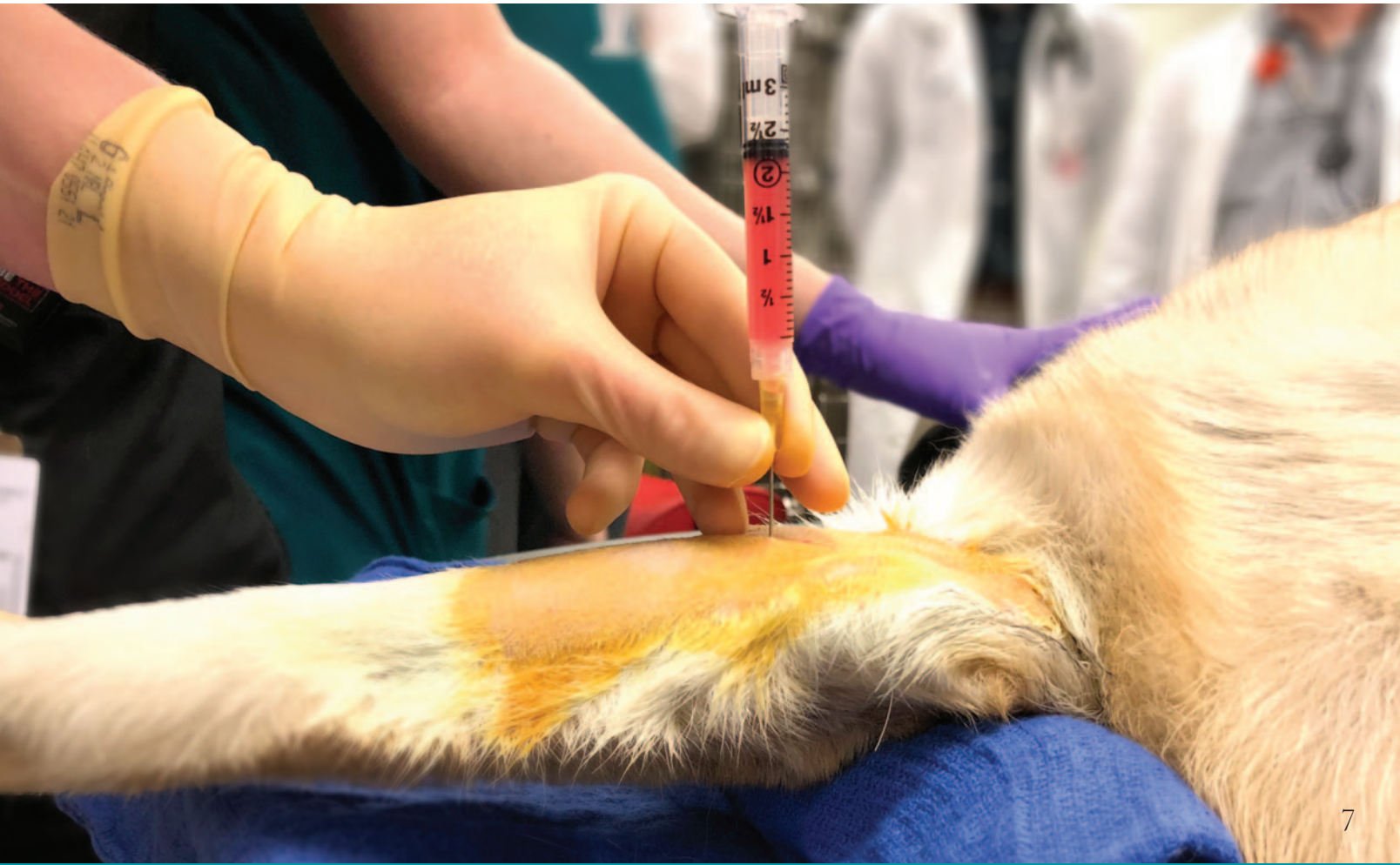
Protocol 2: Administer three intraarticular injections each 2–3 weeks apart.

PRP platelet activation methods:

- 10% Calcium chloride may be added to the PRP. 23 microliters is added per 1ml of PRP.
- Activation may be achieved by one to three cycles of freezing and thawing.
- Aliquot and freeze a solution of bovine thrombin (5000 International Units reconstituted) At time of administration 1ml of this solution is added to every 9mls of PRP. This results in rapid activation and fibrin formation.

PRP CONCEPTS

- PRP is a “platelet rich” biologic that concentrates important growth factors.
- PRP has been extensively evaluated and used for the treatment of osteoarthritis in human and veterinary patients.
- The ideal platelet concentration is uncertain and different values have been studied with varying results.
- The optimal leukocyte concentration in PRP is also debated.



- Most clinicians believe that PRP for intraarticular use should probably have few, if any, erythrocytes.
- Platelet activation releases their growth factors and both in-vitro and ex-vivo methods have been proposed.
- The ideal frequency of PRP injection has yet to be determined and may vary between cases
- When saving PRP for later use it should be stored at -20°C, or as low as -80°C.

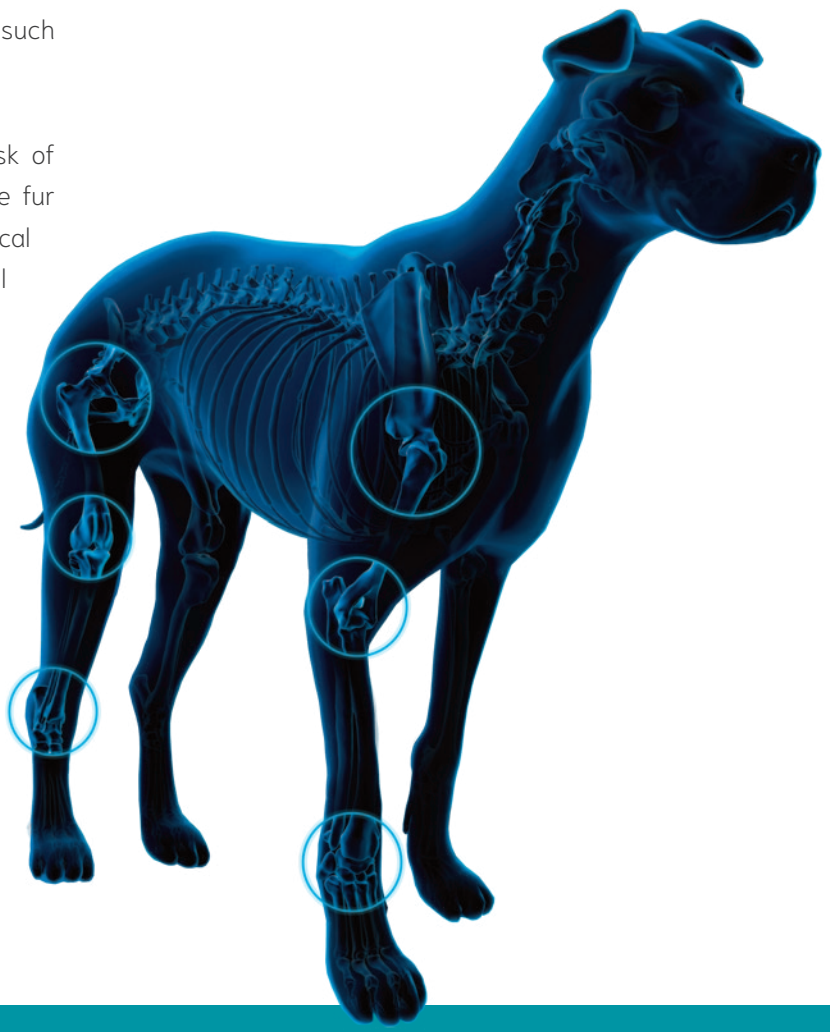
Joint Injection Technique

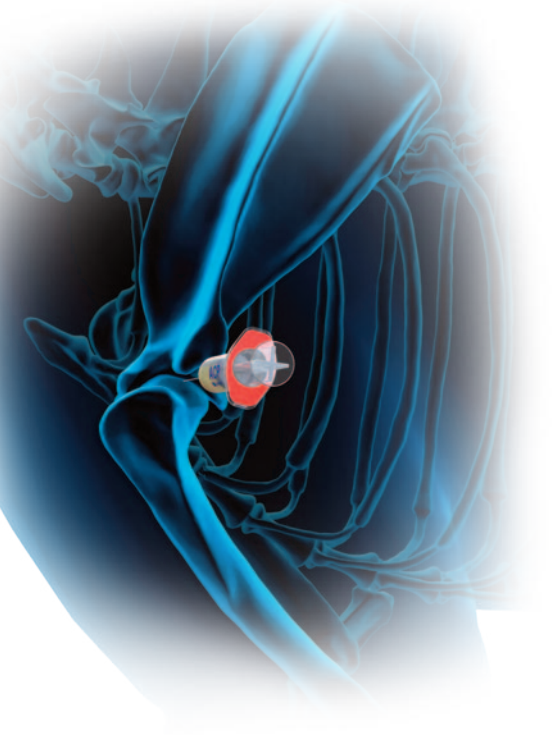
Joint injections are most frequently performed as adjunct therapy for the treatment of osteoarthritis. Joint injections should be performed under sedation and aseptically. Reversible sedation is ideal, as the procedure itself is relatively rapid. An opioid like butorphanol, coupled with dexmedetomidine given IV can be reversed with atipamezole IM. Care must be taken to ensure these medications are safe for each individual patient. Alternatives can be used, particularly in patients with cardiac disease such as alfaxalone.

Aseptic technique is used to decrease the risk of inducing septic arthritis during the procedure. The fur should be clipped over the area, to include palpable local landmarks. The authors prefer to perform an initial dirty prep using chlorhexidine or betadine solution and then completing a final sterile prep. The injection can then be performed.

General supplies needed to perform a joint injection include needles, syringes, and sterile gloves. The clinician should have slides, collection tubes, and culturettes readily available if joint fluid aspirated is suspicious for infection.

After sterile prep of the joint, when the injectate is ready, sterile gloves are donned, and a needle is inserted into the joint. Joint fluid should be aspirated in a syringe to confirm the joint space has been entered. Gross evaluation of the joint should be performed, and if any concern for infection or pathology aside from osteoarthritis (OA) is suspected, cytology should be performed prior to joint injection. In general, joint fluid should be straw-colored, clear, and viscous. Loss of viscosity will be seen in cases of OA. If there is an excessive volume of turbid fluid or serosanguinous fluid, cytology is indicated. Common reasons for not being able to obtain joint fluid include: improper technique (reinsert needle), shallow or deep joint (back needle out and try again, or use a longer needle (common error in joints like the shoulder), tissue plugging needle in joints with significant synovitis (rotate needle, reposition and re-aspirate), or there is little fluid in the joint (chronic hip joint).



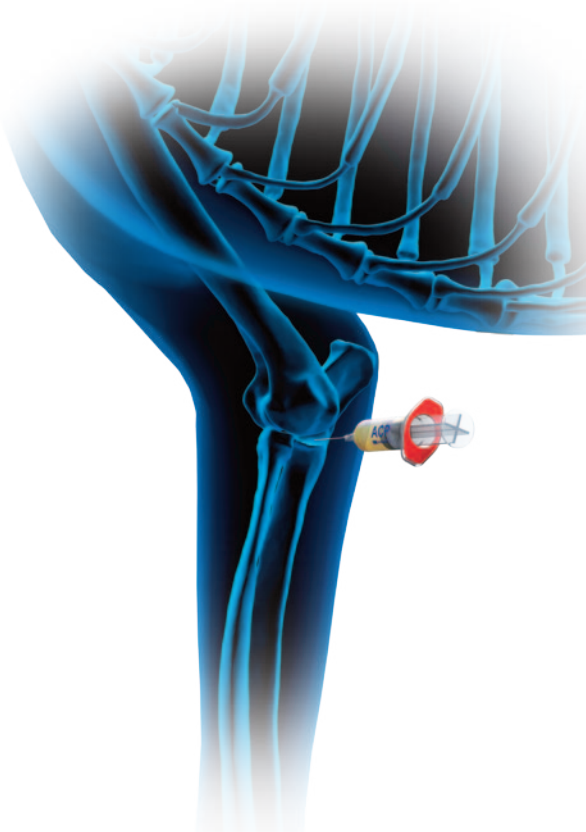


SHOULDER

The patient is placed in lateral recumbency for shoulder injections. The acromion is the main anatomic landmark utilized to locate the shoulder joint. Fur is shaved proximal, distal, cranial, and caudal to the acromion so that it can be palpated during the injection. Observing the morphology of the dog's acromion on radiographs prior to injection can be useful as some dogs have a very low-hanging acromion while others are more proximal. The limb is maintained in a neutral position. On average, however, in a large breed dog, the joint space will be approximately 0.5–1 cm distal to the acromion with the needle inserted perpendicular to the skin. If bone is hit, the needle can be "walked" and angled proximally or distally off the humerus or glenoid to enter the joint space. Typically, in a large breed dog, a 1.5" length needle can reach the joint space, though in well-muscled dogs, or obese animals and giant breed dogs a longer spinal needle may be required to reach the joint space.

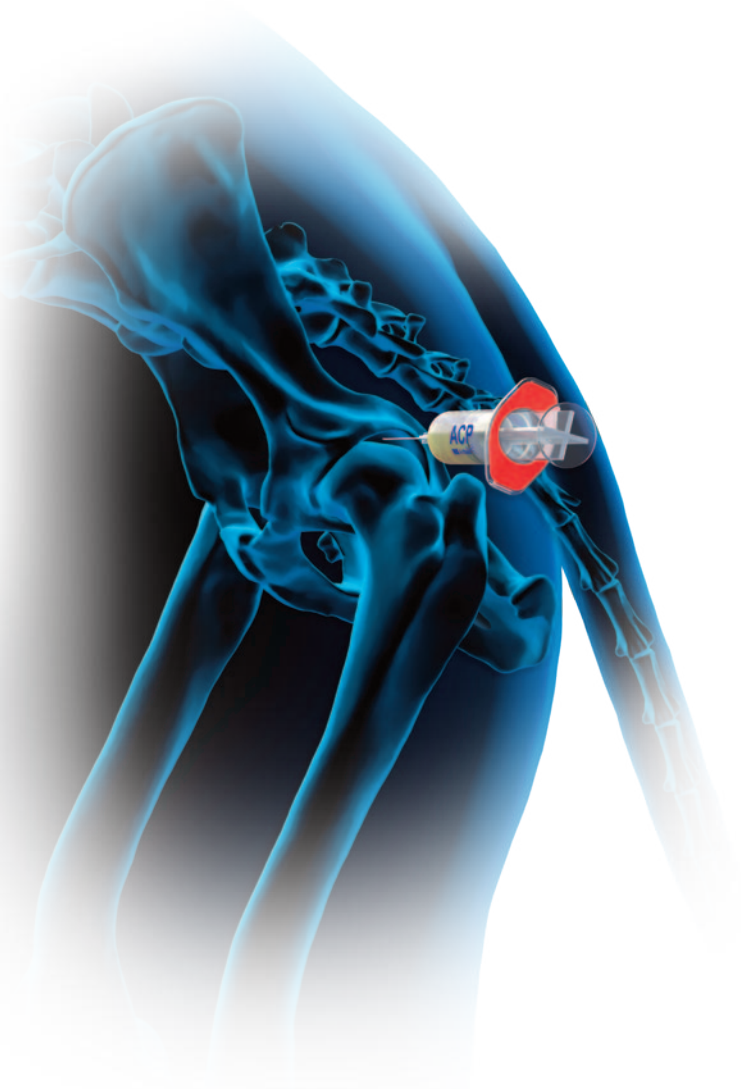
ELBOW

The elbow can be injected via a lateral or medial approach, though the authors prefer a medial approach. The dog is placed in lateral recumbency with the limb to be injected down. The medial epicondyle is the landmark used for this approach, and fur is shaved around the landmark. The limb is extended and pulled from the body wall, while the upper limb is restrained along the body wall. It can be helpful to place a rolled towel below the joint on the lateral aspect to apply a valgus stress to open the joint space medially. The joint space is distal to the medial epicondyle in line with the axis of the humerus, ~1.5–2 cm distal to the epicondyle in the average large breed dog. Radiographic measurements can be made to aide in determining distance to the joint from the epicondyle if needed. If a lateral injection is performed the affected limb is placed up and the fur is shaved from cranial and proximal to the epicondyle and caudally past the olecranon. The joint is entered from halfway between the lateral epicondyle and olecranon with the needle aiming distomedial along the parallel axis of the ulna.



CARPUS

The patient is placed in lateral recumbency with the affected limb up. The radiocarpal joint is most accessible due to its size and is accessed from the dorsal aspect of the limb. The distal radius can be palpated, and the fur shaved surrounding the joint space just distal to this. The carpus can be flexed and extended to locate the joint space. Holding the joint in some flexion (typically ~45°) helps to open the joint space. Palpate the distal aspect of the radius to find the joint space just distal to it. The joint space is accessed just medial or lateral (most commonly medial) to the cephalic vein and the common digital extensor tendon that runs across the joint. The needle is aimed in a dorsal to palmar direction parallel to the joint surface of the radius.



HIP

The patient is placed in lateral recumbency with the affected limb up. The greater trochanter is the primary landmark for this injection. Fur is shaved proximal, distal, cranial, and caudal to the greater trochanter. The joint space is just cranial and proximal to the greater trochanter. The limb is placed in slight abduction with distal traction being applied to help open the joint space. The needle is inserted perpendicular to the skin and long axis of the femur just proximal and cranial to the trochanter. As in the shoulder joint, if bone is hit, the needle can be "walked" proximally or distally to find the joint space. The joint should not be accessed from the caudal to the greater trochanter to avoid iatrogenic damage to the sciatic nerve.

STIFLE

The patient is placed in lateral recumbency with the affected limb up or in dorsal recumbency in a trough. An area from proximal to the patella and distal to the tibial tuberosity is shaved. The joint is flexed to ~90° angle. In lateral recumbency, this is accomplished by having an assistant flex the stifle and abducting the limb, and placing the foot on the table. The needle is inserted parallel to the tibial plateau. This angle will vary based upon the tibial plateau angle and should be assessed on radiographs prior to injection. The needle is inserted approximately ⅓ to ½ of the distance from the patella to the tibial tuberosity, either medial or lateral to the patellar tendon. Some variability exists in the tibial tuberosity and patellar tendon insertion, so this should also be assessed on radiographs to help determine the location of needle insertion. The needle is aimed slightly axially towards the intercondylar notch.

TARSUS

The patient is placed in lateral recumbency with the affected limb up or down. Fur surrounding the entire region of the tarsus is shaved to extend 360° around the joint, distal to the tibiotarsal joint, and proximal to the malleoli. The joint can be accessed from the lateral and medial, both cranial and caudally. Flexing and extending the hock helps to identify the joint space. The joint is accessed distal to the tibia and proximal to the talus dorsally, either lateral or medial to the saphenous vein and extensor tendons. From caudally and laterally, the joint is accessed distal to the lateral malleolus (distal fibula), angling from caudodistal to cranioproximal and distalateral to proximomedial.

Table 1. Needle Size for Average Large Breed Dog

JOINT	NEEDLE SIZE
Shoulder	20 gauge, 1.5" hypodermic needle/2" spinal needle
Elbow	20 gauge, 1.5" hypodermic needle
Carpus	22 gauge, 1" hypodermic needle
Hip	20 gauge, 2–3" spinal needle
Stifle	20 gauge, 1.5" hypodermic needle
Tarsus	22 gauge, 1" hypodermic needle

Table 2. Needle Size for Average Small Breed Dog

JOINT	NEEDLE SIZE
Shoulder	22 gauge, 1.5" hypodermic needle
Elbow	22 gauge, 1" hypodermic needle
Carpus	25 gauge, 1" hypodermic needle
Hip	20 gauge, 1.5" hypodermic needle/ 2" spinal needle
Stifle	22 gauge, 1" hypodermic needle
Tarsus	25 gauge, 0.5" or 1" hypodermic needle

Table 3. Maximum Allowable Blood Volume Draw for Canines

WEIGHT (LB)	WEIGHT (KG)	MAXIMUM BLOOD DRAW VOLUME (mL)
5	2.3	30
10	4.5	60
15	6.8	90
20	9.1	120
25	11.3	150
30	13.6	180
35	15.9	210
40	18.1	240
45	20.4	270
50	22.7	300
55	24.9	330
60	27.2	360

Table 4. Maximum Allowable Blood Volume Draw for Felines

WEIGHT (LB)	WEIGHT (KG)	MAXIMUM BLOOD DRAW VOLUME (mL)
2.5	1.1	12
3.0	1.4	18
3.5	1.6	22
4.0	1.8	25
4.5	2.0	28
5.0	2.3	30
5.5	2.5	35
6.0	2.7	38
6.5	2.9	42
7.0	3.2	45
7.5	3.4	48
8.0	3.6	50

PRP VOLUMES TO INJECT ≤ ML							
	KG	Shoulder	Elbow	Carpus	Hip	Stifle	Tarsus
Toy / Cat	5	0.5	0.25–.5	0.25	0.5	0.5	0.25
Small	5–10	0.5–1	0.5–1	0.25–.5	0.5–1	0.5–1	0.25–.5
Medium	10–20	1–1.5	1–1.5	0.25–1	1–1.5	1–1.5	0.25–1
Large	20–50	1.5–2	1.5–2	0.75–1	1.5–2	1.5–2	0.75–1
Giant	50+	2–3	2–2.25	1	2–3	2–3	1

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