- **Is Platelet Rich Plasma (PRP) a substance which should be included on the drug/substance list; and**

- **Are there factors or limitations that may prevent the podiatric use of this substance?**

COLLEGE OF CHIROPODISTS OF ONTARIO TECHNICAL COMMITTEE

MEMBERS:

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PURPOSE:

The Registrar of the College of Chiropodists of Ontario referred the following questions to the Technical Committee of the College of Chiropodists, in order to respond to an enquiry submitted:

1. Is PRP a substance which should be included on the drug/substance list; and
2. Are there factors or limitations that may prevent the podiatric use of this substance?

(The Committee deem the questions to be related to 'ALL registered member of the College of Chiropodists of Ontario' including BOTH the Chiropodist and Podiatrist class of registrant.)

EXECUTIVE SUMMARY

Definition and Formulations of Platelet-Rich Plasma (PRP)

- By definition, PRP must contain a higher concentration of platelets than baseline. Absolute platelet count varies depending on the platelet concentration in the subject's peripheral blood. PRP devices can be usually divided into lower (2.5 - 3 times baseline concentration) and higher (5 – 9 times baseline concentration) systems. PRP can only be made from anti-coagulated blood. Whole blood is drawn, PRP kits use an anti-coagulant to prevent it from clotting. This is followed by one or two centrifugation steps. The PRP must then be clotted to allow for delivery to the desired site

Potential applications of PRP within the practice of Members of the College of Chiropodists of Ontario

- PRP is generally considered an elective treatment for subacute and chronic conditions. Basic science and animal studies are supportive for the use of PRP. There has been literature on the beneficial effects of PRP for chronic non-healing tendon injuries including lateral epicondylosis, plantar fasciopathy and cartilage degeneration. Technique, number of injections, spacing of injections, number of platelets, concentration of platelets over baseline, with or without leukocytes in the injection, exogenous activation of injected platelets, use of common and validated outcome measures (i.e. VISA scores) in studies and patient selection vary enormously between studies. Therefore, clearly positive high-level human evidence is still lacking in Randomized Double Blind Placebo Controlled Trials (RDBPCT). Until further studies

prove the real translational potential of the promising results, PRP should be considered a second line treatment, and applied in humans within well controlled studies.

Use of PRP under The *Food and Drugs Act, Chiropody Act* & *Regulated Health Professions Act*

The definition of "drug "under The Food and Drugs Act captures PRP, Health Canada holds the position that federal regulatory authorization requirements apply to PRP.

If processed and then immediately used by a physician specialist (all within a clinical setting), professional regulatory bodies such as the College of Chiropodists of Ontario may be involved instead of Health Canada. PRP was considered by the regulating Colleges of Physicians and Surgeons as an established medical practice for that indication.

If PRP fell under our professional scope of practice, and depending under what circumstances this is considered acceptable, Health Canada may then agree that under such circumstances the Food and Drug Regulations do not apply.

If a product is not autologous, i.e. (from another person), if it is stored, or 'processed 'it would require a Drug Information Number. Health Canada to date has **NO** such product approved.

Blood needs to be drawn for any autologous PRP based procedure to be performed. Such Phlebotomy in Ontario is restricted by the Regulated Health Professions Act. It is not a directly or an exempted act that can be performed currently by Members of the College of Chiropodists of Ontario. PRP is not a substance listed under Schedule 1 and as such cannot be currently used or prescribed by Members of the College of Chiropodists of Ontario.

Conclusions / Recommendations to Council of College of Chiropodists of Ontario

The Technical Committee concludes:

- PRP is not a substance listed under Schedule 1, and cannot be currently independently used or prescribed by Members of the College of Chiropodists of Ontario.
- Commercially available PRP kits use anticoagulant and activating agents These agents are not currently on Schedules approved for use by Members of the College of Chiropodists of Ontario.
- Whole blood needs to be drawn for any autologous PRP based procedure to be performed. Currently Member phlebotomy access would only be permissible by delegation or a medical directive, it is not a directly or exempted act that can be performed currently by Members of the College of Chiropodists of Ontario.
- If PRP product is not autologous (i.e. donated / stored/processed) it would require a Drug Information Number. Health Canada to date has NO such product approved.
- Injection techniques of PRP follow similar techniques for soft tissue and intra-articular injections of corticosteroids and Hyaluronic acid visco-supplements and are within the scope of Members

- The application of PRP has been documented in many fields. At present, there are a limited number of studies with fewer RCDBPCT's, producing restricted evidence supporting the use of PRP for foot and ankle pathology
- Current and future (*barring legislative changes*) Members of the College of Chiropodists of Ontario access to and use of PRP is permissible by delegation or a medical directive.

CORE POINTS IDENTIFIED, AND CONSIDERED BY THE TECHNICAL COMMITTEE:

- What is the definition of PRP?
- How is PRP harvested and prepared?
- What are the potential applications of 'PRP' within the practice of Members of the College of Chiropody of and what is the clinical evidence to support its use?
- How is PRP regulated?

METHODOLOGY

A literature review and detailed assessment of the available body of research that addressed the Core points was performed using Medline, Google Scholar, Cochrane Database of Systematic Reviews, National Center for Biotechnology Information and web based search engines. Data was distributed to committee members for analysis and reviewed during a teleconference.

Communication was made directly with Health Canada's Office of Policy and International Collaboration-Biologics and Genetic Therapies Directorate -Health Products and Food Branch via telephone and email

DEFINITION OF PLATELET RICH PLASMA'(PRP)

PRP contains a 3- to 5-fold increase in growth factor concentrations. A number of terms have been loosely used to refer to preparations that isolate and concentrate platelets, such as "plasma rich in platelets." The term "platelet concentrate" has been used, but is inaccurate because this implies a solid composition of platelets without plasma, which would not clot. The term "platelet gel" has also been used, but this is also incorrect because the gel does not contain the cell adhesion molecules present in clot. Platelet-rich plasma differs from "fibrin glue" because the clot in PRP contains only the same concentrations of fibrin as a normal blood clot. (1,2,)

Platelets are small, non-nucleated bodies in peripheral blood that are known primarily for their role in hemostasis. Platelets contain a number of proteins, cytokines, and other bioactive factors that initiate and regulate basic aspects of wound healing. Plasma is the fluid portion of blood and contains clotting factors and other proteins and ions. By definition, PRP must contain a higher concentration of platelets than baseline, however an increase in platelets is a very gross description of PRP and does not accurately describe the variability among different types of PRP. Normal platelet counts in blood range from 150 000/f. lL to 350 000/f.lL. (1,2)

Several parameters need to be considered with PRP, including: platelet concentration above baseline, whether or not leucocytes are included, whether or not the PRP has been anti-coagulated and whether it requires exogenous activation.

Absolute platelet count varies depending on the platelet concentration in the subject's peripheral blood. PRP devices can be usually divided into lower (2.5 - 3 times baseline concentration) and higher (5 – 9 times baseline concentration) systems. Greater platelet concentrations have not been shown to further improve healing, although a number of variables affect the biologic activity of various PRP preparations It would seem intuitive that a higher platelet count would yield more growth factors and better clinical results, however, this has not yet been determined. Graziani et al (3) suggest that '*the optimal concentration of PRP is 2.5x baseline, above this there may be an inhibitory effect*.'

PRP containing white blood cells will have different biologic activity than PRP in which they are absent. The lower platelet count systems separate the whole blood into two components: one with the cellular components and the other consists of serum in which the platelets are suspended. The higher platelet count systems separate the whole blood into three fractions: the red cells, serum and buffy coat. The buffy coat contains both platelets and white blood cells (WBCs). WBC can be further classified into different types. These include neutrophils, monocytes/macrophages, and lymphocytes. Their roles in tissue healing are different. Neutrophils are phagocytic and contain over 40 hydrolytic enzymes. Their activation leads to phagocytosis of debris and the release of oxygen free radicals and proteases. This release of toxic molecules from the neutrophils can lead to secondary damage to the muscle (1,2,3). Whether or not neutrophils have a negative or positive effect on acute or chronically injured soft tissue is unknown. Macrophages are the tissue form of the circulating monocytes. Their role is the removal of debris and they are primarily phagocytic. They also have a role in balancing the pro-inflammatory and anti-inflammatory aspects of healing Since it is not possible to fractionate different types of white blood cells out of PRP, it may be that the absence of macrophages is more detrimental healing than any secondary damage inflicted by neutrophils.

FORMULATION OF PRP

Platelet-rich plasma can only be made from anti-coagulated blood. It cannot be made from clotted whole blood because platelets become part of the clot. (1,2) PRP also cannot be made from serum. Serum is the clear liquid part of the blood that remains after blood cells and clotting proteins have been removed; the serum contains very few platelets.

When whole blood is drawn, many PRP kits will use an anti-coagulant to prevent it from clotting. Most kits use anticoagulant citrate dextrose (ACD) to inhibit clotting. ACD binds calcium and prevents the coagulation proteins from initiating the clotting cascade. The addition of citrate to the blood also makes it more acidic than is physiologic. Since some growth factors are influenced by the pH of the tissue, some protocols recommend buffering the PRP back to a physiologic range prior to injection. (3)

This is followed by one or two centrifugation steps. The first centrifugation step separates the red and white blood cells from plasma and platelets. Red blood cells (7 Jlm in diameter) and white blood cells (7-15 Jlm in diameter) are much larger than platelets (2 Jlm in diameter); these cells separate from the plasma and platelets. The second centrifugation step further concentrates the platelets, producing the PRP separate from platelet-poor plasma.

The PRP must then be clotted to allow for delivery to the desired site. PRP can be activated exogenously by thrombin, calcium chloride or mechanical trauma. Once PRP is activated, a fibrin network begins to form, solidifying the plasma and creating a fibrin clot or membrane. If PRP is activated too strongly, the fibrin network will be a bivalent, unstable network.

Some commercially available systems use bovine thrombin to activate the clotting mechanism. An important point is that clotting leads to platelet activation, resulting in release of the growth factors from the a-granules, otherwise known as degranulation. Many growth factors have short half-lives, so greatest effectiveness may result if they are activated at or just prior to injection. Variable half-lives of growth factors also create a differential PRP make-up depending on how quickly after activation it is used. Approximately 70% of the stored growth factors are released within 10 minutes, and nearly 100% of the growth factors are released within 1 hour. Small amounts of growth factors may continue to be produced by the platelet during the rest of its lifespan (8 to 10 days), The use of bovine thrombin to activate the clotting mechanism and to induce platelet activation can lead to complications associated with formation of antibodies against the bovine thrombin. This is a rare but potentially serious complication that can result in an immune-mediated coagulopathy. Collagen is a natural activator of PRP, thus when PRP is used in soft tissue, it does not need to be exogenously activated. Once activation has occurred at the injection site, release of growth factors initiates an inflammatory response that lasts approximately 3 days

If it is activated in a more physiologic manner, a tetra-molecular stable network forms that enhances enmeshment of cells and growth factors. (1,2) Although this can be useful for surgical procedures, it is undesirable to have the PRP overly viscous when injecting into soft tissue.

Most commercial PRP kits do not activate PRP. Some replace calcium that was bound by ACD to create a more physiological state. Employing inactivated PRP may result in a more normal physiologic activation by the injected tissue. To avoid unintentional activation of platelets, most protocols use large bore needles (>22) to draw the blood and re-inject PRP. In addition, there are different centrifuge protocols with different spin speeds and times. Some centrifuges offer special braking mechanisms to prevent unintentional activation. The optimal regimen to prevent unintentional activation is unclear. (4). Fibroblasts accumulate at the site of injection, which marks the beginning of the proliferative phase of healing that lasts several weeks. After that, remodeling occurs to the collagen matrix that was laid down by the fibroblasts. This remodeling phase that leads to the formation of mature tissue lasts about 6 months. It takes all three phases for new tissue to form and provide long-term stability to tissue (1,2,3,).

BLOOD HARVEST AND CENTRIPETAL PRP PREPARATION METHOD

The technical specifications for PRP preparation are varied as are the clinical applications of prepared material. Akundov et al (4) describe the following technique:

Harvesting of whole blood from the patient vein directly can be accomplished into four 4.5 mL citrate (3.8% sodium citrate)-containing Vacutainer tubes (clinical grade borosilicate glass of non-pyrogenic, non-cytotoxic and nuclease free) or, alternatively, a syringe can be used to take 3.8% citrate solution sterilely from a pharmaceutical preparation, and then attached to the butterfly valve just before drawing blood from the patient.

This is done in an out-patient clinic situated next to a hospital preparation laboratory for rapid transfer and preparation. Under a laminar flow hood, the blood from the tubes or syringe is transferred gently to a 50 ml centrifuge tube.

Centrifugation is accomplished with a centrifuge at 280 g for 15 min at room temperature. After the first centrifugation, the PRP is carefully removed with a pipette inserted above the buffy coat and transferred to a new, sterile centrifuge tube. A second centrifugation process is then made under the same conditions. Following the second centrifugation, the concentrated PRP is taken with a sterile syringe for clinical application. The volume obtained depends on the required concentration yielding of 2-4 ml and is dependent on the clinical application

Certified laboratory technicians, cellular biologists, or other health care professionals who have had PRP training, and are familiar with proper aseptic technique could safely carry out the PRP preparation following this or a similar protocol (1). After the blood withdrawal, PRP can be prepared in a laboratory, operating room or out-patient clinic requiring only a table-top centrifuge for preparation, although a laminar flow hood can increase security. Any physician or health care practitioner using PRP techniques in therapy needs to be familiar with specific

guidelines in the use of blood products and also have a clear understanding of possible complications.

Overall, the PRP preparation technique described could be implemented in most clinical settings and by trained medical staff, as they are already aware of all risks related to harvesting, transportation, processing, and injection or application of the PRP to the patient. (1,4)

However, The International Cellular Medical Society stresses the need to establish standards for PRP preparation protocols, techniques, and traceability. (1)

Specifically:

- PRP use is considered within the practice of medicine.
- Physicians who perform PRP injections should be familiar with the peer reviewed literature and the usual treatment of the diagnoses they are considering for PRP treatment and the benefits, risks, and methods of PRP injections.
- There are no governing bodies to accredit the application or performance of PRP.
- Attendance at training courses on the preparation and use of PRP or extensive peer instruction on the use of PRP grafts by a physician accustomed to PRP therapies.
- Appropriate conservative measures should have been exhausted to physicians and patient satisfaction prior to PRP use.
- The physician must have training and the understanding of appropriate graft selection and preparation of such a graft with or without additive supports (calcium, thrombin, etc.). The physician must be trained in the recognition and management of any complications. The physician must have the training and comfort with use of proper pain management strategies for post-procedure pain control. Optimizing patient outcome by use of adjunctive bracing, physical therapy, medications and other strategies is strongly encouraged
- A number of studies that demonstrate improved accuracy of the ultrasound guided and blind injections (5, 6). This is especially important with injections that may be in a more anatomically difficult location, such as a hip joint or deep tendon, rather than a superficial, easily felt joint or tendon. Guided injections as the general standard with PRP injections. Individual physician ability and patient preference may alter this choice on a case-by-case basis.

HISTORICAL PERSPECTIVE OF PRP

The application of PRP has been documented in many fields. First promoted by M. Ferrari in 1987 as an autologous transfusion component after an open heart operation to avoid homologous blood product transfusion, there are now entries in the NCBI for PRP ranging in fields from orthopedics, sports medicine, dentistry, otolaryngology, neurosurgery, ophthalmology, urology, wound healing, cosmetic, cardiothoracic and maxillofacial surgery. (1)

In recent years, scientific research and technology has provided a new perspective on platelets. Studies suggest that platelets contain an abundance of growth factors and cytokines that can affect inflammation, postoperative blood loss, infection, osteogenesis, wound, muscle tear and

soft tissue healing. Research now shows that platelets also release many bioactive proteins responsible for attracting macrophages, mesenchymal stem cells and osteoblasts that not only promote removal of degenerated and necrotic tissue, but also enhance tissue regeneration and healing. Musculoskeletal practitioners began using PRP for tendinopathy in the early 1990s. (1) These early practitioners were primarily trained in the use of prolotherapy. The popularity of PRP grew as physicians began to see clinical results in concentrating a patient's own blood factors. The PRP procedure is significantly more complex and requires additional equipment to perform successfully, but many practitioners have seen a relatively more robust response, fewer treatments and improved tissue health compared to prolotherapy. The growth of PRP therapy has relied primarily on anecdotal or case reports. Historically, there have been few controlled trials to prove the efficacy of PRP. Of these existing trials, the sample sizes tended to be too small to allow for generalization of findings. Moreover, lack of consensus on technique, number of injections, spacing of injections, number of platelets, concentration of platelets over baseline, with or without leukocytes in the injection, exogenous activation of injected platelets and even a definition of appropriate candidates for the procedure are lacking.

Recently, however, there has been an emerging literature on the beneficial effects of PRP for chronic non-healing tendon injuries including lateral epicondylosis, plantar fasciopathy and cartilage degeneration

REGULATION

USA

Blood products such as PRP fall under the prevue of FDA's Center for Biologics Evaluation and Research (CBER). CBER is responsible for regulating human cells, tissues, and cellular and tissue-based products. (7) The regulatory process for these products is described in the FDA's 21 CFR 1271 of the Code of Regulations. Under these regulations, certain products including blood products such as PRP are exempt and therefore do not follow the FDA's traditional regulatory pathway that includes animal studies and clinical trials. The 510(k) application is the pathway used to bring PRP preparation systems to the market. The 510(k) application allows devices that are "substantially equivalent" to a currently marketed device to come to the market. There are numerous PRP preparation systems on the market today with FDA clearance; however, nearly all of these systems have 510(k) clearance for producing platelet-rich preparations intended to be used to mix with bone graft materials to enhance bone graft handling properties in orthopedic practices.

The use of PRP outside this setting, for example, an office injection, would be considered "off label." Clinicians are free to use a product off-label as long as certain responsibilities are met. Per CBER, when the intent is the practice of medicine, clinicians "have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound

medical evidence, and to maintain records of the product's use and effects." Finally, despite PRP being exempted, the language in 21 CFR 1271 has caused some recent concern over activated PRP; however, to date, the FDA has not attempted to regulate activated PRP.

CANADA

HEALTH CANADA

Summary of Health Canada's stance on PRP:

If the PRP is an autologous product it is not regulated by Health Canada, but regulated by individual "Colleges" whose members administer the product. Hence Health Canada does not regulate autologous PRP because:

- it is autologous therefore minimal risk of reaction
- it is not stored before re-injection therefore minimal risk of wrong product being injected
- blood vial is taken, spun, plasma injected, whole process occurs within 30 mins and patient never leaves
- it is not "processed"
- If product is NOT autologous i.e. from another person, it would be covered by the Food and Drug Act, since it would require a Drug Information Number. Health Canada to date has no product approved

The following communication was received from the Director of Health Canada's Office of Policy and International Collaboration-Biologics and Genetic Therapies Directorate -Health Products and Food Branch indicated: 'The *Food and Drugs Act provides Health Canada the authority to regulate drugs under the Food and Drug Regulations; prohibits the manufacturing of drugs under unsanitary conditions; and prohibits drug misrepresentation. The definition of "drug" under this Act is broad enough to capture platelet rich plasma, and so generally speaking Health Canada holds the position that federal regulatory authorization requirements apply to PRP; however, there are some other important considerations that may affect this position'.*

Such considerations were defined as '*products that can be processed and then immediately used by a physician specialist (all within a clinical setting), professional regulatory bodies may be involved instead of Health Canada'*

Health Canada's prior discussions concerning PRP were in the context *'where autologous PRP was fractionated from whole blood in an orthopaedic and sports medicine clinical setting using centrifugation, and then injected immediately to speed wound healing.'* The understanding at

that time was that PRP was considered by the regulating Colleges of Physicians and Surgeons as an established medical practice for that indication.

Health Canada noted it was not clear if *'PRP fell under our professional scope of practice, and under what circumstances this is considered acceptable'.*

If it is*, 'Health Canada could then agree that under such circumstances the Food and Drug Regulations does not apply'.*

Appendix Communication, Health Canada 2016

ONTARIO

Members of the College of Chiropodists practice under the Chiropody Act, 1991, S.O. 1991, and its related Regulations and Standards.

Authorized Acts

In the course of engaging in the practice of chiropody, a member is authorized, subject to the terms, conditions and limitations imposed on his or her certificate of registration, to perform the following:

Administering, by injection into feet, a substance designated in the regulations.

Prescribing drugs designated in the regulations.

Idem

A member may administer by injection into the foot a substance set out in Schedule 1 to this Regulation, if the member complies with the standards of practice set out in SCHEDULE 1 section 2. O. Reg. 338/08, s. 1. **(see Appendix)**

PRP is not a substance currently indicated in Schedule 1 as a permitted substance. PRP kits use an anti-coagulant to prevent it from clotting. PRP kits use anticoagulant citrate dextrose (ACD) or 3.8% sodium citrate to inhibit clotting. ACD binds calcium and prevents the coagulation proteins from initiating the clotting cascade. The addition of citrate to the blood also makes it more acidic than is physiologic. Since some growth factors are influenced by the pH of the tissue, some protocols recommend buffering the PRP back to a physiologic range prior to injection

Some commercially available PRP systems use bovine thrombin to activate the clotting mechanism prior to application.

Bovine thrombin is not on the schedule of drugs or substances for use by Members of the College of Chiropodists of Ontario

PHLEBOTOMY

Blood needs to be drawn for any PRP based procedure to be performed (*30 min approx. from drawing blood to injecting PRP*)

Phlebotomy in Ontario is restricted by the Regulated Health Professions Acts (RHPA, 1991). (8) which states: "27. (1) No person shall perform a controlled act set out in subsection (2) in the course of providing health care services to an individual unless, (a) the person is a member authorized by a health profession Act to perform the controlled act; or (b) the performance of the controlled act has been delegated to the person by a member described in clause (a). 1991, c. 18, s. 27 (1); 1998, c. 18, Sched. G, s. 6".

In these regulations, RHPA includes a number of exceptions that permit persons who are not members of regulated professions to perform controlled act procedures in defined circumstances. The ability to perform controlled acts can be authorized in four ways.

- By direct authorization
- By delegation or medical directive
- Through exceptions
- Through exemptions

Direct Authorization:

The governing statutes of regulated health professions directly authorize them to perform controlled acts or components of controlled acts. Registrants of these professions may perform these controlled acts when they are practicing within their professions' scopes of practice, and when they have the appropriate knowledge, skills and judgment to perform them according to the standard of practice of the profession. The Controlled acts provided through the Chiropody Act does not include phlebotomy

A Delegation or Medical Directive is the process by which a person who is a member of a regulated health profession that is authorized to perform controlled acts within their profession, delegates the authority to perform one or more of these controlled acts or components of the controlled acts to another person, who is then authorized to perform these acts.

Delegation or Medical Directives must be:

- given in advance by physicians/ordering authorizers to enable an implementer to decide to perform the ordered procedure(s) under specific conditions without a direct assessment by the physician or authorizer at the time.
- written and have essential components.

Exception:

- Exceptions are circumstances, defined in law, where the restrictions on performing controlled acts do not apply (i.e. in an emergency).

Exemptions:

- Exemptions are controlled acts, or components of controlled acts, that are exempted from the performance restrictions on these acts. The current exemptions for controlled acts are contained in a regulation made under the authority of the RHPA.

Other:

- The taking of a blood sample from a vein or by pricking the skin is exempt from subsection 27 (1) of the Act if the person taking the blood sample is employed by a laboratory or specimen collection centre licensed under the Laboratory and Specimen Collection Centre Licensing Act.

Phlebotomy or taking a blood sample from a vein is not a controlled act permitted to be performed or delegated by Members of the College of Chiropodists of Ontario. However, it may be permissible by a medical directive or future exemption, though legal clarification should be on this matter.

CLINICAL INDICATIONS.

Unfortunately, many published clinical trials evaluating PRP fail to include sufficient experimental detail or report even the basic attributes of PRP formulations used, including platelet and leucocyte concentrations and the method of activation. This precludes interpretation of the exact nature of PRP formulations delivered (including growth factor profiles) in studies to date, prevents comparison between studies, and does not permit other investigators to replicate conditions. This is a particular challenge given the complexity of biological therapies and the wide array of preparation methods, protocols and methods of delivery now widely used (26)

Any invasive procedure can be associated with potential complications Even though the success of PRP therapy is still questionable, the complication rate associated with PRP injections appears to be very low. There may be increased pain at the injection site, but the incidence of other problems — infection, tissue damage, nerve injuries — appears to be no different from that associated with cortisone injections. Reaction to the blood products has not been a problem because the patient's own blood products are used so no cross reaction would be expected. (28)

One problem is the cost. This procedure is still considered experimental by most insurance companies so patients often have to pay out of their own pockets. This can be expensive as the equipment needed to prepare the blood can be expensive. (28)

PRP AND WOUND CARE

Autologous PRP contains fibrin and high concentrations of growth factors and has the potential to aid wound healing.

Chronic wounds (or ulcers) are breaks in the skin that do not heal, or require a long time to heal, and frequently recur. Chronic wounds include pressure ulcers, venous leg ulcers, arterial ulcers, neurotrophic ulcers, and foot ulcers in people with diabetes. Autologous PRP is a potential wound healing treatment because it has components such as fibrin (a substance produced in the liver that makes the blood clot) and high concentrations of growth factors that are thought to help healing. Martinez-Zapata et al (9) reviewed the evidence on the effect of autologous PRP on wound healing in people aged 18 years or older with chronic wounds from any cause (such as pressure ulcers, arterial ulcers, venous ulcers).

The results were non-conclusive as to whether autologous PRP improved the healing of chronic wounds generally compared with standard treatment. Autologous PRP may increase the healing of foot ulcers in people with diabetes compared with standard care, but it is unclear if autologous PRP has an effect on other types of chronic wound, but this conclusion is based on low quality evidence from two small RCTs.

It is unclear whether PRP influences the healing of other chronic wounds. The overall quality of evidence of autologous PRP for treating chronic wounds is low. There are very few RDBPCT evaluating PRP, they are underpowered to detect treatment effects, if they exist, and are generally at high or unclear risk of bias. (9)

PRP IN FOOT AND ANKLE PATHOLOGIES

PRP is generally considered an elective treatment for subacute and chronic conditions. Generally, healing slows or stops 6-12 weeks after an acute injury. (10)

Basic science and animal studies are supportive for the use of PRP in tendinopathy. Lab studies have shown improved tenocyte proliferation, collagen deposition and endogenous growth

factors (10,11,12). Animal models with surgically induced lesions are common and show good results.

Technique, number of injections, spacing of injections, number of platelets, concentration of platelets over baseline, with or without leukocytes in the injection, exogenous activation of injected platelets, use of common and validated outcome measures (i.e. VISA scores) in studies and patient selection vary enormously between studies. Therefore, clearly positive high-level human evidence is still lacking in RDBPCT.

This is inconclusive acceptance reflected in the literature surrounding Podiatry (21). Baravarian & Chandler noted the literature and their own success with PRP, the authors indicate PRP is an effective non-invasive treatment that can obviate further surgery for plantar fasciosis. While DeHeer, stated PRP is not the "magic bullet" it might appear to be for plantar fasciitis, emphasizing that physicians must have a strong grasp of biomechanics and equinus to treat the condition.

Vanninia et al (25) systematically reviewed all the literature available on the clinical application of PRP for the treatment of foot and ankle pathologies, to understand its potential and best indications for clinical use. Considering the literature currently available, no clear indications for using PRP in the foot and ankle district emerged

TENDINOPATHIES

The etiology, pathogenesis, and pain generators in chronic tendinopathy remain to be elucidated. Biologic therapies, such autologous blood (AB) and PRP injections, aimed at stimulating healing of degenerative tendons, have shown promise but clinical research is limited. (11) Biologic therapies such as AB and PRP injection were moderately effective for treatment of recalcitrant tendinopathy, and PRP appeared to be more effective than AB.

Bell et al (12) found the administration of two unguided peri tendinous autologous blood injections one month apart, in addition to a standardised eccentric training program, provided no additional benefit in the treatment of mid-portion Achilles tendinopathy. This was confirmed by DeVos et al (11) found no effect of PRP on ultra-sonographic tendon structure and neovascularisation in chronic mid-portion Achilles tendinopathy

In a prospective randomized comparative study Monto (13) found PRP was more effective and durable than cortisone injection for the treatment of chronic recalcitrant cases of plantar fasciitis. In a systematic review of PRP injections for chronic plantar fasciopathy: Franceschi et al (14) found evidence for the use of PRP in PF showed promising results. However, the number of studies available is limited and randomized placebo-controlled studies are required.

LIGAMENT SPRAINS

Most ligament studies on humans to date have been in combination with surgical anterior cruciate ligament reconstruction.

Rowden et al (15) studied patient function among patients suffering acute ankle sprains randomized to receive standard therapy plus PRP, compared to patients who receive standard therapy plus sham injection (placebo) in this small study, PRP did not provide benefit in either pain control or function over placebo.

Conversely syndesmotic sprains though less common injuries require prolonged recovery seem to show a better response to PRP. Laver et al (16) studied the influence of ultrasound-guided injections of (PRP into the injured antero-inferior tibio-fibular ligaments (AITFL) in athletes on return to play (RTP) and dynamic stability. Athletes suffering from high ankle sprains benefited from ultrasound-guided PRP injections with a shorter RTP, re-stabilization of the syndesmosis joint and less long-term residual pain.

Overall, the evidence suggests improved pain, healing and graft quality (16). The sports medicine literature with regard to non-surgical care is lacking at this point in time, though anecdotal evidence indicates improved time of healing, reduced pain and reduced time to return to sport.

MUSCLE STRAINS

Muscle strains are a very common source of pain in dysfunction, particularly in the athlete. Muscles are rich in blood supply and generally heal with usual care, approximately 8 times faster than ligaments. If a subacute or chronic condition developed, consideration for PRP treatment would be acceptable. In rare situations, the delivery to an acute injury in an attempt to facilitate function could be considered, but there is insufficient evidence to endorse this currently (17). A study by Sanchez has shown faster recovery of acute muscle tears with PRP injection (19). If applicable to larger scale human use, it is unknown if this is relevant clinically, functionally or for return to sport.

Hamid et al (17) found several in vivo laboratory studies suggested beneficial effects of PRP in accelerating muscle recovery. Evidence to suggest similar effects on humans is however limited, as valuable information from robust human controlled trials is still not available. This was reflected in a trial by Reurink, et al (18) who noted that although a 95% confidence interval still allows for a small chance that there was a clinically relevant between-group difference, their study demonstrated no benefit for intramuscular PRP injections, as compared with placebo injections, in patients with acute hamstring injuries.

JOINTS

Osteoarthrosis (OA) is a chronic degenerative condition of hyaline cartilage. There are few validated interventions that improve the clinical condition of a patient once the degenerative process becomes symptomatic. Given the lack of response of the body's healing mechanisms to degenerative conditions generally, injection of growth factors and cytokines is sensible. Lab and animal models exist for using PRP in OA with generally favorable results (1). Animal models describe improved healing in meniscus, glenohumeral labrum and OCD with induced defects, but human studies are currently lacking in these areas. (1,27) An article by Kon et al (20) indicated improved functional outcomes when compared to hyaluronic acid visco-supplementation. It is unknown whether PRP acts by local paracrine factors to alter pain, by new hyaline or fibrocartilage formation or a combination of both or neither.

NERVES

Entrapment neuropathies that have failed "conservative management" have traditionally been treated with surgical release/decompression (neurolysis). With the advancement of musculoskeletal ultrasound, peripheral nerves and their adjacent structures can now be clearly visualized. There is growing experience in performing percutaneous release of nerves using different solutions (termed hydrodissection or hydroneurolysis) (1)

Although there are many published (*in vivo* or *in vitro*) animal studies (and some anecdotal clinical reports) about the use of PRP in peripheral neuropathies, literature cannot yet give a convincing answer about the value of this therapeutic strategy. Nevertheless, results of the so-far published clinical studies are encouraging. It is obvious that more clinical trials are needed to yield more secure evidence regarding the beneficial effect of PRP usage in peripheral neuropathies. (22)

There is insufficient information to endorse PRP treatment for this use, however, in cases of ischemic damage to a nerve due to scar tissue banding, there is theoretically a role for PRP during percutaneous procedures. (22,23,24)

FRACTURE NON-UNION

Fracture non-union is a debilitating, albeit fortunately rare complication in the care of fractures. PRP has been shown to be inferior to recombinant BMP-7 to speed non-union healing in one randomized human study (1). The role in acute fractures in humans has not been well evaluated and seems impractical given the rate of successful healing without intervention. PRP has been used in spinal and joint fusion surgeries with success.

CONCLUSION

PRP is not a substance currently listed under Schedule 1, and as such cannot be currently used or prescribed by Members of the College of Chiropodists of Ontario. Commercially available PRP kits use anticoagulant, and activating agents These agents are not currently on Schedules approved for use by Members of the College of Chiropodists of Ontario.

Currently whole blood needs to be drawn for any autologous PRP based procedure to be performed. Such phlebotomy in Ontario is restricted by the Regulated Health Professions Acts (RHPA, 1991). Currently Member access would only be permissible by delegation or a medical directive, it is not a directly or exempted act that can be performed currently by Members of the College of Chiropodists of Ontario.

The Food and Drugs Act provides Health Canada the authority to regulate drugs under the Food and Drug Regulations. The definition of "drug" under this Act is broad enough to capture platelet rich plasma, Health Canada holds the position that federal regulatory authorization requirements apply to PRP. However, products that can be processed and then immediately used by a physician specialist may under certain circumstances have professional regulatory bodies such as the College of Chiropodists of Ontario involved instead of Health Canada. Health Canada is unclear if 'PRP to falls under our professional scope of practice, and under what circumstances this is considered acceptable'. . If it is, 'Health Canada may then agree that under such circumstances the Food and Drug Regulations does not apply'.

If product is not autologous i.e. (*from another person*), if it is stored, or 'processed', it would be covered by the Food and Drug Act, it would thus require a Drug Information Number. Health Canada to date has **NO** such product approved

Injection techniques of PRP follow similar techniques for soft tissue and intra-articular injections of corticosteroids and Hyaluronic acid visco-supplements. Platelet Rich Plasma (PRP) Guidelines of the International Cellular Medical Society suggest guided injections as the general standard with PRP injections.

The application of PRP has been documented in many fields. At present, there are a limited number of studies with fewer RCDBPCT, producing restricted evidence supporting the use of PRP for foot and ankle pathology.

The technical specifications for PRP preparation are varied, as are the clinical applications of prepared material PRP cannot be univocally defined and, there are too many different PRP formulations applied in clinical practice.

Until further studies prove the real translational potential of the promising results suggested by preclinical studies PRP should be considered a second line treatment,

O. Reg. 338/08, s. 2
SCHEDULE 1

SUBSTANCES ADMINISTERED BY INJECTION INTO THE FOOT

Betamethasone sodium phosphate beta-acetate

Dexamethasone sodium phosphate

Hydrocortisone sodium succinate

Methylprednisolone acetate

Triamcinolone acetonide

Denatured alcohol 4% (ethyl alcohol)

Bupivacaine

Lidocaine hydrochloride (with or without epinephrine)

Mepivacaine hydrochloride

Sterile saline solution

B12- Cyanocobalamin

From: *Maggy Ghaly [mailto:maggy.ghaly@hc-sc.gc.ca]* ***On Behalf Of*** *BGTD.OPIC*
Sent: *Friday, 05 August, 2016 11:07 AM*
To: *Oliver, Tracy*
Cc: *'BGTD.OPIC'; Oliver, Tracy*
Subject: *RE: PRP - MECS #: 16-109042-230*

Dear Ms. Oliver,

The Food and Drugs Act provides Health Canada the authority to regulate drugs under the Food and Drug Regulations; prohibits the manufacturing of drugs under unsanitary conditions; and prohibits drug misrepresentation. The definition of "drug" under this Act is broad enough to capture platelet rich plasma, and so generally speaking Health Canada holds the position that federal regulatory authorization requirements apply to PRP; however, there are some other important considerations that may affect this position.

With respect to products that can be processed and then immediately used by a physician specialist (all within a clinical setting), professional regulatory bodies may be involved instead of Health Canada. This is because medical professional activities are regulated under provincial authority. Health Canada's Policy on Manufacturing and Compounding Drug Products in Canada may help you to understand factors that may be considered in determining whether or not your activities are regulated under the Food and Drug Regulations. I have provided a link to it here: http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/pol_0051-eng.php

Health Canada's prior discussions concerning PRP were made in the context where autologous PRP was fractionated from whole blood in an orthopaedic and sports medicine clinical setting using centrifugation, and then injected immediately to speed wound healing. Health Canada's understanding at that time was that PRP was considered by the regulating colleges of physicians and surgeons as an established medical practice for that indication. It is not clear whether your professional college considers PRP to fall under your professional scope of practice, and under what circumstances this is considered acceptable. For this reason, you are encouraged to contact your college to determine whether they consider your activities in processing and administering PRP to be within the scope of established practice. If it is, Health Canada could then agree that under such circumstances the Food and Drug Regulations does not apply. If it is not, but you are still interested in administering PRP for Chiropody indications, then you are encouraged to contact Health Canada's Office of Regulatory Affairs to better understand how to prepare a Clinical Trial Application for Health Canada. Such an application has a 30-day review period and has no associated submission fees.

Kind regards

Office of Policy and International Collaboration | Bureau de la politique et de la collaboration internationale
Biologics and Genetic Therapies Directorate | Direction des produits biologiques et des thérapies génétiques
Health Products and Food Branch | Direction générale des produits de santé et des aliments
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