The Efficacy of Platelet-rich Plasma Injection in the Treatment of Patellar Tendinopathy

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Abstract

Background: Patellar tendinopathy is one of the leading causes of tendon related injuries affecting active individuals. Because of the chronic nature of tendinopathy, traditional measures aimed at treating inflammation have not been effective. Platelet-rich plasma (PRP) has gained favor because of the theorized ability to accelerate tissue healing and regeneration. Will the injection of PRP be an effective treatment for patellar tendinopathy?

Methods: An exhaustive literature search was performed using Medline, Web of Knowledge, SPORTDiscus, CINAHL, and the NIH clinical trials site using the keywords: platelet-rich plasma and tendinopathy. The selected articles were analyzed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results: Four studies were included that met inclusion and exclusion criteria. A randomized control trial with 23 patients treated with PRP showed superior Victorian Institute of Sport Assessment – Patellar questionnaire (VISA-P) score improvements as compared to 23 patients treated with extracorporeal shock wave therapy at 6 and 12 months follow-up. A prospective cohort followed 43 patients and showed stable improvements in VISA-P at 2, 6, and 84 month follow-up. One prospective cohort analyzed 14 patients who had prior injection and/or surgical treatment with 22 patients who had not received any injection or surgical treatment before. Both treatment groups had decreased pain, but the group who had not received prior treatments showed improved VISA-P. Another prospective cohort examined 24 patients at 20 days post injection and 6 months post injection. No significant improvement was seen at 20 days, but VISA-P did improve at the 6 month follow-up.

Conclusion: The use of PRP for treating patellar tendinopathy has shown to be effective in these studies by increasing VISA-P. To date, no randomized control trials comparing PRP to saline or dry-needling have been conducted. Thus, future research should focus on identifying proper treatment time, optimal dosage and number of injections, and ideal PRP concentration.

Keywords: platelet-rich plasma, injections, patella, tendinopathy, and jumper’s knee

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Subject Categories
Medicine and Health Sciences

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Joel Horst

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 9th, 2014

Faculty Advisor: Eric Foote, PA-C, MS
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
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Acknowledgements

[Redacted for privacy]
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List of Abbreviations

VISA-P............................Victorian Institute of Sport Assessment – Patellar Questionnaire
PRP………………………………………………..………………….Platelet-Rich Plasma
GRADE….….Grading of Recommendations, Assessment, Development and Evaluations
ESWT………………………………………….......… Extracorporeal shock wave therapy

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The Efficacy of Platelet-rich Plasma Injection in the Treatment of Patellar Tendinopathy

BACKGROUND

According to the National Center for Health Statistic National Health Interview Survey\textsuperscript{1} conducted in 2008, musculoskeletal disorders and diseases are the leading cause of physical disability in the United States. Tendon related injuries account for approximately 30-50% of sports related injuries.\textsuperscript{2} Patellar tendinopathy, or jumper’s knee, among non-elite athletes has been reported at 8.5% with a 2:1 ratio of men to women\textsuperscript{3} while elite athletes have a slightly higher percentage at 14.2%.\textsuperscript{4}

Patellar tendinopathy is one of the most common tendon injuries and is marked by tenderness at the superior or inferior pole of the patella.\textsuperscript{5} Tendinopathy describes the degeneration seen in the tendon due to disordered healing in the absence of inflammation.\textsuperscript{6} Pain associated with jumper’s knee is difficult to quantify, thus the need for a validated and widely used assessment tool that allows practitioners to reliably assess a patient’s symptoms, function, and ability to undertake physical activity. The Victorian Institute of Sport Assessment – Patellar questionnaire (VISA-P) is the only published clinical scale validated for patellar tendinopathy. The VISA-P is comprised of eight questions, six of which are scored on a visual analogue scale from 0-10 with 10 representing optimal health.\textsuperscript{7} See Appendix.

Standard of care treatment options for jumper’s knee includes rest, ice, non-steroid anti-inflammatory drugs, and eccentric based exercise programs.\textsuperscript{8-12} Various
injections and surgery are utilized once conservative measures have failed. Recently, the use platelet-rich plasma (PRP) for tendon healing has gained popularity due to its potential ability to regenerate tissue and accelerate the body’s healing process.

PRP is an autologous product that has been utilized and studied since the 1970’s in many fields. PRP is made from anticoagulated blood that has been centrifuged to increase the concentration of platelets compared to whole blood. Platelets are the first cell to arrive at an injury site to begin hemostasis through cell membrane adherence, aggregation, and clot formation. During degranulation, they release growth factors, cytokines, and bioactive proteins that enhance and regulate tissue healing. The aim of this review is to assess the efficacy of platelet-rich plasma for the treatment of patellar tendinopathy.

METHODS

An exhaustive literature search was performed using Medline, Web of Knowledge, SPORTDiscus, CINAHL, and the NIH clinical trials site using the search terms “platelet-rich plasma” and “tendinopathy.” A cited reference search was also utilized to find relevant sources. Results were then narrowed to include only articles in the English language, on human subjects, and published since 2012. Only articles that utilized PRP for use in treating patellar tendinopathy were included. Studies were also excluded if they did not utilize the VISA-P as a means for measuring outcomes. The selected articles were analyzed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).
RESULTS

The initial result of the search yielded 160 articles for review. A total of four relevant articles remained after screening with inclusion and exclusion criteria. These articles included one randomized control trial\textsuperscript{21} and three prospective observational studies.\textsuperscript{22-24} Table I provides a summary of the studies that were included in the systematic review. A search on the NIH clinical trials site reveals 109 current studies being conducted on the use of Platelet-rich plasma, three of these trials are randomized control trials that are in various stages of enrolling or recruiting.

Vetrano et al Trial

Patient Selection—This randomized control trial\textsuperscript{21} was conducted to compare the effectiveness and safety of PRP injections and extracorporeal shock wave therapy (ESWT) in athletes with jumper’s knee. Primary outcomes were defined as an improvement of VISA-P score. Forty-six patients were randomly allocated to receive one of two treatments via computer-generated randomization. Each of the recruited patients had the diagnosis of jumper’s knee confirmed by the same clinician as well as undergoing ultrasound (US) examination. Only patients with chronic unilateral tendinopathy at the insertion of the patellar tendon at the lower pole of the patella were included in this study. Additional inclusion criteria regarded having the diagnosis for at least 6 months before treatment, failure of non-operative management, a 12 week washout period between any non-operative therapy and beginning this study, participants aged 18 to 50 years, and patients being involved in sporting activities as either an elite or non-elite athlete. Exclusion criteria included patients with bilateral complaints, with
coexisting knee lesions, with a history of knee surgery or injection therapy with corticosteroids in the past 3 months, with systemic disorders, on current anticoagulation therapy, a platelet value less than 150,000/mm3, or who are pregnant. The two groups were equivalent in all baseline patient characteristics. Additionally, the authors note that no patients were lost to follow up or had undergone any surgical intervention during the follow-up period of 12 months.21

**PRP Preparation**—PRP was obtained by a single centrifugation of whole blood to isolate platelet using MyCells Autologous Platelet Preparation System. There was 10ml of venous blood collected and mixed with acid-citrate-dextrose to prevent early clotting. The blood was then centrifuged for 10 minutes at 1300 to 1500rpm to garner a mean platelet concentration of 0.89 to 1.1 X 10^9 ml which is 3 to 5 times baseline concentration. Then 1ml of this PRP was sent to the laboratory for analysis of platelet concentration while the remaining 3 to 5ml was used for patient injection without activation.21

**PRP Injection**—Patient’s received two autologous PRP injections under US guidance over 2 weeks by the same clinician. A 22-g needle was inserted into the designated location via a single skin portal. Approximately 2ml of PRP was then injected under color Doppler guidance placing multiple small aliquots into the tendinous lesion with no local anesthesia being applied.21

**Post Injection Protocol**—Patients rested in a supine position for 15 minutes without moving the leg. Full weight bearing of the limb was tolerated as well as normal daily activities. One week after the final treatment, patients were given a standardized stretching and muscle strengthening protocol to be adhered to for 2 weeks.21
**Patient Outcomes**—Both treatments (PRP and ESWT) were effective in improving VISA-P throughout the study, however, PRP showed greater improvements at the 6 month and 12 month follow-up. VISA-P at baseline, 2 months, and 12 months was 55.3, 76.2, and 91.3, respectively. For ESWT, these same measurements were 56.1, 71.3, and 77.6, respectively. See Table I. In addition to an improved VISA-P, after 12 months patients who received PRP reported a 91.3% (21/23) level of satisfaction as compared to only 60.8% (14/23) for ESWT.21

The authors note several limitations to their study. These limitations include a small patient enrollment, lack of placebo control group, and use of qualitative outcome measures rather than clinical and instrumental measurements (eg, color US and MRI). Additionally, the authors report no clinically relevant side effects of either treatment.21

**Filardo et al Trial**

**Patient Selection**—This prospective study22 was evaluating the therapeutic effects of multiple PRP injections at medium-term follow-up by showing the quality and duration of clinical improvement as seen with the VISA-P. Forty-three patients affected by chronic patellar proximal tendinopathy were enrolled, 11 of these patients were affected bilaterally for a total of 54 patellar tendon treatments. Inclusion criteria were: exercise-associated pain for greater than 3 months, pain or tenderness on palpation, and degenerative changes in the patella tendon on either MRI or US.22

**PRP Preparation**—150ml of venous blood was collected and centrifuged two times. The first centrifuge ran at 1480 rpm for 6 minutes to separate the erythrocytes, the second ran at 3400 rpm for 15 minutes to concentrate the platelets. The sample was then divided
into four equal parts of 5ml. One unit was sent to the laboratory for quality control, two of the units were stored for later use at -30 C, while the final unit was used for the first injection within 2 hours of collection.22

**PRP Injection**—Patients underwent three US guided intra-tendinous injections of 5ml PRP, two weeks apart. Prior to administration of the 2\textsuperscript{nd} and 3\textsuperscript{rd} units, the samples were thawed and injected with 10% calcium chloride to activate the platelets. A 22-g needle was then inserted under US control directly into the lesion site with multiple penetrations of the tendon.22

**Post Injection Protocol**—Patients were instructed to begin a rehabilitation program between the 2\textsuperscript{nd} and 3\textsuperscript{rd} injections based on eccentric exercises to be implemented for 12 weeks.22

**Patient Outcomes**—Patients reported an improvement in VISA-P over the course of the study. VISA-P increased from 44.1 at baseline to 61.4 at 2 months, 76.6 at 6 months, and 84.3 at four years’ follow up. There was 79.1% of the patients satisfied with the treatment and would repeat the treatment if needed, while 81.4% returned to previous sports activities. Patients affected by bilateral pathology and presenting with a long history of pain obtained significantly poorer results. However, the patient characteristics of age, BMI, previous conservative or surgical treatment did not influence the results in this study.22

Limitations listed by the authors include lack of a randomized control group and only performing imaging evaluations on some of the patients rather than all at various points throughout follow-up.22

**Gosens et al Trial**
Patient Selection—Another prospective cohort study\textsuperscript{23} was conducted to evaluate the outcome of patients with patellar tendinopathy treated with PRP, and whether certain characteristics, such as activity level and previous treatment affected the outcome. Thirty-six patients with chronic patellar tendinopathy were assigned to two treatment groups based on prior treatments. Group 1 was comprised of 14 patients who had previously been treated with cortisone, ethoxysclerol and/or surgical treatment, while Group 2 had 22 patients who had not received an injection or surgical treatment before. Both treatment groups had been through physical therapy and performed eccentric exercises before entering the study. Diagnosis was made on clinical grounds as well as an MRI showing edema at the origin of the patellar tendon in 21 (58.3\%) of the cases. No other inclusion or exclusion criteria were noted by the authors. At baseline, the two groups did not differ in regards to demographic or clinical characteristics.\textsuperscript{23}

PRP Preparation—27ml of whole blood was collected and placed in a syringe with 3ml sodium citrate. The preparation was then made according to manufacturer instructions for the Recover System (Biomet Biologics, Warsaw, Indiana) and then spun at a speed of 3200 RPM for 15 minutes. 3ml of PRP was obtained for each patient, with the PRP begin buffered to a physiological pH using 8.4\% sodium bicarbonate and Bupivacaine HCL 0.5\% with epinephrine (1:200000) was added. No activating agent was used.\textsuperscript{23}

PRP Injection—Using a 22-g needed, 1ml of the prepared PRP was injected into the area of maximal tenderness, while the remaining 2ml of PRP was injected into the patellar tendon origin on the patella utilizing a “peppering technique” which involves a single skin portal and then five penetrations of the tendon.\textsuperscript{23}
**Post Injection Protocol**—Patient’s rested in a supine position without moving the leg for 15 minutes after the injection, they were then sent home with instructions to rest the leg for an additional 24 hours. After 24 hours, the patients were to start a standardized stretching protocol to follow for an additional 2 weeks, after which an eccentric focused muscle and tendon strengthening program would begin.23

**Patient Outcomes**—The results did show a statistically significant improvement from baseline to follow-up after treatment with PRP in regards to VISA-P. However, patients who had no prior treatments showed a greater improvement. Patients completed the VISA-P at baseline and at a mean follow-up period of 18.4 months. The mean VISA-P for Group 1 improved from 40.1 at baseline to 57.7, while patients in Group 2 increased from 39.1 to 58.6.23

**Ferrero et al Trial**

**Patient Selection**—A prospective cohort24 evaluated 28 patellar tendons in 24 patients for the effectiveness of US-guided PRP injection to treat jumper’s knee. Inclusion criteria were the presence of patellar tendinopathy, pain at palpation and during physical activity for a minimum of 3 months as well as US or MRI evidence of tendon degeneration. Patients were between the ages of 21 and 57 who had previously utilized other treatments with unsatisfactory outcomes. Exclusion criteria were systemic disease, antiplatelet therapy in progress, intake of NSAIDs less than 5 days before procedure, and hemoglobin <11 g/dl and platelets <150,000/mmc.24

**PRP Preparation**—110 ml of venous blood was collected from the patients a few hours before the procedure, it was then centrifuged and activated in the laboratory.24
**PRP Injection**—Prior to PRP injection, US-guided scarification was performed on the degenerated region of the tendon using a 21G needle to produce a small amount of bleeding. The same needle was then reused to administer 6ml of the autologous PRP preparation into the degenerated region under US-guidance. Two treatments were performed at a mean distance of 3 ± 0.52 weeks.24

**Post Injection Protocol**—Patients were to minimize physical activity for 48 hours after the injection with a gradual return to activity with the aide of physical therapy.24

**Patient Outcomes**—Statistically significant improvement was seen in VISA-P at the 6 month point, but not at the 20 day post procedure follow-up. VISA-P at baseline, 20 days, and 6 months was 56, 60, and 74, respectively. The authors note that there were no complications during or after the procedure.24

**DISCUSSION**

Jumper’s knee is a common condition in active individuals due to overuse. To date, non-operative conservative treatment methods such as rest, ice, NSAIDs, injections, and eccentric exercises have all been used with varying degrees of success. New therapies, such as PRP are directed at supporting the body’s own reparative process to obtain complete regeneration.24 The lack of reported side effects, ease of preparation and minimally invasive aspect of the procedure are just a few of the promising features of this treatment.19

Each of the studies21-24 showed that PRP is an effective treatment for patellar tendinopathy, but the magnitude of the treatment effect is inconsistent. See Figure I. Vetrano et al21 were able to prove that PRP is superior to ESWT treatment at 6 and 12 months follow-up. The percentage of patients who were also satisfied with the PRP
compared with ESWT was also much higher at those follow-up dates. The only other study to have two separate treatment groups was Gosens et al,\textsuperscript{23} who compared patients that had previously been treated with cortisone, ethoxysclerol, and/or surgery prior to PRP treatment and those who had not received any injections or surgical treatment. The patients who had not been previously treated showed a larger improvement and thus, a greater healing potential. Filardo et al\textsuperscript{22} found that patients with bilateral tendinopathy and also patients who had longer symptom duration appeared to have lower improvements. These observations imply that future research should focus on PRP interventions being used earlier.

In fact, when PRP therapy is used in other tendinopathies, this approach has not consistently demonstrated superiority to other approaches. A recent RCT conducted on the supraspinatus by Rha et al\textsuperscript{25} compared PRP injection vs dry needing. The authors noted that the range of motion between the two groups was equal, but the PRP provided greater symptomatic relief and functional improvement at six-month follow-up. However, two recent RCT\textsuperscript{26,27} comparing PRP to saline injections conducted on the Achilles tendon did not show any greater improvement.

To date, there are at least 16 commercially available PRP preparation systems available for practitioners to choose from. Systems vary in the amount of whole blood collected, final PRP obtained, total PRP concentration, and whether or not an activator is used.\textsuperscript{16} While each of the studies\textsuperscript{21-24} reported a positive effect, each prepared and administered differing amounts of PRP to their patients. Vetrano et al\textsuperscript{21} administered 2ml of PRP after a single centrifuge of 1500 rpm X 10 minutes with no added activator. Filardo et al\textsuperscript{22} injected 5ml after two centrifugations of 1480 rpm X 6 minutes and 3400
rpm X 15 minutes. Two of the samples had 10% calcium chloride added as an activator that had been stored at -30°C and then thawed in a dry thermostat at 37°C for 30 min prior to injection. Gosens et al\textsuperscript{23} injected 1ml into the area of maximal tenderness while another 2ml was administered with a “peppering” technique. Ferrero et al\textsuperscript{24} administered 6ml PRP, but did not mention how the PRP was prepared. In addition to the amount of PRP injected, the number of injections and the timing of the injections also varied from study to study. Gosens et al\textsuperscript{23} and Ferrero et al\textsuperscript{24} utilized single injections. Vetrano et al\textsuperscript{21} administered two injections one week apart, while Filardo et al\textsuperscript{22} injected three times with two weeks in between injections. It is interesting to note that Gosens et al\textsuperscript{23} were the only study not to perform their injection under US guidance. See Table II. These different approaches could confound the results.

These studies\textsuperscript{21-24} had several limitations. Mainly, all four had precision issues as they were conducted on small sample sizes. More specifically, Vetrano et al\textsuperscript{21} lacked blinding and quantitative measures like the use of ultrasound measured outcomes. Lastly, a more directly relevant comparison between treatment and a control group is lacking. This results in an overall very low quality of evidence. See Table I.

**CONCLUSION**

The use of platelet-rich plasma injections for the treatment of patellar tendinopathy may be an effective treatment for reducing pain and improving function related to sport activity. PRP has the potential to limit down time for patient’s and allow for earlier return to training and competition. The aforementioned studies used various techniques as well as varying amount of PRP to treat patellar tendinopathy, yet they all showed improvements in VISA-P. Patients with bilateral tendinopathy and those who
had previously been treated with injections or surgical procedures had lower rates of improvement. The potential advantages of PRP outweigh the risks at this time. No side effects of the treatments were listed, and because the preparation is autologous, risk of infection is low.

The overall quality of evidence for these studies is very low. In order for PRP to become a proven treatment for tendon injuries, well-designed prospective randomized control trials must be conducted with long-term follow-up. Specific attention should also be focused on timing of treatment, number and amount of doses, and the actual preparation of the PRP.
REFERENCES


23. Gosens T, Den Oudsten BL, Fievez E, van 't Spijker P, Fievez A. Pain and activity levels before and after platelet-rich plasma injection treatment of patellar tendinopathy: A


<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Design</th>
<th>No of Patients</th>
<th>Intervention</th>
<th>Follow Up</th>
<th>VISA-P mean (SD)</th>
<th>Conclusion</th>
<th>Quality of evidence</th>
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<tr>
<td>Vetrano et al21</td>
<td>2013</td>
<td>RCT</td>
<td>PRP group 23</td>
<td>Two injections US guided over two weeks 2 months, 6 months, and 12 months</td>
<td>2 months, 6 months, and 12 months</td>
<td>55.3 (14.3)</td>
<td>91.3 (9.9)</td>
<td>PRP greater effect than ESWT over 12 months Low due to small sample size, lack of blinding, and failure to utilize quantitative measures</td>
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<td>Filardo et al22</td>
<td>2013</td>
<td>Prospective Cohort 43</td>
<td>Three US guided injections two weeks apart 2 months, 6 months, and 48 months</td>
<td>44.1 (15.6)</td>
<td>84.3 (21.6)</td>
<td>Positive effect Very low Due to small sample size and lack of a comparison group</td>
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<tr>
<td>Gosens et al23</td>
<td>2012</td>
<td>Prospective Cohort 14</td>
<td>Group 1 Single injection Mean follow up 18.4 months</td>
<td>41.8 (14.3)</td>
<td>56.3 (26.2)</td>
<td>Greater effect for those with no previous interventions Very low Due to small sample size and failure to utilize US guided injection</td>
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<tr>
<td>Group 2 22</td>
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<td></td>
<td></td>
<td>39.1 (16.6)</td>
<td>58.6 (25.4)</td>
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<tr>
<td>Ferrero et al24</td>
<td>2012</td>
<td>Prospective Cohort 24</td>
<td>Two injections three weeks apart under US guidance 20 days and 6 months</td>
<td>56 (18)</td>
<td>74 (14)</td>
<td>Some effect Very low Due to small sample size and lack of a comparison group</td>
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**Table I. Characteristics of Reviewed Studies, GRADE profile**
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<td>2</td>
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<td>2 weeks apart</td>
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<td>3 ml</td>
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<td>-</td>
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Figure I. VISA-P Results
Appendix. VISA-P Questionnaire

1. For how many minutes can you sit pain free? (from 0 min to 100 min)

```
0  1  2  3  4  5  6  7  8  9  10
```

2. Do you have pain walking downstairs with a normal gait cycle? (from strong severe pain to no pain)

```
0  1  2  3  4  5  6  7  8  9  10
```

3. Do you have pain at the knee with full active non-weight bearing knee extension? (from strong severe pain to no pain)

```
0  1  2  3  4  5  6  7  8  9  10
```

4. Do you have pain when doing a full weight bearing lunge? (from strong severe pain to no pain)

```
0  1  2  3  4  5  6  7  8  9  10
```

5. Do you have problems squatting? (from unable to no problems)

```
0  1  2  3  4  5  6  7  8  9  10
```

6. Do you have pain during or immediately after doing 10 single leg hops? (from strong severe pain/unable to no pain)

```
0  1  2  3  4  5  6  7  8  9  10
```

7. Are you currently undertaking any sport or other physical activity?

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<th>10</th>
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<td></td>
<td>Not at all</td>
<td>Modified training +/- competition</td>
<td>Full training +/- competition but not at same level</td>
<td>Competing at the same or higher level</td>
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8. Complete EITHER A, B, or C in this question

* If you have **no pain** while undertaking sport complete Q8a only

- **8a.** For how long can you train/practice?

```
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<th>7-15 min</th>
<th>&gt;15 min</th>
</tr>
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<td>points</td>
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<td>points</td>
</tr>
</tbody>
</table>
```

* If you have **pain while undertaking sport, but it does not stop you** from completing the activity, please complete Q8b only

- **8b.** For how long can you train/practice?

```
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<th>6-10 min</th>
<th>7-15 min</th>
<th>&gt;15 min</th>
</tr>
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<td>points</td>
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<td>points</td>
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</table>
```
* If you **have pain that stops you from completing sport activities**, please complete Q8c only

- **8c.** For how long can you train/practice?

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<th>6-10 min</th>
<th>7-15 min</th>
<th>&gt;15 min</th>
</tr>
</thead>
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<td>points</td>
<td>points</td>
<td>points</td>
<td>points</td>
<td>points</td>
</tr>
</tbody>
</table>

**TOTAL VISA-P SCORE**