

Intra-Articular Injection of BPC 157 for Multiple Types of Knee Pain

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ABSTRACT

Introduction • Knee pain, a common complaint in primary care, has many causes, the most common of which is osteoarthritis (OA). Other common causes are meniscus tears, tendinosis, ligament tears or sprains, rheumatoid arthritis, lupus and septic arthritis. Also, referred pain from hip joint pathology like slipped capital femoral epiphysis can result in knee pain.¹ The use of peptides BPC157 and thymosin-beta-4 (TB4) has not been studied in the treatment of knee pain.

Methods • A retrospective study was done at the Institute for Hormonal Balance in Orlando, Florida, USA to see whether intra-articular injection of the peptide BPC 157, alone or combined with TB4, helped relieve knee pain. A 1-year chart review from 2019 to 2020 was performed. Since this was a retrospective study, patient follow-up varied, with most patients having had an injection of peptide into their knee 6 months to 1 year prior to the study. Of the 17 patients in the study, 16 were contacted by phone to follow up on the status of their knee pain. Only 1 patient could not be reached for the survey. Patients were asked to rate their pain prior to injection, the length of time the peptides helped ease the pain and the degree to which the injection helped them. No specific tools were used to measure their improvement in function, quality of life, stiffness or activities of daily living. The survey's main goal was to determine whether BPC157 helped with multiple types of knee pain in a primary care setting.

Results • Of the 16 patients, 12 had received only BPC 157 as an intra-articular injection. In this group, 11 of the 12 patients (91.6%) had significant improvement in knee

pain, whereas 1 patient (8.3 %) had no improvement. The other 4 patients received a combination of 2 peptide injections of BPC 157 and TB4. Of the patients who received both peptides, 75% showed significant improvement, but 25% had no relief of their knee pain. Overall, 14 of 16 patients (87.5%) had relief of their knee pain when BPC 157 or a combination of BPC 157 and TB4 was used.

Conclusion • This small study suggests that intra-articular injection of BPC-157 helps with multiple types of knee pain.

Clinical Implications • BPC157 is a peptide with regenerative properties that can be used to relieve multiple types of knee pain.^{2,3} Future studies are needed to look at the different causes of knee pain with follow-up magnetic resonance imaging scans (MRIs) to document the peptide's benefits. BPC157 has the potential to repair tears, build cartilage and reduce the number of knee surgeries. Because of its reparative properties, treatment with BPC157 offers advantages over the use of steroids.

Results • BPC157 is a peptide with regenerative properties that can be used to relieve multiple types of knee pain.^{2,3} Future studies are needed to look at the different causes of knee pain with follow-up MRIs to document the peptide's benefits. BPC157 has the potential to repair tears, build cartilage and reduce the number of knee surgeries. Because of its reparative properties, treatment with BPC157 offers advantages over the use of steroids. (*Altern Ther Health Med.* 2021;27(4):8-13).

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INTRODUCTION

The science of peptides has grown since 1902, when the word “peptides” was introduced at a scientific meeting in Germany.⁴ In general, peptides have a short half-life and have multiple effects.^{5,6} Researchers working on the Human Proteome Map have estimated that the human body has close to 300 000 peptides and think we know only a fraction of what these peptides do.⁷ Although peptides interact with

many receptors, most of those studied act on the G protein-coupled receptor or the tyrosine kinase receptor.⁸⁻¹⁰ Some hormones are peptides like thyroid-stimulating hormone, insulin, adrenocorticotrophic hormone and growth hormone-releasing hormone.¹¹ Peptides consist of chains of amino acids, generally between 2 and 100 amino acids in length.^{12,13} Longer chains of amino acids are considered proteins. Recent debate has redefined peptides as consisting of 50 or fewer amino acids.^{14,15}

In 1993, Dr. Predrag Sikiric of Croatia isolated the peptide BPC 157 from human gastric juice.^{4,16} In animal studies, BPC 157 has been shown to have many restorative properties. It can help with repairing tendons, ligaments, muscles, nerves, bone fractures, teeth and corneas and promote recovery from traumatic brain injury.¹⁷⁻²⁹ It also reduces blood clots and protects the liver and the endothelium.³⁰⁻³⁴ In 2005, Dr. Sikiric and his associates injected BPC157 intraperitoneally (not in the detached Achilles), resulting in tendon-to-bone healing. In 21 days, BPC157 improved the quantity of type 1 collagen, promoted better organization of collagen fibers and advanced vascular appearance.^{20,35} In addition, BPC 157 improved the biomechanical function of the healed Achilles tendon.²⁰

Because Sikiric's study showed that BPC157 accelerated healing of a ruptured tendon, many athletes have been using it to help heal their injuries.²⁰ BPC157 has been available on the internet for individuals to purchase and has been used extensively for more than 10 years by athletes, including professional athletes. Currently, however, no study using BPC157 in humans has been published, nor has this peptide received US Food and Drug Administration (FDA) approval in the United States. The FDA may even restrict the use of BPC157 in the future. As a result, few FDA-approved compounding pharmacies produce BPC157.

During this study, thymosin-beta-4 (TB4) was also used. TB4, a naturally-occurring peptide that comes from the thymus gland, was FDA-approved as an orphan drug in 2004 and in 2013.³⁶ It possesses a wide range of regenerative activities such as accelerating recovery from skin wounds, traumatic brain injury, stroke, multiple sclerosis and other serious conditions.^{19,37+43} In addition, it has been shown to reduce inflammatory markers and pain. Because of these proven effects in other studies, intra-articular injection of thymosin-beta-4 was added to BPC157 to reduce inflammation and pain.^{16,20,21,26,35,44-47}

Knee pain is a common complaint in primary care practices. The most common therapies for knee pain consist of one or more of the following: rest, physical or massage therapy and steroid injection. This study was done to see if an alternative treatment besides steroids can decrease knee pain.

METHODS

Study Design

We conducted a retrospective study by doing a chart review from 2019 to 2020 at the Institute for Hormonal Balance in Orlando, Florida.

Inclusion Criteria

In 2019 at the Institute for Hormonal Balance, an experimental trial using peptides was offered to patients to help with multiple types of knee pain. All patients were informed that BPC157 is an experimental peptide that has not been FDA-approved in the United States. They were told that it had not been previously studied in human clinical trials although it was well-tolerated during animal studies in which no serious adverse events were noted.

In the beginning of the trial, TB4 with BPC 157 was offered since research exists showing that these peptides help reduce inflammation.^{48,49} Anecdotal evidence among healthcare providers who use peptides in their practices indicates that the combination of TB4 and BPC157 may reduce knee pain. No human clinical trials using BPC157 to help with knee pain have been published. Later in the trial, only BPC157 was offered since I observed that patients were improving with both peptides. I wanted to test the hypothesis that injecting BPC157 alone can decrease knee pain. All patients interested in enrolling in the study signed a consent form for the experimental trial using peptides to treat their knee pain. All the patients paid for the peptide and for the injection; none of the treatment was covered by their medical insurance.

Exclusion Criteria

Patients who showed signs of infection or who had had a total knee replacement were excluded from the study. In addition, pregnant women, individuals ≤ 10 years of age and patients undergoing cancer treatment were excluded from the study.

Patients

A total of 17 patients, average age 60 years, received peptide therapy for their knee pain. Only 16 patients could be contacted for the follow-up questions. The test group consisted of 9 women (56%) and 7 men (44%), age 19 to 77 years. One patient was of Hispanic descent, one of Korean descent and the rest were white.

Procedure

The peptides were created via solid phase peptide synthesis and compounded by Tailor Made Compounding in Nicholasville, Kentucky. BPC157 was compounded at 2000 mcg/ml concentration and TB4 at 3000 mcg/ml concentration. Both were buffered with sodium phosphate buffer and benzyl alcohol for sterility and stability.

After patients consented to the intra-articular injection of BPC157 or BPC157 with TB4 they were brought to the procedure room. Patients were seated on the exam table with their legs hanging down. The injured knee was cleaned with betadine and alcohol. No lidocaine was used to anesthetize the area. A 25 G 1.5-inch needle was inserted into the knee via the medial tibia plateau area and 2 cc of BPC 157 was injected into the knee joint. Injections of BPC 157 with TB4 ranged from 1 cc of BPC157 plus 1 cc of TB4 to 2 cc of BPC

157 plus 2 cc of TB4. An intra-articular injection was made with a 25 G 1.5-inch needle and the 2 peptides were injected separately into the joint. The procedure was performed without ultrasound guidance.

In the beginning of the experimental trial, BPC157 and TB4 were used, but after the fourth patient, I wanted to test whether BPC157 alone would work. Only 2 patients had a repeat injection of BPC157 since they reinjured their knee during the period of chart review.

Retrospective CHART review and follow-up questions

A retrospective study of BPC157 was carried out to see whether this non-FDA approved peptide would help with knee pain from OA, ruptured anterior cruciate ligament or other maladies. A chart review at 1 medical clinic that performed an intra-articular injection of BPC 157 alone and of BPC 157 plus TB4 was done. Of the patients, 17 had an intra-articular knee injection of BPC 157 from 2019 to June, 2020. One person could not be contacted for the follow-up questions and was excluded from the study. Patients' average age was 60 years, including 9 women and 7 men who ranged in age from 19 to 77 years. Most of the injections were done in 2019, and a college student volunteering in the office conducted the follow-up surveys by phone.

First, patients were asked to rate their pain before and after the peptide injection from zero to 10, with 10 being the worst. Then, they described their degree of mobility, tolerance for exercise, ability to climb stairs and quality of sleep. Measurements were all subjective; no objective testing was performed to verify their improvements. Finally, they were questioned about adverse events experienced and given an opportunity to comment on their treatment.

On the chart review, only 4 out of 16 patients had an MRI of the knee before the procedure. Of these, 1 patient had a meniscus tear and a sprain of the medial collateral ligament, the second had only a meniscus tear, the third had an anterior cruciate ligament tear, and the last patient had popliteal bursitis. None of them had reports of x-ray of the knee. The first patient in this group of 4 with an MRI had knee surgery for a torn meniscus 6 months prior to injection but without relief of her knee pain. Of the 16 patients, 5 stated that they had previously been diagnosed with OA of the knee by another physician.

RESULTS

In the group of patients who received only BPC157, 11 out of 12 (92%) had improvement in their knee pain. Of patients receiving BPC157 plus TB4, 3 out of 4 (75%) had improvement in their knee pain. Overall, 14 out of 16 patients (87.5%) had improvement in their knee pain when treated with BPC157 or with BPC157 and TB4.

The dose of BPC 157 was 2 cc or 4 mg (2000 mcg/ml). The dose of BPC 157 with TB4 varied from a low dose of BPC157 of 2 mg (1 cc) and 3 mg (1 cc) of TB4 to a high dose of BPC 157 of 4 mg (2cc) combined with 6 mg (2cc) of TB4.

Table 1. Results in 12 Patients Who Received Only BPC157

| BPC157 | Dose of BPC 157 | Improvement | No improvement |
|-------------|-----------------|-------------|----------------|
| 12 patients | 4 mg | 11 of 12 | 1 of 12 |

Table 2. Results in the 4 Patients Who Received BPC157 Plus TB4

| BPC157 w/TB4 | BPC157 Dose | TB4 Dose | Results |
|--------------|-------------|----------|----------------|
| Patient 1 | 2 mg | 3 mg | No improvement |
| Patient 2 | 2 mg | 3 mg | Improvement |
| Patient 3 | 3 mg | 4.5mg | Improvement |
| Patient 4 | 4 mg | 6 mg | Improvement |

Abbreviations: TB4, thymosin beta 4.

Table 3. Results in the 4 Patients With Magnetic Resonance Imaging Scans Prior to Peptide Injection

| | MRI results | Peptide | Results |
|-----------|--|--------------------------------|-------------|
| Patient 1 | Tear of medial meniscus and sprain of medial collateral ligament | 3 mg of BPC157 + 4.5 mg of TB4 | Improvement |
| Subject 2 | Tear of meniscus | 4 mg of BPC157 + 6 mg of TB4 | Improvement |
| Subject 3 | Tear of the anterior cruciate ligament | 4 mg of BPC 157 | Improvement |
| Subject 4 | Popliteal bursitis | 4 mg of BPC 157 | Improvement |

Abbreviations: MRI, magnetic resonance imaging; TB4, thymosin beta 4.

Table 4. Duration of Improvement in Knee Pain After Receiving Only BPC157

| Length of time | 24 hours | Up to 3 months | 3 to 6 months | 6 months to 1 year |
|--------------------|--------------------|---------------------|---------------------|---------------------|
| Number of patients | 1 out of 12 (8.3%) | 2 out of 12 (16.7%) | 2 out of 12 (16.7%) | 7 out of 12 (58.3%) |

Table 5. Duration of Improvement in Knee Pain Reported by 4 Patients Receiving BPC157 and TB4

| Length of time | Up to 3 months | 3 to 6 months | 6 months to 1 year |
|--------------------|------------------|------------------|--------------------|
| Number of patients | 1 out of 4 (25%) | 1 out of 4 (25%) | 2 out of 4 (50%) |

Abbreviations: TB4 = thymosin beta 4

Figure 1. Overall pain in all 16 patients; 14 out of 16 (87.5%) had improvement in knee pain.

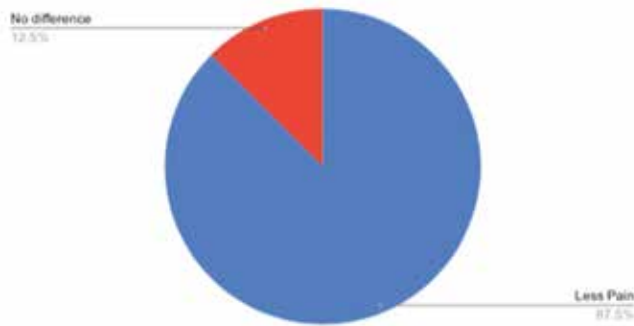


Figure 2. Overall mobility in all 16 patients; 75% had improvement in mobility.

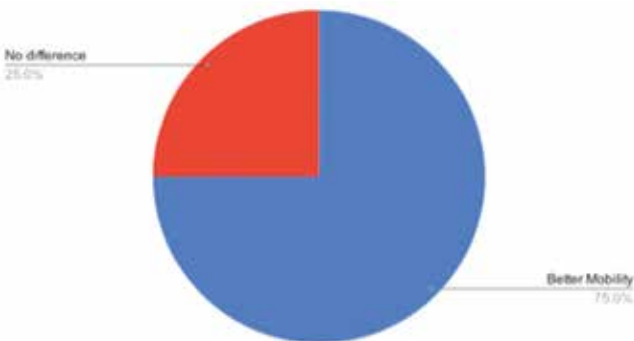
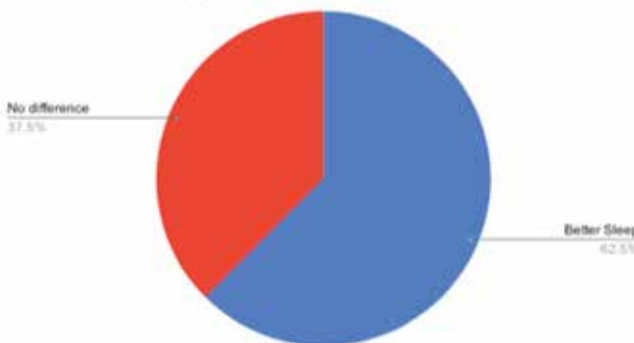


Figure 3. Overall sleep in all 16 patients; 62.5% had better sleep.



DISCUSSION

Knee pain is a common complaint in primary care. OA of the knee is the single most common cause of disability in the elderly.⁵⁰ It was the most likely common cause of knee pain in the patients in this study, whose average age was 60 years, since their conditions were not diagnosed with radiologic studies and blood tests. This study was limited because the patients did not all share the same condition; that is, OA of the knee. Since my medical practice is a wellness center, I see many types of knee pain. Only 25% (4 out of 16 patients) had MRIs of the knee, including 2 patients with meniscus tears, one with an anterior cruciate ligament tear and one

with popliteal bursitis. Of the patients with a meniscus tear, one also had a sprain of the medial collateral ligament. All 4 patients with MRI scans had improvement in their knee pain.

BPC157 has been used extensively by athletes, especially weight-lifters who have injured their muscles, tendons, ligaments and joints. An experimental study was done to test whether BPC157 can help with knee pain in humans. Although impressive animal data and *in vitro* studies with BPC157 have been done, published research on human clinical studies or case reports has so far been lacking.

BPC157 is a non-FDA approved peptide that has regenerative properties. It has been shown to increase the production of type 1 collagen, help repair tendons, ligaments and muscles and also reduce inflammation.^{2,16,20-22,26,35,51} In a study of rats with surgical detachment of their Achilles tendon, BPC157 demonstrated complete healing of the detached Achilles tendon onto the calcaneus bone.³⁵ More blood vessels and dilated capillary beds were noted at the injury site in the early healing.³⁵ In addition, BPC157 modulates nitric oxide synthesis.⁵² Because the combination of BPC157 and nitric oxide increases blood supply in a hypovascularized region, BPC 157 may assist in clearing out the toxic cytokines, reduce inflammation of the knee and help improve the extracellular matrix for the knee to heal.⁵³ Finally, BPC157 may also activate the FAK/paxillin pathway and increase growth hormone receptors in tendon fibroblasts to help repair tears of the tendon.⁵⁴

Intra-articular injections of steroids are commonly used to reduce the inflammation of knee pain associated with OA for only a few weeks.^{55,56} However, steroid injections do not repair torn tendons, ligaments, meniscus or muscles. Furthermore, a recent clinical trial highlighted a small but potentially deleterious effect of repeated corticosteroid injections on knee joint cartilage.^{57,58}

In this study, BPC 157 has been shown to improve knee pain beyond 3 months in 9 out of 10 patients (90%) and beyond 6 months in 7 out of 8 patients (87.5%) in the study group. Intra-articular injections with steroids provide only short-lived benefits of 1 to 4 weeks as documented in several studies. Although this study included relatively few patients, it is noteworthy that most of the patients had improvement of knee pain for at least 6 months or longer, better results overall than those afforded by steroid injection. A future study is needed to compare the difference in outcomes using steroids vs BPC157.

Intra-articular injections of hyaluronic acid are controversial, with most clinical guidelines advising against their use or providing uncertain recommendation. Currently, no study exists showing that BPC157 helps with the production of hyaluronic acid.^{19,59,60}

Platelet rich plasma (PRP) treatment has been reported to help with OA of the knee. A total of 83 randomized controlled trials comparing PRP with hyaluronic acid have shown that PRP is a safe treatment with the potential to provide symptomatic benefit of OA for least 1 year.⁶¹⁻⁶³

A randomized placebo double-blind study is underway in Australia and New Zealand to test whether platelet rich

plasma (PRP) will help with OA. There are 288 patients enrolled in this study, all older than age 50 years. The patients in the study will receive either 1 injection of PRP or 1 injection of normal saline solution each week for 3 weeks into the knee joint. In addition, MRIs of the knee will be done after 1 year to study any structural changes since no research currently exists showing that PRP improves the structure of the knee joint.⁶⁵ Similar studies on BPC157 also need to be done. Treating knee pain with BPC157 is a faster and less complex procedure than treating it with PRP since it takes time to process PRP from a patient. A study should be done to compare PRP vs BPC157 to see which is more effective.

This proof-of-concept trial using 4 mg of BPC157 showed that 11 out of 12 patients (92%) had relief from knee pain while 3 out of 4 (75%) showed improvement with varying amounts of BPC157 and TB4. This retrospective study covered a wide range of injuries and of patients age 19 to 77 years.

Of the 2 patients who did not improve with the peptide injection, the first had received the standard dose of 4 mg of BPC157. However, 1 year later, her knee pain had not increased. Because she had not had an x-ray of her knee, the presumptive diagnosis for this 72-year-old patient may have been hip pain presenting as knee pain. More studies are needed for her.

The second patient had temporary improvement using BPC157 and TB4 for 24 hours. She was able to sleep well without any knee pain but afterwards did not have any relief of her knee pain. She also received the lowest dose of 2 mg of BPC157 and 3 mg of TB4. It is not known whether this patient would have benefited more from a higher dose of the 2 peptides since all 4 patients who received the higher dose of 4 mg of BPC157 and 6 mg of TB4 reported improvement.

BPC157 has been shown to improve the healing of a rat's transected Achilles tendon without surgery in 21 days. Type I collagen was shown to increase in quantity with better organization of collagen fibers. That study showed that methylprednisolone slowed down the healing while BPC 157 substantially improved it when combined with methylprednisolone.³⁵ Another study on rabbits with a surgically induced defect of the radius demonstrated that BPC157 significantly improved the healing of the bone defect over 6 weeks.⁶⁵ BPC157 has also been shown to accelerate wound and fracture healing in rats.⁶⁶ In conjunction with all these positive animal studies for BPC157, we were able to show that BPC157 helped improve a wide range of knee pain in humans. This peptide was well tolerated with no adverse events noted.

Although insomnia may have many causes, it was interesting to find that patients enjoyed improved sleep, as well as mobility, when knee pain decreased. In this study, no one received physical therapy after the peptide injection.

CONCLUSION

BPC157 has been shown in this retrospective study to help reduce knee pain, a common complaint in the primary care field. After receiving a 4-mg injection of BPC157, 11 out of 12 patients (92%) experienced relief from knee pain. This

peptide was shown to have a prolonged effect over 6 months compared with the short-lived benefit of steroid use. BPC157 offers advantages over steroids since the latter do not repair torn tendons, ligaments, meniscus or muscles. Future, larger studies are needed to focus on improvement in structural changes and increased collagen production in patients with OA. BPC157 alone and BPC157 with TB4 have helped relieve knee pain in 14 out of 16 patients (87.5%).

CONFLICT OF INTEREST

The authors declare there are no conflicts of interest in the authorship or publication of this manuscript.

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