Resolution of Pudendal Neuralgia in Chronic Pelvic Pain; A Single Site Observational Study Using a Novel Regenerative Therapy

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Abstract

Background: Chronic pelvic pain (CPP) is a relatively common and debilitating condition among women that greatly affects their quality of life. Unfortunately, it is a poorly understood condition, often difficult to treat and many patients with CPP have neuropathic pain associated with the territories innervated by the pudendal nerve.

Methods: A retrospective chart review study was conducted in 64 patients presenting with a pudendal neuralgia component to their CPP who were treated with a transvaginal wall injection of an amniotic tissue regenerative product. Follow up assessment was performed 6 weeks after treatment.

Results: 67% of the patients reported complete or near complete resolution of their CPP pain with an additional 23% reporting moderate pain relief, and 9% reported no relief. Likewise, pressure on the pudendal nerve induced pain in all subjects prior to treatment and 89% reported complete or near complete relief of pain, 8% reported moderate relief and 3% reported no relief.

Conclusions: In this study we demonstrate that treatment of women with CPP having a pudendal neuralgia component using a commercially available and novel regenerative amniotic tissue product resulted in complete to moderate pain relief in almost 90% of patients treated. Considering the well known difficulty in treating CPP patients, this study opens a new therapeutic option that is effective in the majority of qualifying CPP patients.

Key words: Pelvic pain, regenerative medicine, allograft, amniotic fluid, pudendal neuralgia, microRNA, growth factors.

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INTRODUCTION

Chronic pelvic pain (CPP) is a relatively common and debilitating condition among women that greatly affects their quality of life. It affects 1 in 6 women aged 18–50[1] and occurs in approximately 20% of all outpatient referrals for gynecological help.[2] Moreover, its economic burden is estimated to be $881.5 million per year in the U.S. based on the most recent analysis of 1995-1996,[3] and hence, likely considerably more expensive today. CPP in women is defined as persistent, noncyclic pain perceived to be in structures related to the pelvis and lasting more than six months. It is a poorly understood condition and often difficult to treat largely because CPP typically has multiple etiologies including endometriosis, interstitial cystitis (IC), inflammatory bile syndrome (IBS), pudendal neuralgia and vulvodynia. In addition, most women with CPP develop pelvic myalgias which also significantly contribute to their daily pain. There is significant overlap between these conditions, and they frequently occur in combination in individuals, making the treatment of CPP complex. In addition, studies show that over 50% of CPP patients have depression which further contributes to a poor quality of life.[4] Many patients with CPP have neuropathic pain associated with the territories innervated by the pudendal nerve. Hence, significant pain relief, albeit temporary, is achieved in many patients in response to analgesic applications to the area of the pudendal nerve in Alcock's canal.[5,6] Neuropathic pain, which occurs from damage to, or dysfunction of, the peripheral or central nervous system, is a major source of chronic pain. In addition, it can have numerous etiologies including diseases (cancer, viral infections, etc.) and injuries/trauma (i.e., stroke, surgery, spinal cord injuries), all of which may lead to neurogenic inflammation and pain sensitization. Accordingly, pudendal neuralgia likely is a contributing factor responsible for pain in many CPP patients.[7] Prior studies have suggested that stem cells might offer a way to inhibit chronic pain by modulating neuroinflammation[8,9] potentially providing a more complete and definitive strategy

for treating neuropathic pain, and thus possibly also relief of pain associated with CPP. The healing benefits of amniotic tissue have been studied for over 100 years, first appearing in 1910 for the treatment of burns,[10] and currently have their widest application in ophthalmology where the amniotic membrane has been approved by the FDA for corneal regenerative repair almost 20 years ago.[11] Amniotic tissue (amnion + amniotic fluid) transplantation has been shown to have anti-inflammatory and immunomodulatory properties[12] and promotes epithelial healing, reduces inflammation, increases comfort, and decreases the severity of insufficient vascularization in many settings.[13] The distinctive properties of amniotic tissue preparations include its ability to promote wound healing and suppress pain, fibrosis, and bacterial complications.[14] In utero, amniotic fluid aids in fetal growth and provides mechanical cushioning, and has antimicrobial properties that protect the fetus due to a host of nutrients, growth and regenerative factors within it.[15]

In the present communication, we report on the efficacy of an FDA regulated and commercially available injectable amniotic tissue product in relieving pain in patients with pudendal neuralgia as part of their CPP.

METHODS

This study was approved by the Sterling IRB (Atlanta, GA), and is a retrospective, chart review (i.e., open label) of 64 patients who presented to a local female pelvic medicine and reconstructive surgical facility in Franklin, TN, and were treated by a single board certified urogenital physician (BKJ). Baseline responses from all patients were obtained at the time of treatment and follow-up responses were obtained 6 weeks following treatment. Additional concomitant standard of care therapies were ongoing at the time of treatment in 63 patients, none of which were reported to have significant therapeutic effects. All patients were evaluated and those determined to have pudendal neuralgia as a component of their CPP as determined by presenting symptoms and digital pressure on the area of Alcock's canal were included in this study. To treat pudendal neuralgia, all subjects were injected transvaginally with 1 cc of the amniotic tissue transplant diluted with 2 cc of sterile saline to infiltrate the area around the pudendal nerve at the level of Alcock's canal. Following the procedure, the patients were evaluated 6 weeks later by documenting their self-reported level of pain improvement using 3 categories: 1) pain completely or near completely gone, 2) pain moderately improved, or 3) no improvement in pain. The patients were also examined by digital pelvic exam in which the area around Alcock's canal was palpated and their self-reported level of tenderness and pain was documented. Tenderness in this area was characterized as: 1) tenderness completely or near completely resolved, 2) improved but still tender, 3) continued tender as prior to surgery.

The amniotic membrane transplant was provided by Amnio Technology, LLC (Scottsdale, AZ), an FDA registered and American Association of Tissue Banks (AATB) certified tissue bank. The placental sac and amniotic fluid were collected by a separate FDA registered and AATB certified procurement team from scheduled Caesarian section deliveries occurring at multiple facilities. The collection process follows strict guidelines, which includes a prescreening of all donors. The donors must be between the ages of 18 and 35 years old, be healthy and have no previous history of substance abuse of any kind. Before delivery their social life and medical history were recorded in a careful history, and the patients were serologically tested for a variety of communicable diseases as required by the FDA. In addition, the placental tissue and amniotic fluid was tested again at the site of manufacture. The amnion was separated by blunt dissection from the chorion and subjected to freeze-fracture at -80°C to form membrane fragments approximately 50 – 200 microns in size. The final injectable allograft was prepared using a mixture of the freeze-fractured amnion to which amniotic fluid was added to form a slurry (total volume 1cc), followed by freezing at -80°C until shipped to the clinic on dry ice and immediately stored at -80°C until application.

Statistics: Statistical analysis was completed by using chi square tests. The tests were used to compare the proportions of those with pain at baseline and after treatment. All data are expressed as means ± st dev.

RESULTS

A total of 64 charts of patients who presented to the clinic between 06/30/2014 and 10/31/2016 were reviewed. All patients presented to the clinic with

symptoms consistent with CPP and ranged in age from 19 – 78 years (mean 45.7, ± 11.8), had BMIs ranging from 18.0 – 37.1 (mean 28.02 ± 6.75) and were a mix of ethnic and socioeconomic backgrounds. The responses of all patients having pelvic pain with a pudendal nerve component to their pain were reviewed. Of these, 63 (98%) had both bilateral pain and 1 (2%) had unilateral pain. Likewise, 63 patients had multifactorial pain and 1 had isolated pain. Pain duration varied with 13 patients reporting pain durations greater than 10 years, 15 were 5 – 10 years, 31 were 1 – 5 years and 5 were less than 1 year with a mean duration of approximately 5 years. As shown in Figure 1, we found that 43 patients (67%) self-reported that their pain was completely or near completely resolved compared to the moderate pain relief group (21 patients or 33%; $p<.005$). Combining the complete pain relief and moderate pain relief groups revealed highly significant clinical pain relief ($p<.001$) compared to the 6 patients (9%) who reported no improvement at all. In addition, the area around Alcock's canal was palpated, and there was a significant decrease in reported pain with and 57 patients (89%) self-reported their pain completely or near completely improved leaving 7 patients with some level of pain ($p<.001$). There were 5 (8%) reporting their pain level improved but still with some residual tenderness, while only 2 patients (3%) reported no improvement at all. No patients responding to this therapy returned for additional therapy and the longest duration of pain relief from this treatment was 28 months. None of the patients in this study reported any adverse events associated with treatment demonstrating the safety of the amniotic tissue injectate in this procedure.

DISCUSSION

Chronic pelvic pain is a relatively common disorder that has historically been very difficult to treat, thereby leaving most patients impaired with poor quality of life, often for many years. CPP includes a cluster of conditions with endometriosis and interstitial cystitis among the most common conditions that place women at risk for chronic pelvic pain. Related conditions include pudendal neuralgia vulvodynia, pelvic inflammatory disease, irritable bowel syndrome, scarring after abdominal surgery, fibromyalgia and chronic fatigue syndrome. CPP is a complex pain disorder with many patients having a component of pain from the pudendal nerve. Based on multiple contributing components, a clear singular etiology has not been possible to delineate. Standard of care for CPP is patient specific and includes medications (analgesics, antidepressants and possible hormone treatments), physical therapy, trigger point injections with analgesics, surgery and psychotherapy. While most patients are successfully treated for CPP, many patients fail to respond adequately and endure painful symptoms for years. Historically it is well know that placing analgesics to the area of Alcock's canal through which the pudendal nerve passes provides significant, albeit transient, relief for a variety of the pelvic floor disorders associated with CPP.[16] Thus, in many patients with CPP, the pudendal nerve serves as a common pathway conducting afferent pain signals from the pelvic floor to the brain. Pudendal neuropathy has recently been identified as a clinical entity[17] and contributes to CPP in general, and constitutes a defective component associated with the pudendal nerve, e.g., an inflammatory or immune defect in many CPP patients, however the incidence of pudendal neuralgia in CPP, to our knowledge, it has not yet been reported.

Because on the well characterized anti-inflammatory and immunomodulatory actions of mesenchymal stem cell treatments,[17] we explored the use of a readily available regenerative preparation which, other than hematopoietic and corneal treatments, remains the only other stem cell therapy regulated by the FDA.[19] Moreover, it's covered by some insurance providers including Medicare. The amniotic tissue products i.e., the amniotic sac and amniotic fluid combination, has actions very similar to those of the mesenchymal class of stem cells (MSCs) since they contain several subtypes of MSCs in both the amniotic membrane and amniotic fluid.[20] In the present communication we present data showing that infiltrating the pelvic territory involving the pudendal nerve (Alcock's canal) can provide considerable relief for patients with CPP having a pudendal neuropathy component. As shown, we found that nearly 90% of patients treated with the amniotic tissue product experienced moderate to complete pain relief within 6 weeks of treatment ($p<.00$). In addition, 98% had moderate to complete improvement of tenderness on local palpitation of the area around Alcock's canal showing statistically significant ($p<.001$) improvement. In fact, less than 10% of the treated patients failed to respond at all. Considering the ease of treatment, i.e., all 64

subjects were treated in an outpatient office setting, this therapy offers considerable potential for urogynecologists to provide effective, relatively easy to apply and comparatively inexpensive regenerative therapy for a condition well know to be otherwise difficult to treat.

Just how the amniotic tissue product achieves its therapeutic effects is not clear at his time. However, Venturi, et al.,[21] recently reported successful treatment of women with pudendal neuralgia using a stem cell rich autologous lipoaspirate fraction to infiltrate the area of Alcock's canal. Lipoaspirates are a rich source of MSCs (i.e., adipose-derived stem cells),[22] similar to the amniotic membrane[19] and amniotic fluid.[20] They found significant improvement in pain severity with 10 out of 12 patients (83%) reporting they were free of pain 12 months after the procedure. Only 2 patients (17%) failed to show improvement and no mortality or adverse events were observed. Hence, our study, in conjunction with the Venturi study, supports the possibility a regenerative component in the mechanism of action of the placental tissue products. MSCs, like adipose-derived stem cells, and those associated with the amniotic tissue product secrete a large variety of growth factors, anti-inflammatory and immunomodulatory molecules[23] as well as microRNAs capable of regulating gene expression in target cells.[24] Moreover, MSCs as a class are immunoprivileged, i.e., they invoke little to no immune response when applied allogeneically due to their relatively low expression of MHC class II antigens.[23] Based on prior studies, cell replacement by MSCs differentiating to the defective target cell phenotype appears unlikely since cell-free media conditioned with MSCs have equivalent regenerative activity as media containing MSCs.[25] Thus, secreted exocrine factors likely possess the molecular machinery underlying the regenerative, anti-inflammatory and immunomodulatory properties inherent in MSCs. Hence, we speculate that these exocrine factors activate quiescent resident tissue-specific stem cells that, in turn, accomplish the cell replacement, and/or tissue repair as suggested by others.[26] Moreover, we suggest that traditional anti-inflammatory mechanisms do not underlie tissue restoration since local infiltration of corticosteroids, a time honored anti-inflammatory therapy into the area of Alcock's canal, unlike analgesics, fail to provide pain relief.[27]

In conclusion, the Venturi report, coupled with our findings demonstrate a new, novel, effective and easy to administer therapy for patients suffering from CPP with a pudendal neuralgia component. Tissue regeneration likely underlies the therapeutic activity, but unlike other regenerative therapies, the amniotic tissue product does not involve the unattended teratogenic effects associated with fetal stem cells or induced pluripotent cells, does not require harvesting tissue from the patient with its attendant harvest site morbidities, does not invoke ethical issues and is in compliance with the FDA.

Study Limitations: the current study has obvious limitations as it is underpowered, a single institution observational retrospective study that lacks controls subjects. However, these limitations notwithstanding, our real world findings, and those of the Venturi study demonstrate a clear need to conduct a prospective, randomized, double blinded, placebo controlled multicenter study before this therapy can advance to recommended care for patients with CPP with a pudendal neuralgia component.

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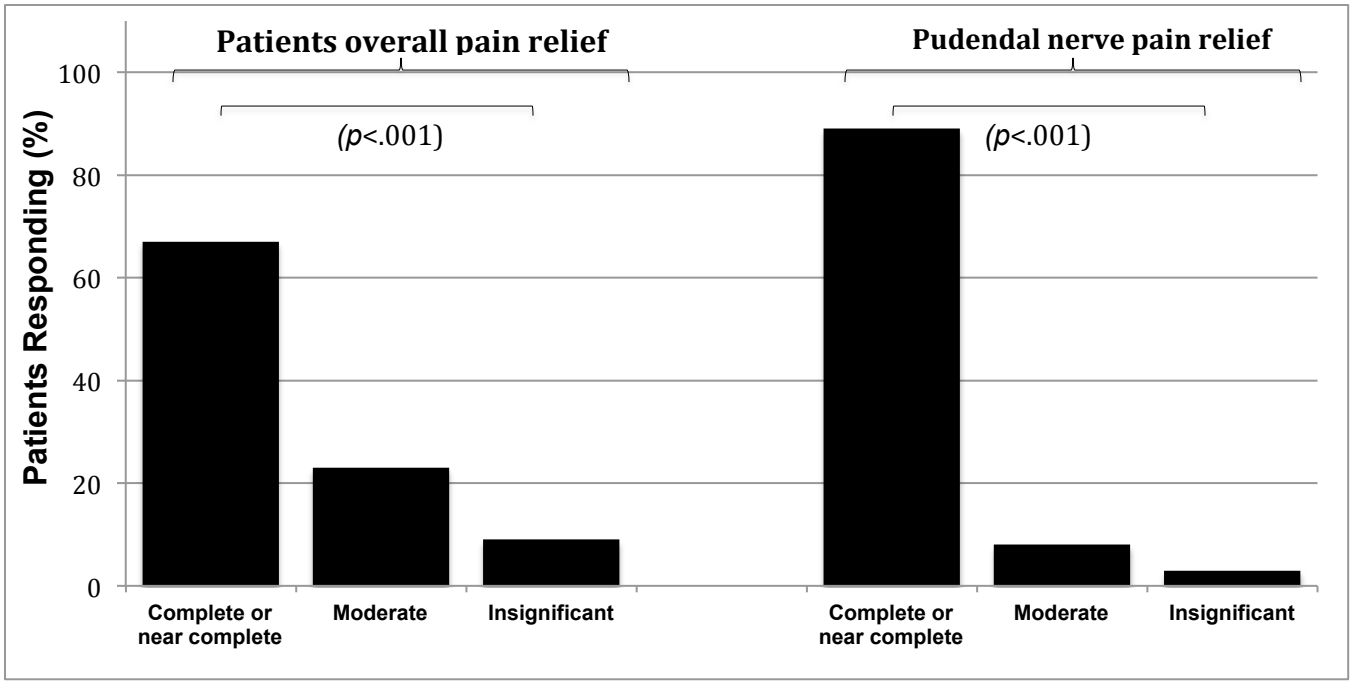

***Figure 1*: Pain relief in patients treated with the amniotic tissue product**. As shown, 67% of patients (n=43) reported complete to near complete overall pain relief at 6 weeks post treatment (p <.001), while 23% (n=15) reported moderate relief and 9% (n=6) reported no relief. Pressure on the area of Alcock's canal induced pain in all subjects and 6 weeks post treatment 89% (n=57) reported complete to near complete pain relief (p <.001) while 8% (n=5) reported moderate pain relief and only 3% (n=2) reported no pain relief. Combining complete and moderate pain relief data demonstrates 90% (n=66) responding to therapy for pudendal neuralgia and 97% (63) responding to therapy locally at Alcock's canal.