Brief Commentary

The Treatment of Chronic Neuropathic Pain: Bio (Regenerative) Pain Treatment through Lipofilling. A Short Communication Case Series

Haico de Gast, MD, Bart Torrensma, MSc, PhD, Eillis Fitzgerald, MSc, FRCSI, and Hieronymus Stevens, MD, PhD

From: DC Clinics and Bergman Clinics, Anaesthesiology and Pain, Netherlands

Address Correspondence:
Haico de Gast, MD
Pain Specialist, Anaesthesiologist
DC Clinics and Bergman Clinics
Anaesthesiology and Pain
Nauerna 4
Assendelft, 1566 PB
NETHERLANDS
00316215446 80
E-mail:
haicodegast@hotmail.com

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The following case series describes the treatment of neuropathic pain in post-surgical scars, using adipocytes and adipose-derived stem/progenitor cells (ASCs).

Two cases are described in which patients underwent lipofilling to treat painful scars after cosmetic surgery. The primary indication for lipofilling was pain reduction and not improved cosmesis.

Numeric rating scale (NRS) values were reported before the intervention and at regular intervals after the lipofilling. We found a notable long-lasting reduction in the NRS values after the "modified" lipofilling treatment. The results are promising and reinforce earlier data on the positive effect of lipofilling and pain in scars.

Key words: Neuropathic pain, regenerative pain, lipofilling

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Neuropathic pain refers to pain that originates from pathology of the nervous system. Often it develops as a result of disease or lesion of the central or peripheral somatosensory nervous system (1). The aetiology is varied: autoimmune disease, infection, drugs, nerve trauma or compression, and abnormal healing of surgical or traumatic cutaneous wounds, may all be responsible. It is estimated that it affects 1% of the population (2). Chronic neuropathic pain syndromes can be divided into 2 groups based on a central or peripheral location of the nervous system lesion. It is probable that both peripheral and central nervous system mechanisms contribute to the persistence of most types of neuropathic pain. Examples of peripheral neuropathic pain syndromes include entrapment neuropathies, iatrogenic neuralgias, nerve compression, post radiation plexopathy, radiculopathy, trigeminal neuropathy, postherpetic neuralgia, diabetic neuropathy, and posttraumatic neuralgias. Examples of central chronic neuropathic pain syndromes include HIV myelopathy, multiple sclerosis, poststroke pain, and syringomyelia. Peripheral neuropathic pain is now believed to be due to a non-physiological repair of the injured nerve leading to neuromata, altered nerve conduction, and spontaneous firing of the nerve. A cascade of neuroinflammation-related events is set off when a peripheral nerve is damaged, very often maintaining or worsening the original injury (3,4).

Neuropathic pain is usually treated with antidepressants and/or anticonvulsant drugs but significant pain relief (a reduction of 50% or greater) is achieved in less than 50% of the patients. Furthermore, these drugs have a significant side effect profile (5). Opioids are considered less effective in neuropathic pain than in nociceptive pain (6). Other treatment modalities include local infiltration with corticosteroids and/or local anaesthetics, transcutaneous electrical nerve stimulation, and psychological or cognitive therapies.

Efficacy of all these treatments is less than that achieved with antidepressant/anticonvulsant drugs, a response rate of 30% compared to placebo (3). Thus, while suboptimal, these medications are very often the mainstay of treatment.

Where pharmacological relief of neuropathic pain is insufficient, electrical stimulation may provide relief. Spinal cord stimulation has proven to be efficacious in failed back surgery syndrome and complex regional pain syndrome type 1. Other promising electrical stimulation techniques include implanted peripheral stimulations and motor cortex stimulation.

Interventional pain management techniques are widely used for peripheral neuropathic pain syndromes.

We believe that the bio-regenerative pain treatment described in this article will find its way into the treatment of various chronic peripheral pain syndromes, approaching the problem from a new perspective.

The use of adipocytes and stem cells provides a novel approach to an old problem, focusing on regeneration and immunomodulation. The term "regenerative surgery" has been applied to the use of autologous adipose tissue as a filler for soft tissue defects (7). It has been adopted as a term in recognition of the fact that lipoaspirate does not act simply as an inert filler, but that it is a promising source of adult stem cells (8). It has been demonstrated that adipose-derived stem/progenitor cells (ASCs) can differentiate into various cell lineages including osteogenic, chondrogenic, adipogenic, cardiomyogenic, and neurogenic lines. These lineages can contribute to the repair of damaged tissue. There are several published studies that support this theory (9-12). Recent *in-vivo* studies have been published suggesting peripheral nerve regeneration after the introduction of ASCs (13,14). ASCs have also been shown to have immunomodulatory effects on the neuroinflammatory cascade (2). In view of these demonstrated properties, we postulated that post-surgical neuropathic pain could be improved through the introduction of fat to the scar (7,15).

Methods

The treatment of 2 patients is reported in this short case series. Both were women, and had developed pain in scars from aesthetic surgical procedures. Pharmacological management of the pain was initially in accordance with the WHO Pain Ladder (16), and had failed to offer adequate relief. Tricyclic antidepressants had been tried without success in one case. The patients were asked to rate their pain using the numeric rating scale (NRS) prior to the lipofilling procedure, and at 3 months following each episode of lipofilling. They were also asked to rate how likely they were to recommend the treatment to other patients on a scale of one to 10, where 10 indicated that the treatment would be highly recommended.

For the harvesting of the lipoaspirate, a microfat harvesting cannula was used, type Sorrenson. Donor sites were the upper legs and abdomen in all patients. After centrifugation at a speed of 3000 RPM for 2.5 minutes, the oily top layer and serum layer were discarded, preserving the pre-adipocyte rich pellets (17,18). Micro fat grafts were injected subcutaneously in the entire area of skin were pain was experienced, using a curved cannula (7).

As this was an observational case series, Research Ethics Committee approval was not required.

Patients

We studied 2 patients, both women who had undergone cosmetic surgery. Neuropathic pain had developed in relation to the surgical scar within a year of surgery. Initial management was with analgesics, prescribed in accordance with the WHO Pain Ladder, and in one case with antidepressants when the pain failed to resolve. In one patient, the pain had also proved refractory to intralesional corticosteroid and botulinum toxin injections. Lipofilling was performed in the affected areas in an attempt to soften the scar tissue, provide padding, and reduce the persistent pain. All interventions took place at the Bergman Clinics in the Hague, and were carried out by the same surgeon. The patients were followed up during outpatient check-ups and later by telephone.

Results

Patient 1

Facelift, 55-year-old woman, ASA 1

A 55-year-old woman underwent a face and neck lift, via a U-shaped scar with no extension into the post-auricular hair-bearing area, in November 2006. Her postoperative course was complicated by seroma formation in the neck, which required 3 aspirations over a 15-day period. In the immediate postoperative period, she developed a sharp burning pain bilaterally in the distribution of the greater auricular nerves. Wound healing was normal, with no suggestion of hypertrophic or keloid scarring. The pain was rated at 9 on the NRS. She was initially commenced on analgesics in ac-

cordance with the WHO guidelines, with no relief. The addition of amitriptyline in 2007 initially improved her symptoms (NRS reduced to 4), however the effect was short-lived, with a return of the pain (to a NRS of 9) after 2 weeks. In 2009, a combination of triamcinolone and lidocaine was injected in the scar and subcutaneously in the distribution of the pain, with no improvement. Later that year, botulinum toxin injections (50IU of Botox® diluted in 1.75 mL of 0.9% saline) were equally distributed throughout the dermis of the affected area, again without improvement in the NRS. In an attempt to alleviate the patient's symptoms, it was decided to attempt lipofilling, which was carried out in March 2010. Under general anaesthetic and following local infiltration with lidocaine, 12 mL of lipoaspirate was injected to each side. A rapid improvement was seen, with the NRS reducing to zero by one week postoperatively. At 3 months, the NRS was one to 2. This improvement has been sustained, with a NRS of one to 2 recorded in January 2014 (almost 4 years postoperatively). The patient recommends the treatment for other patients (scored 9 on the recommendation scale).

Patient 2

Breast augmentation, 35-year-old woman, ASA 1

A 35-year-old woman with no significant medical history (ASA 1) was referred following a subpectoral bilateral breast augmentation via an inframammary approach in February 2010. Shortly after the initial procedure, she developed pain on the lateral aspect of the left breast. The pain was burning in nature and radiated towards the axilla. Treatment with paracetemol, nonsteroidal anti-inflammatory drugs (NSAIDs), and tramadol were unsuccessful. Despite these medications, she continued to report NRS values between 8 and 9. The pain was refractory to these analgesics.

In February 2012 (2 years following the original surgery), the first lipofilling treatment was performed. Under general anaesthesia, a total of 80 mL of lipoaspirate was injected to the lateral chest wall and breast in the distribution of the fourth intercostal nerve. Recovery was uncomplicated. At one week postoperatively, the NRS score was zero; by 3 months, it had increased to 5, and a second treatment was planned. In July 50 mL was injected as before, with no postoperative complications. The NRS was zero at one week and 3 months postoperatively, and to date (28 months later), the pain has not recurred. The patient rated the treatment at 9 – 10 on the recommendation scale.

Discussion

It is now believed that the sensitizing role of pro-inflammatory cytokines in pain transmission is one of the components in the generation of neuropathic pain over time (3) and that the imbalance of the inhibitory and anti-inflammatory cytokines can prolong the period of pain, thus making the pain chronic (19). Bio-regenerative pain treatment is an exciting new development in the treatment of chronic pain. Our hypothesis is that through lipofilling and the introduction of ASCs into scar tissue, pain reduction takes place. This effect may be attributed to the padding effect of the fat, but we believe it is also due to tissue regeneration and immunomodulation (20) stimulated by the stem cells. Further trials examining the effect of adipocytes and ASCs on scar regeneration and its subsequent impact on pain are warranted.

Neuropathic pain remains a complex, common, and unsatisfactorily managed problem. Current treatments are frequently ineffective, and side effects are common. The success we have seen with lipofilling in the 2 patients reported herein is an exciting development: it hints to something completely novel, an entirely new way to influence the pathways responsible in the formation of neuropathic chronic pain. With our increasing knowledge of the patho-physiological mechanisms of chronic pain and the results achieved to date with ASCs, we may have a new tool in hand to counter chronic neuropathic pain.

Cost-effectiveness is a hot item in modern day pain treatment. The calculated cost is approximately the cost of having lipofilling done under local anesthetic or under sedation. The price in the Netherlands for day care lipofilling under sedation or general anesthesia is about $2800 USD. If a second session is needed, the cost is halved at our clinic. The procedure can also be done using local anesthetics, reducing the costs further. The initial purchase of specialized equipment is around $1990 USD. As to the effectiveness of the procedure we are currently applying for approval to conduct a prospective randomized clinical trial and hope to report to you on that in the future.

Conclusion

Both cases show a sustained decrease in the NRS of pain after one or 2 lipofilling treatments. It appears to be an effective and safe option in the management of neuropathic pain resistant to drug treatment.

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