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Minimally invasive scar release by autologous adipose tissue transfer for post-traumatic neuropathic pain[☆,☆☆]

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ABSTRACT

Introduction: Addressing post traumatic lower limb neuropathic pain is challenging across medical specialties. To address this potentially devastating condition, several invasive and non-invasive approaches have been proposed with inconsistent results. Adipose fat transfer (AFT), also known as fat grafting, is a regenerative medicine technique in which a patient's own fat is harvested from one area of the body (usually through liposuction) and then injected into another area for various purposes, such as aesthetic contour enhancement or reconstruction and regeneration of scarred tissues.
Methods: We analyze the effects of fat grafting for neuropathic pain combined with neuroma excision (hybrid technique, hAFT) or alone (AFT). A retrospective review was conducted on 22 patients with neuropathic lower limb pain, after trauma or orthopedic surgery treated with hAFT (n = 9) or AFT (n = 13).
Results: Reduction in VAS scale more than 50 % was observed in 6 patients (66 %) treated with hybrid technique and in eleven patients (85 %) treated with AFT alone. Among these, complete pain reduction (>91 %) was achieved in 33.3 % of hAFT and 54 % of AFT technique. A 3.2 points reduction in VAS was found in the hAFT group versus 5.8 points in the AFT group (p = 0.035).
Conclusion: This pioneering use of AFT emerges as a minimally invasive breakthrough, promising significant improvement in reconstructing scarred subcutaneous tissue and managing neuropathic pain.

1. Introduction

Neuropathic pain is characterized by hypersensitive patches of skin (allodynia) where peripheral nerves are injured or inflamed [1–3]. This condition negatively affects patients' quality of life and represents a financial burden to the health system in direct and indirect costs [4].

Most frequently, neuropathic pain results from trauma or surgery. A randomized controlled trial conducted in post-traumatic lower limb surgery, six months post-injury, showed that up to 30 % of patients suffered from neuropathic pain [5]. The prevalence of neuropathic pain has been estimated in the general population to be superior to 10 % [6]. To address this relevant issue, several multidisciplinary treatments have been proposed in the literature and clinical practice [7]. Interventional clinical studies are difficult to conduct and interpret due to lack of objective outcome measures (the most widely employed being the subjective evaluation of pain,

Abbreviations: AFT, Autologous Fat transfer; hAFT, hybrid Autologous Fat transfer.

☆ The study was conducted in Global Medical Institute, Avenue Jomini 8, 1004 Lausanne, Switzerland.

☆☆ The data collection was conducted as a retrospective quality assessment study and all procedures were performed in accordance with the ethical standards of the national research committee and the 1964 Helsinki Declaration and its later amendments. All patients have signed an informed consent allowing the authors to anonymously use the retrospective data.

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on a visual analog scale or VAS), and limited possibilities of controlled study design for surgical approaches [8].

The treatment strategy for neuropathic pain is centered on pharmacotherapy with unpredictable outcome in most of the cases [9]. Perfusions and targeted infiltrations (interventional pain management) complete the most widely employed therapeutic options leading to an overall 30–50 % success rate [6]. Refractory cases may be considered eligible for surgical procedures such as neuroma excision and minimally invasive targeted neurectomies, which may further increase the percentage of successfully treated patients [10]. Unfortunately, these approaches are prone to recurrences and are only available in highly specialized centers.

Novel, cost-effective and broadly available approaches are in high demand, as several patients worldwide continue to suffer from post-traumatic neuropathic pain despite the above-mentioned options [9].

Traumatized tissues and scars, particularly in the lower extremity, seem to play a central role in the development of neuropathic pain [5]. Depleted subcutaneous tissue and non-physiological adherences between the skin and the deeper layers, including sensitive nerve branches are found most of the time in proximity of the affected areas [1]. As a consequence, the release of the mechanical constraints of scars on surrounding tissues may contribute to pain relief. The simple hydrodissection under ultrasound guidance may lead to partial or complete improvements in selected cases where the scar burden is limited [11]. The release of the adherences with subcisions (percutaneous needle scar release) could as well contribute to transient neuropathic pain improvement [12]. The main limitation of this approach is the induction of inflammation and bleeding which are both conductive to more scarring and cause relapses or worsening of the symptoms [13].

To decrease these limitations, a regenerative interface such as fat tissue can be used to reconstruct the subcutaneous tissues while mechanically releasing the scars [14].

Autologous fat transfer (AFT), also called fat grafting, is a simple surgical technique in which fat cells are extracted in one part of the body (i.e. the abdomen or flancs) through a blunt micro perforated cannula (as in a small liposuction) and transferred via injections to replenish another site such as the subcutaneous tissue [15]. In plastic surgery, AFT has been used for several years with satisfactory outcomes to reconstruct soft tissue defects such as in the breast post radiotherapy [16,17]. AFT in breast reconstruction has been shown to improve the quality of irradiated skin and decrease thoracic pain [18].

Early clinical evidence has suggested a role of AFT, in combination with neuroma excision, as a cost-effective treatment option to modulate post traumatic neuropathic pain [19–22].

In the literature, there is no consensus about the methods of adipose tissue extraction and injection protocol for pain interventions. In addition, AFT alone for the treatment of neuropathic pain has not been extensively investigated to date.

2. Patients and methods

We reviewed the charts of 50 patients treated by drs. Pietramaggiori and Scherer in Global Medical Institute in Lausanne for neuropathic pain, as defined in 1994 by the International Association for the Study of Pain (IASP) as: “pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system” [2]. Twenty-two patients were included, 7 males and 15 females, average age 55.5 years old (range 23–87). All patients had a history of lower limb trauma and orthopedic surgery. All patients signed an informed consent to treat retrospective data. At least one year after surgery/trauma, after the orthopedic issue was deemed solved, patients complained of chronic neuropathic pain, painful or hypersensitive scars, allodynia and decreased function of the affected limb and work ability. The minimum pain threshold that we considered to be eligible for surgery was 4/10 on the visual analog scale (VAS) during most of the day. Allodynia was present in all patients and defined as pain response to stimuli (light touch, simple movements without resistance, bed sheets or clothes contact with the skin). Included patients failed to respond to oral and topical medications for neuropathic pain (as defined as non-significant or inconsistent reduction of pain, and, or unbearable side effects) and conservative approaches (physical therapy, ergotherapy for skin desensitization).

Patients were included when a positive targeted nerve block with ultrasound guidance [23] could significantly reduce the pain (>50 % temporary reduction in VAS). Patients with negative response to the nerve block, undefined pain (not corresponding to a plausible nerve lesion) or with disproportionate symptoms (like patients possibly suffering from CRPS) were excluded.

Tactile detection thresholds and allodynia patches were determined by Weinstein monofilaments (Aesthesio, San José, CA). All assessments were performed by a single assessor (G.P.) with the patients in a seated position, legs extended and closed eyes. The monofilaments exert pressure ranging from 0.008 to 300 g/mm^2. The filaments were applied perpendicular to the skin until they bent 2–3 mm. Measures were taken in the middle of the allodynic area before treatment and 12 months post-op.

Before surgery, patients had a pain threshold <10 g.

Patients eligible for surgery were treated by autologous fat transfer (AFT) infiltrated in the subcutaneous tissue in the allodynic zones and under the scars. They were divided in two groups (Table 1).

- **Group 1:** Nine patients were included in this group, in which neuroma-like structures of a main branch of a sensitive nerve (saphenous nerve, peroneal nerve and or tibial) were confirmed by ultrasound or MRI. Surgical approach included neuroma excision (proximal resection of neuroma and burial of the proximal nerve stump in muscle tissue) and AFT (hybrid technique, hAFT). The neuroma was sent to pathology to confirm the clinical diagnosis.
- **Group 2:** Thirteen patients were included, suffering from allodynia, without definitive clinical proof of neuroma (like for example when scars located in peripheral zones, such as saphenous nerve in the knee, peroneal or tibial nerve in the foot, or the neuroma could not be identified by radiological investigations). These patients were treated with AFT alone (AFT).

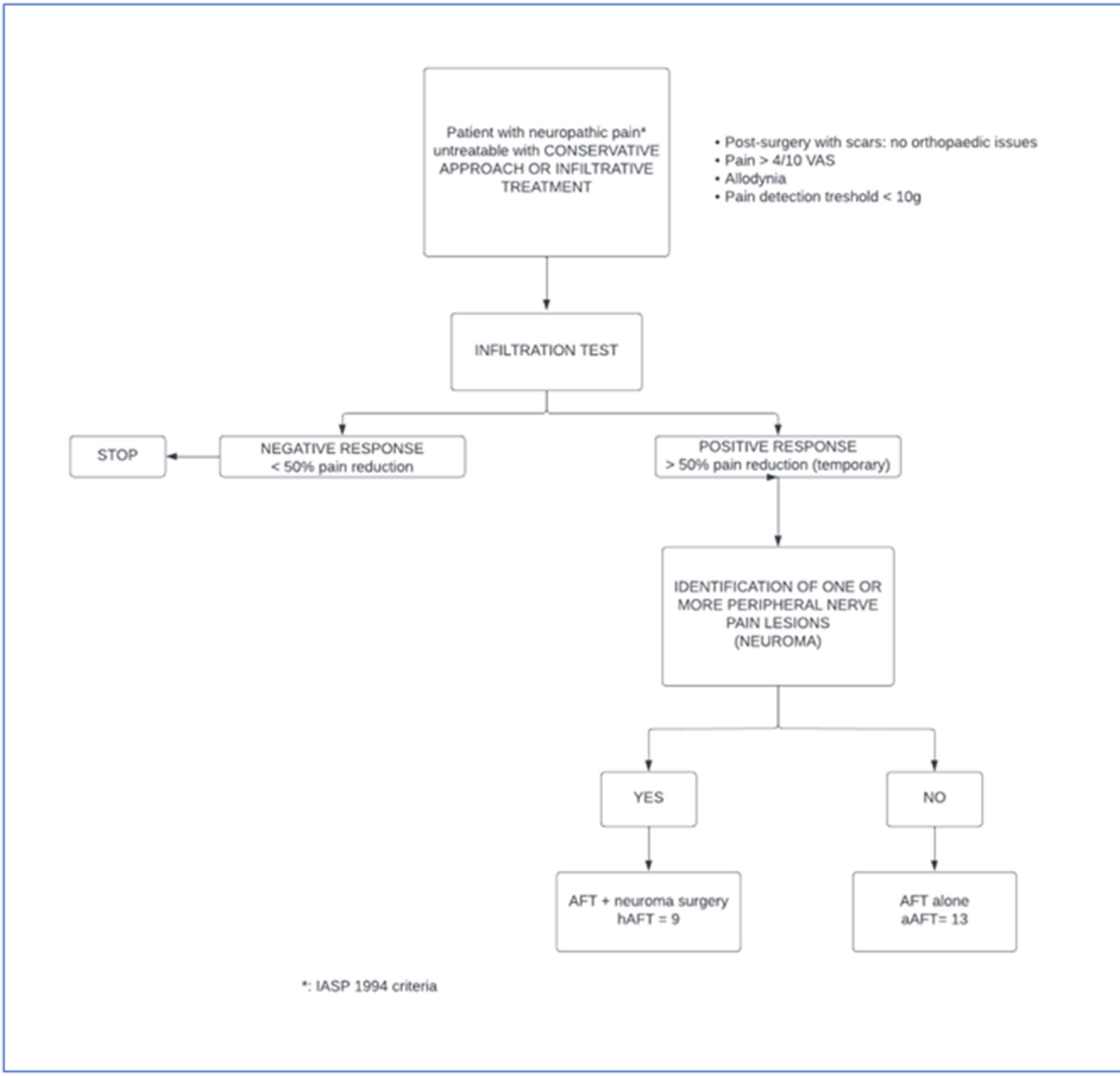
To confirm the engraftment of AFT under the scars, an ultrasound was carried out 3 months after the procedure.

The Visual Analog Scale (VAS, 0 no pain, 10 maximum pain) was used to estimate pain before treatment and at 1 year follow up. Results were divided in significant pain reduction after surgery (50–90 % VAS improvement, corresponding to pressures between 4 and 60 g of monofilament without pain) and patients with a significant major improvement (>90 % VAS improvement, more than 100 g without pain) 12 months post-operation. Improvements less the 50 % were considered non-significant.

Two-tailed paired t tests were used to compare intensity of pain reported before surgery (baseline) and during the last visit. A p value less than 0.05 was considered significant.

The analysis of the results was approved by an internal review board. All surgeries were performed under general anesthesia.

Table 1
Selection of the patients for the retrospective study. Patients meeting the criteria for post traumatic neuropathic pain, failing to respond to conservative approaches were subjected to selective nerve blocks under ultrasound guidance. Positive response after infiltration (defined as temporary >50 % improvement of pain) lead to inclusion in the study. In group 1, neuroma excision was associated to autologous fat transfer (hybrid technique, hAFT). In group 2, patients received AFT alone.



2.1. Technique of AFT harvest and infiltration

Fat tissue donor site (usually the abdomen and or flancs) was prepped and draped.

The subcutaneous tissue was infiltrated with a solution of 0.5 L of NaCl and 0.5 mg of epinephrine via an infiltration cannula (Gems tumescent Infiltrator, 2.1 mm 14G, Tulip Medical, USA). Usually, 200 ml of solution were infiltrated per zone (i.e. 200 ml in the lower abdomen, under the umbilicus and 200 in the flank). Lidocaine was not added to the solution due to its potential lipotoxic activity [24]. After allowing 10–15 min for the epinephrine to act, subcutaneous fat was manually extracted via a 18G blunt cannula (Tonnard Harvester, 2.1 mm, Tulip Medical, USA or equivalent) attached to a 20cc luer lock (BD, Canada), pre-filled with 5 ml of Ringer solution (RL) (Video 1). Four 20cc syringes were used for each procedure.

Supplementary video related to this article can be found at doi: 10.1016/j.reth.2023.12.017

The AFT was rinsed with RL multiple times to the point of a perfectly yellow graft (no blood) and transparent fluid (AFT was rinsed 3–5 times on average) (Video 1). After the fat harvest, the donor site was injected with 20 cc lidocaine 1 % and epinephrine. The AFT was transferred to 1 cc syringes and injected in the subcutaneous tissue via a 18G blunt injection cannula (gems spoon tip injector, 2.1 mm, Tulip Medical, USA or equivalent) with a fanning technique to detach the adherences underneath the scars and to recreate the subcutaneous tissue layer (Video 1).

No sharp cannula was used to limit tissue injuries and bleeding.

Fat was injected while retracting the cannula (Video 1) [25]. The amount of AFT transferred averaged 15 cc depending on the extent of the painful zone (usually corresponding to 10–20 cm^2).

After fat transfer, to reduce swelling and avoid shear forces, a double layer bandage (cotton in contact with the skin to warm the lymph and then elastic bandage) was applied, and patients were instructed to limit orthostatic position for ten days.

3. Results

Included patients were referred to our clinic on average 5 years after pain onset (range 1–40 years). All patients exhibited allodynia with pain evoked by light touch (corresponding to monofilament pressure inducing pain between 0.6 and 10 g). VAS score before treatment averaged 7.5 and did not differ between groups. The AFT was infiltrated under the scars and allodynic patches of skin to release the adherences with the deeper layers (muscle, fascia, nerve branches) and reconstruct the subcutaneous tissue (Fig. 1A and C, Video 1 and Video 2).

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Pathology examination of excised nerves after hAFT surgery confirmed the presence of neuroma characterized by disorganized neurogenic tissues, spindle cells proliferation (nerve fibers, Schwann cells and fibroblasts) embedded in fibrotic tissue (Fig. 1B).

In the hAFT group, three patients (33 %) had a significant improvement (50–90 %) and three (33 %) reported almost complete (>90 %) regression of the symptoms (Fig. 2). Globally, 66 % of the patients had a significant improvement (>50 %) and 33 % did not show any improvement (Fig. 2). These results correspond to a 3.2-point reduction in pain evaluation (1.7 fold decrease, $p < 0.05$).

In the AFT treatment group, 7 patients reported significant, major pain reduction (>90 %) and four patients reported significant improvement (50–90 % pain reduction) (Fig. 2). Together, 85 % of the patients treated with AFT improved >50 % after surgery, while two patients did not show any improvement (Fig. 2).

Results in the AFT group correspond to a 5.8 points reduction in pain evaluation (4.4 fold decrease, $p < 0.035$). Comparing VAS decrease between AFTh and AFT, we observed a trend toward greater decrease after AFT surgery.

No surgical complications were reported.

4. Discussion

Results from this study show that autologous fat transfer, alone or in combination with neuroma surgery, is effective to improve post traumatic neuropathic pain and allodynia.

While AFT in conjunction with open surgery (hAFT) improved neuropathic pain as previously suggested [20,21], it is interesting to note that results did not exceed the one obtained by AFT alone in this small case series. Conversely, hAFT and AFT were found to be mostly effective during the first few months after surgery (not shown), but only AFT alone seem to obtain longer improvement, however this difference was not statistically significant. It is possible that patients included in the hAFT group had a more severe injury, as confirmed by the visible neuroma. On the other hand, nerve injuries, scar adhesions and microscopic neuromas may still be the main root cause of neuropathy in more distal, smaller branches. In these cases, the surgical reconstruction can be even more challenging due to smaller caliber nerves and lack of soft tissues, and AFT could be attempted first.

It is not unusual that patients suffering from post-traumatic allodynia have to deal with the pain for months or years, during which they feel increasingly estranged from their family, social and professional networks, with an overall negative impact on their health [26]. The lack of defined underlying orthopedic issue and disproportionate pain, pose a critical challenge among healthcare providers and insurers. A multidisciplinary approach is mandatory for these patients. Once topical or oral medications and infiltrative approaches have failed, AFT can be considered as a valuable option, before more invasive ablative approaches such as neuroma surgery and radiofrequency or cryotherapy, or palliation such as implantable neurostimulators.

The methods described do not require expensive equipment and can be adopted in any surgical center by a trained physician. In our experience, the acceptance of this approach is very high, being minimally invasive, with basically no down time (no open wounds to heal in an already traumatized limb) and limited risks.

Surprisingly, patients did not report any pain in the affected limb immediately after the procedure (regardless of the outcome) although no local anesthesia was infiltrated (not to compromise the vitality of the fat cells). It is possible that the anti-inflammatory and analgesic (opioid-like) molecules secreted by the fat functioned as a targeted drug release system [27].

It is also known that adipose stem cells, such as the stromal vascular fraction (SVF), contained in AFT, stimulate nerve

Fig. 1. Group 1. Hybrid technique (hAFT): open neuroma treatment + adipose fat transfer (AFT). A. AFT is injected in the subcutaneous tissue under the scars and the area of allodynia in the attempt to detach all scars. The open wound is used as one of the entry points of the cannula to transfer fat. B. The neuroma is isolated, resected and sent to pathology. C. **Group 2**. Adipose fat transfer alone (AFT). Entry points are made via a stab incision and AFT is transferred under the scars and distributed in the zone of allodynia.

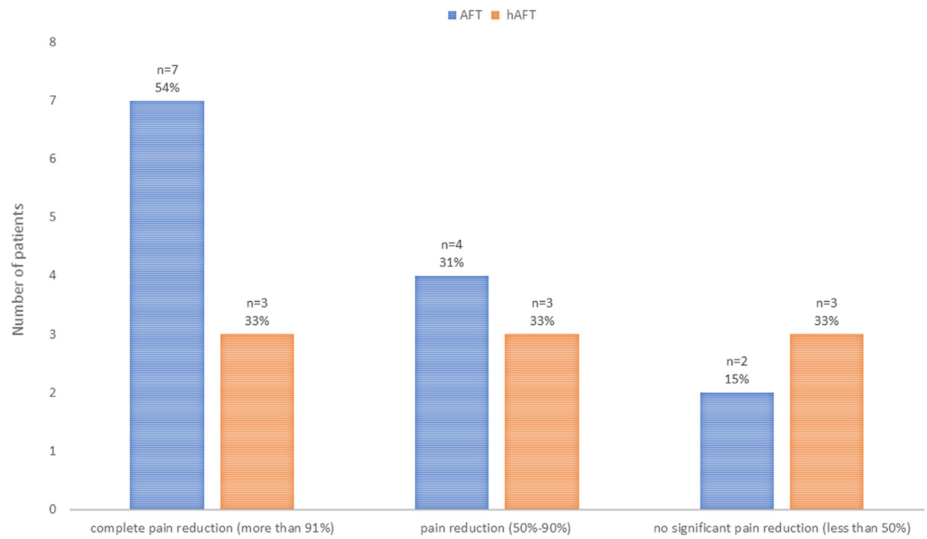

Fig. 2. Differences in pain reduction after hybrid technique (open neuroma treatment + adipose fat transfer, hAFT) and adipose fat transfer alone (AFT). The highest number of patients with more than 90 % neuropathic pain improvement was found after AFT (7 out of 13, while 3 out of 9 had similar results in the hAFT group, $p < 0.05$). Comparable 31–33 % proportion of patients reported an improvement between 50 and 90 % in both groups. Two and three patients did not exhibit any significant improvement (<50 %) in the AFT and hAFT groups, respectively.

regeneration, and mitigate chronic neuropathic pain due to the release of neurotrophic factors [27]. While the method described here did not concentrate fat derived stem cells, further research and enrichment of AFT with SVF cells may further improve the outcome and promote cell engraftment and tissue regeneration for longer periods of time [22].

Regardless of the exact mechanism through which a neuroma or other nerve lesion transmits neuropathic pain, AFT seems to act effectively against it.

We hypothesize that AFT grafts may contribute to the formation of a biological protective layer around the nerve fibers and prevents adherence formation. The reconstitution of the subcutaneous layer may disconnect scar tissue from nerve fibers and thereby reduce mechanical stimulation especially in moving joints. This is particularly important for nerve lesions below the knee where soft tissue is scarce and scar adhesions may impinge nerve fibers [5].

5. Conclusions

Fat tissue, a pivotal focus in regenerative medicine, holds widely unexplored therapeutic potential. While the use of adipose fat transfer (AFT) for peripheral nerve pain is still in its infancy, these findings support its efficacy to release scar adherences and reconstruct subcutaneous tissues, marking a critical step toward an innovative, yet safe and effective solution. Additional research is warranted to better understand AFT's mechanisms of action on neuropathic pain and further refine this promising approach.

Declaration of competing interest

Authors declare no conflicts of interest.

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