Autologous fat grafting seems to alleviate postherpetic neuralgia – a feasibility study investigating patient-reported levels of pain

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Publication: The case-report of the first patient included has previously been published in the British Journal of Pain.

**Presentation:**

- The preliminary results from the first eight patients were presented as a short oral presentation at the yearly meeting of the Danish Society of Plastic- and Reconstructive Surgery, Copenhagen. May 2019.
- The results of the complete study were presented as an oral presentation at the annual meeting of the International Federation for Adipose Therapeutics and Science (IFATS) in Marseille, France. December 2019.

**Data Access and Responsibility**

The principal investigator, Martin Sollie, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Potential conflicts of interest:** None

**Financial support:** This research did not receive any financial support.
Abstract:

Background:
Post-herpetic neuralgia (PHN) is a relatively common side effect after an outbreak of herpes zoster, characterised by chronic neuropathic dermal pain. No effective treatment exists today. Fat grafting has shown promise in alleviating neuropathic pain, yet the exact mechanism of action, at a biological level, is not yet known. We report on the first human study using autologous fat grafting for treating PHN. Our hypothesis was that fat grafting can alleviate pain and improve Quality of Life (QoL) in patients suffering from PHN. If successful, this could be a safe, cost-effective alternative to analgesics. This safety and feasibility study aimed to investigate the possible pain-relieving effect of autologous fat grafting on PHN.

Methods:
Ten adult patients suffering from PHN underwent autologous fat grafting to a dermal area of neuralgia, with a 12-week follow up. The primary endpoint was patient-reported pain. Secondary endpoints were patient-reported changes in QoL and the degree and quality of the neuropathic pain.

Results:
The pain was measured using a VAS-scale (range 0-10). We observed improvements in both the average and maximum level of pain with a reduction of (- 4.0 ± 3.1) and (- 5.1 ± 3.9), respectively (Δ mean ± SD), P<0.05. All parameters investigating neuropathic pain were significantly reduced. No improvement was seen in the QoL. The average amount of fat grafted was 207.5 ml. We observed no serious adverse effects.
**Conclusion:**

This study suggests that autologous fat grafting can relieve chronic pain resulting from herpes zoster. The next step toward routine clinical translation is to perform a randomised, blinded, placebo-controlled trial with a more extended follow-up period.

**Keywords:** Autologous fat grafting, Post-herpetic neuralgia, Post-herpetic pain, Shingles, Pain, Fat transplant, Adipose-derived stem cells, Pilot Study

**Trial Registration:** This pilot trial is registered at ClinicalTrials.org # NCT03584061 and is registered, and approved by the Regional Ethics Committee, Region of Southern Denmark # S-20180007.

**Funding:** This study received no funding.

This study was reported using the CONSORT GUIDELINES, with an added extension for pilot and feasibility trials.
Introduction:

Postherpetic neuralgia (PHN) is a neuropathic pain syndrome occurring after an outbreak of herpes zoster (HZ), also known as shingles. HZ is a distinctive clinical condition caused by the reactivation of latent varicella-zoster (chickenpox) virus following initial infection. It causes a painful unilateral vesicular eruption of blisters in the skin, which usually occurs within a limited dermatomal distribution\(^1\). Pain is the predominant symptom of all phases of the disease and has been reported up to 90% of patients\(^2\). The majority of patients describe three types of pain; a constant deep, aching or burning pain, a paroxysmal, lancinating pain, and allodynia\(^3\). When the pain persists for more than three months after the resolution of the rash, the condition is called PHN\(^4\).

One in four people will suffer from HZ in their lifetime. The risk is markedly increased after the age of 50 years, with an incidence of almost 50% in elderly individuals. The risk of developing PHN after an outbreak of HZ is reported being between 5 to 30% and the prevalence will likely increase in the future as the population ages\(^5\). The resolve of the disease is slow and the pain has been reported to last up to 10 years after an outbreak, and affecting Quality of Life (QoL) negatively\(^5\)–\(^8\).

Studies of the pathophysiology of PHN have demonstrated extensive damage to both the peripheral and central nervous system\(^9\). The damage consists of both axonal demyelination and neuronal cell death leading to deafferentation and fibrosis\(^10\). Neuroinflammation is also induced, a process that usually promotes regeneration and healing. If the neuroinflammation is not resolved, it may result in chronic pain\(^11\)–\(^12\). The direct damage and neuroinflammation lower the threshold for action potentials, causing the nerves to fire painful signals, even by non-painful stimuli\(^13\). Skin biopsies from patients affected by HZ and PHN have also detected lower numbers of free epidermal nerve endings\(^14\).
Treatment of PHN is complex, and the neuropathic pain is exceptionally drug-resistant\(^3\). There is currently no internationally accepted guideline for treating PHN, although several treatment recommendations have been published\(^{15-17}\). However, the management of neuropathic pain remains challenging because the response to most drugs remains unpredictable\(^{18}\).

One approach to treating PHN could be autologous fat grafting, where fat is harvested from one part of the body and injected into the area to be treated. In most individuals, fat tissue is abundant and easily accessible by liposuction. Autologous fat grafting has proven to be a safe procedure when used for cosmetic purposes\(^{19}\). Autologous fat grafting has shown promise in treating other kinds of neuropathic pains, such as scar related pain and pain following breast surgery\(^{20-22}\).

The exact mechanism of action of fat grafting in alleviation of pain is not known. The current leading theory is that the effects are caused by the content of adipose-derived stem cells (ADSC), growth factors and anti-inflammatory molecules in the injected fat\(^{23}\). In studies on mice, ADSC has demonstrated the ability to revert established neuropathic hypersensitivity, blunting of neuroinflammation and restoration and skin innervation\(^{25}\). It is, therefore, believed that the potential of fat grafting for reducing pain is substantial. Currently, there is only an empirically background in literature that fat grafting may have the potential to alleviate pain associated with PHN. Literature does not provide an explanation to the exact mechanism of action at a biological level of how fat grafting would reduce pain, nor which molecules/GFs or how a stem cell could possible modulate pain.

Fat grafting has not been used previously to treat PHN. The results of our first patient in this trial were published as a case-report earlier this year\(^{26}\). The hypothesis is that fat grafting is feasible and safe when used to alleviate pain following PHN. The proposed mechanism is that the content of ADSC, growth factors and anti-inflammatory molecules
could revert hypersensitivity, reduce neuroinflammation and restore the skin innervation. We expect to find an alleviation of the main outcome pain compared to baseline values following fat grafting patients with PHN. The aim of this pilot trial was to investigate the feasibility, safety, and efficacy of autologous fat grafting as treatment of post-herpetic neuralgia.

Methods:

This study was reported using the CONSORT GUIDELINES, with an added extension for pilot and feasibility trials.27,28

Study design and eligibility criteria

We conducted a prospective, open-label, single-arm and single-centre feasibility and safety study investigating autologous fat grafting for the treatment of PHN. We recruited patients from referrals to our department or via our hospital's website where information on ongoing projects can be found. We planned to enrol ten patients suffering from PHN. All procedures were performed at the Department of Plastic Surgery, Odense University Hospital.

The eligibility criteria were as follows: age over 18 years, more than three months since the resolution of the shingles rash, chronic pain in the dermal area of the previous outbreak of herpes zoster, pain present at minimum four days a week with an intensity of >3 on a visual analogue scale (range 0 to 10), written informed consent and the ability to understand the Danish language. The exclusion criteria were as follows: a psychiatric illness that could affect participation in the project.
Interventions:

All included patients were treated with autologous fat grafting to the dermal area with chronic pain, hereafter referred to as the area of interest (AOI). All procedures were performed by the same plastic surgeon (the senior author of this paper). Prior to surgery, the area of pain was marked by the surgeon guided by the patient (Photo 1). The area of liposuction was the abdomen or the thigh. All procedures were performed under general anaesthesia. A ringer-adrenalin solution was installed at the donor site (Ringer/lactate + 1 mg Adrenaline). Liposuction was performed using body-jet (Human med AG, Schwerin, Germany, http://www.humanmed.com).

The harvested fat was then sedimented for ten minutes and was then decanted. The decanted fat was transferred to 10 mL Luer-lock syringes and injected evenly in thin layers into the AOI using an injection cannula. The total amount of injected fat was dependent on the size of the marked area. The incisions were sutured using a Monocryl 4-0 suture.

Outcomes:

All patients reported outcomes were collected using questionnaires. The questionnaires were filled out by patients at baseline, before to surgery and at follow up, three months after surgery. The primary outcome measure was the level of pain, as perceived by the patient within the AOI, assessed using a visual analogue scale (range 0-10). We asked the patient to report on their maximum and average level of pain during the last two weeks. Our secondary outcome measures were QoL, measured using the Short-Form 36 (SF-36) and the quality of neuropathic pain, measured using the Neuropathic Pain Inventory Scale (NPSI)\textsuperscript{29–31}. The SF-36 reported on eight parameters; general health, pain, social functioning, emotional well-being, energy/fatigue, role limitations due to emotional problems, role limitations due to
physical health and physical function. The NPSI investigated the quality and degree of neuropathic pain following treatment. It measures neuropathic pain on five parameters; superficial spontaneous pain (burning pain), deep spontaneous pain (pressing pain), paroxysmal pain, evoked pain and paresthesia/dysesthesia. The SF-36 and the NPSI have both been validated in Danish.

Sample size and statistical methods

This study was a hypothesis generating feasibility study and we planned to use the collected data to calculate a preliminary sample size for a randomized controlled trial. We chose to include a total of ten patients in this trial. Data were analyzed using SPSS version 25. All variables were analyzed using the paired sample t-tests.

Results

We assessed and found ten patients eligible for inclusion in our study. There were no exclusions. Inclusion began in May 2018, and we performed the treatments between June 2018 and February 2019. The ten patients had a mean age of 76 (range 53-94 years), all suffered from PHN with a mean duration of 47 months (range 5 - 139 months). The mean BMI was 24 kg/m² (range 20-30). See Supplemental Table S1 for additional baseline data.

The mean amount of harvested fat was 297 ml (range 120 - 400 ml). Seven patients had fat harvested solely from the abdomen, while the remaining three had fat harvested from both the abdomen and the thighs. The mean amount of fat injected was 208 ml (range 100 - 300 ml). The characteristics of the procedures can be seen in supplemental Table S2.
The full table of the patient-reported outcome measures can be found in table 1. The assessment of the pain of the AOI was measured at baseline and at 12-weeks. Measured on a VAS-scale ranging from 0-10, a statistically significant reduction in the average level of pain of four points was observed, falling from $7.0 \pm 1.6$ at baseline to $3.0 \pm 3.0$ at follow-up ($\text{mean } \pm \text{ SD})(P <0.05)$. In the same period, a reduction of five points in the maximum level of pain, from $8.6 \pm 1.3$ to $3.5 \pm 3.1$, $P<0.05$ was observed (Fig. 1). Five patients reported little or no pain after the procedure with their VAS ranging from 0-2. Three patients reported an effect but were not pain-free. Two patients did not experience an effect of the procedure, with one of the two reporting a slight increase in pain.

All of the parameters measured using the NPSI were statistically significantly reduced from baseline to the 12-week follow-up, $P<0.05$. The NPSI uses a scale ranging from 0-10. The reported average degree of pain was high on all NPSI-parameters with an average ranging from 5.8 - 7.2. At 12-weeks, the average pain was significantly lower with a range of 1.8 - 3.0 (Fig. 2).

None of the eight QoL-parameters measured by the SF-36 were found to be statistically significantly affected by the intervention (Fig. 3).

All results of the individual patients can be found in supplemental pain S3.

<table>
<thead>
<tr>
<th>Table 1 - Table of results</th>
<th>Baseline mean±SD</th>
<th>12-weeks follow up mean±SD</th>
<th>Change mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain (VAS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average pain</td>
<td>7.0 ± 1.6</td>
<td>3.0 ± 3.0</td>
<td>4.0 ± 3.1</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Maximum pain</td>
<td>8.6 ± 1.3</td>
<td>3.5 ± 3.1</td>
<td>5.1 ± 3.9</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td><strong>Quality of Life (SF-36)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>63.0 ± 23.2</td>
<td>45.5 ± 27.3</td>
<td>17.5 ± 27.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Pain</td>
<td>38.8 ± 28.4</td>
<td>49.8 ± 26.4</td>
<td>-11.0 ± 39.7</td>
<td>0.40</td>
</tr>
<tr>
<td>Social functioning</td>
<td>53.3 ± 32.9</td>
<td>59.5 ± 32.6</td>
<td>-6.2 ± 40.6</td>
<td>0.64</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>55.1 ± 23.2</td>
<td>55.3 ± 23.6</td>
<td>-0.2 ± 19.6</td>
<td>0.97</td>
</tr>
</tbody>
</table>
Figure 1. The graph illustrates the results from the VAS-questionnaire investigation the degree of average and maximum pain on a scale ranging from 0-10. The black lines are the
associated standard deviation

Figure 2: The graph illustrates the results from the NPSI-questionnaire investigating the degree and quality of neuropathic pain. The black lines are the associated standard deviation.

Figure 3. The graph illustrates the results from the SF-36 questionnaire investigation QoL.
Harms

Approximately half of the patients reported some soreness after the procedure, mainly from the area of liposuction. This soreness resolved within a week. No unexpected or serious adverse effects were seen.

Discussion:

Fat grafting resulted in a significant reduction in the level of pain in all pain-related parameters investigated.

The exact mechanism of action of autologous fat grafting on alleviating neuropathic pain is not known. The current leading theory is that the effects are caused by the content of ADSC, growth factors and anti-inflammatory molecules in the injected fat\textsuperscript{23}. The use of ADSC has proven to have a pain-relieving effect in people affected by neuropathic trigeminal pain\textsuperscript{33}. In in vitro studies, ADSC has shown the ability to secrete several different growth factors, with the potential of repairing damaged nerves\textsuperscript{34}. Sub-dermal fat grafting has shown to have an anti-inflammatory effect in both the dermal area of fat grafting and in the spinal cord in a mouse model by Huang et al\textsuperscript{35}. This may explain why a single sub-dermal autologous fat injection could treat a disease with nerve damage in other areas of the body. The study by Huang et al. also detected a reduction in the level of neuropathic pain using fat grafting\textsuperscript{35}. It is possible that the fat acts as a filler that cushions the area and thereby decreases the level of pain in the area. As the amount of fat injected in this study is small, we find the cushion-theory to be unlikely. However, we cannot exclude that there is a micro-cushioning effect present.
No study has previously investigated the effect of autologous fat grafting on PHN. Our study population was relatively small, with ten patients included. Despite this, our results, regarding the degree of pain, indicate that fat grafting may be a treatment modality for PHN. Five out of ten patients reported their pain being very low, ranging from 0-2 on a VAS scale, after just a single treatment. Three additional patients had a partial effect, and only two reported no effect. One patient reported an increase in the level of pain when looking at the VAS-questionnaire. When interviewed about this, the patient stated that the pain-level he experienced was the same before and after the procedure.

We have only performed a single treatment of fat grafting on the included patients. Further studies will show if there is an additive effect of multiple treatments.

The study was designed as an open-label, single-arm study, and there is, therefore, a risk of a placebo effect. The included patients consisted of chronic pain patients that had a history of trying several different medical treatment regimens. This may have influenced their perception of the treatment effect and is a possible confounder of this study. However, as they have not experienced an effect of previous treatments, the improvement seen is likely to be caused by the treatment with fat grafting.

No effect was detected in the measured QoL-parameters. The treatment effect regarding pain was quite convincing when assessed by the NPSI-scale, and we had expected to see an improvement in the QoL. The SF-36 is a standardized QoL-questionnaire and does not specify type or area of pain. The lack of effect seen can be caused by the patients having other types of pain or pain in another area. This is a possible confounder of our study.

The small sample size and relatively short follow-up is a limitation of our study. Larger prospective randomised trials with longer follow-up periods are needed to validate these promising results.
Fat grafting is a relatively inexpensive treatment. When the liposuction equipment has been acquired, the cost of each individual treatment is low. Although no cost-benefit analysis has been performed, we would argue that a single treatment of fat grafting is preferable compared to a lifetime of medications with doubtful effect.

Regarding the amount of fat for injection, relative to the area of pain, we did not measure the exact size of the area of pain. We are therefore not able to stratify and conclude on the amount of fat needed to obtain an effect. The amount of injected fat was decided by the surgeon in each individual case. This was based on an estimation of the size of the AOI. All patients received a small amount of fat evenly distributed to the AOI, and at follow-up, there were no visible remnants of the fat injection in the skin. We aimed to inject the same amount of fat per AOI in correlation to its size. In future studies, we aim to inject a specific volume of fat per volume of tissue/AOI.

In conclusion, results from this study suggest that autologous fat grafting is a safe procedure with the potential for relieving chronic pain resulting from herpes zoster. The nature of the procedure is appealing as it utilizes autologous tissue that can be obtained in large quantities with minimal discomfort, using a safe and minimally invasive surgical procedure. The next step toward routine clinical translation is to perform a randomized, blinded, placebo-controlled trial including an internal pilot study for sample-size calculation with a longer follow-up period.

Other information:

Conflict of interest statement: None
Registration: This pilot trial is registered at clinicaltrials.org. (ClinicalTrials.gov Identifier: NCT03584061)

Funding: None

Ethical approval: This pilot trial was approved by the Regional Ethics Committee, Region of Southern Denmark # S-20180007.

References


### Supplemental Table 1S

<table>
<thead>
<tr>
<th>Pt ID</th>
<th>Age</th>
<th>BMI</th>
<th>Time since outbreak VZV (months)</th>
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<td>1</td>
<td>60</td>
<td>22,2</td>
<td>36</td>
<td>Breast + back - Right side</td>
</tr>
<tr>
<td>2</td>
<td>83</td>
<td>22,8</td>
<td>60</td>
<td>Arm + shoulder - Left side</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>29,9</td>
<td>7</td>
<td>Arm + shoulder - Left side</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>27,1</td>
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</tr>
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<td>53</td>
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</tr>
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<td>Thorax - Left side</td>
</tr>
<tr>
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<td>23,3</td>
<td>56</td>
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<tr>
<td>8</td>
<td>68</td>
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<td>13</td>
<td>Back - Right side</td>
</tr>
<tr>
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<td>Abdomen - Left side</td>
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<td>71</td>
<td>23,5</td>
<td>25</td>
<td>Thorax - Left side</td>
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</table>

*Table 1S. Overview of baseline characteristics of included patients. BMI = Body mass index.*

### Supplemental Table S2

<table>
<thead>
<tr>
<th>Pt ID</th>
<th>Donor Site:</th>
<th>Amount of harvested fat</th>
<th>Amount of injected fat (ml)</th>
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<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>300</td>
<td>270</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
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<tr>
<td>4</td>
<td>A</td>
<td>300</td>
<td>260</td>
</tr>
<tr>
<td>5</td>
<td>A + T</td>
<td>190</td>
<td>150</td>
</tr>
<tr>
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<td>115</td>
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<td>A + T</td>
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<tr>
<td>10</td>
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*Table 2S. Overview over procedure characteristics. Donor site A = Abdomen, T = Thighs.*

### Supplemental Table S3

<table>
<thead>
<tr>
<th>Visual Analogue Scale</th>
<th>Neuropathic Pain Symptom Inventory</th>
</tr>
</thead>
</table>

*Table S3. Visual Analogue Scale and Neuropathic Pain Symptom Inventory.*
Supplemental table S3. The results of the patient reported outcome measures on patient-level. NPSI: Neuropathic Pain Symptom Inventory, VAS: Visual Analogue Scale. Columns display results at baseline and at 12 weeks postoperatively respectively.