Venous interventions in venous treatment and recurrence avoidance an overview

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Introduction

Common, distressing and expensive

Most patients with venous ulcers have superficial reflux
Introduction

No difference in ulcer healing

Surgery reduces venous ulcer recurrence
Impact of ESCHAR

The number of superficial venous procedures has decreased since 2008
Interpretation of ESCHAR: “Patients with open ulcers do not benefit from treatment of superficial reflux”

No difference in ulcer healing.
A quarter of procedures were SFJ or SPJ ligation alone (local anaesthesia)

20% of patients randomised to surgery, refused an operation

The study was not powered to assess ulcer healing (C5/C6 & mean time to treatment 7 weeks)
Venous interventions 2014

THERMAL

NON-THERMAL
Venous interventions 2014

Chronic Venous Ulcer: Minimally invasive treatment of superficial axial and vein reflux speeds healing and recurrence

Healing and recurrence rates following ultrasound-guided foam sclerotherapy for superficial venous reflux in patients with chronic venous ulceration

Effect of foam sclerotherapy on healing and long-term recurrence in chronic venous leg ulcers

Keywords:
- Foam sclerotherapy
- Chronic venous ulcer
- Healing rate
- Recurrence rate

Introduction:
The ESCVAR trial showed that ultrasound-guided foam sclerotherapy in chronic venous ulceration achieved a 24-week healing rate of 65% and 23-month recurrence rate of 12%. Foam sclerotherapy is an alternative to surgery. The aim of this study is to assess the effect of foam sclerotherapy in ulcer recurrence and healing in chronic venous leg ulcers.

Methods:
Blind randomization to ultrasound-guided foam sclerotherapy and compression (Group A) or surgery alone (Group B). The primary outcome was ulcer recurrence at 24 weeks. The secondary outcome was healing at 24 weeks.

Results:
Two hundred and twenty patients with chronic venous leg ulcers (160 Group A and 60 Group B) were treated with foam sclerotherapy. Complete occlusion was achieved in 185/220 (83.6%) limbs, short segment occlusion in 14/20 (70%) limbs and one leg segment failed to occlude. One patient suffered an asymptomatic occult deep vein thrombosis (DVT) diagnosed on duplex scan at 24 weeks, and another presented with an occult DVT three weeks following a normal scan at 24 weeks. One patient developed an asymptomatic occult DVT at 30 weeks following a normal occult DVT diagnosis on initial ultrasound scan. Eighty patients were lost to follow-up (37 from Group A and 43 from Group B) at 24 weeks. Healing was achieved in 71.3% and one leg and four-year recurrence rates were calculated using Kaplan-Meier survival analysis.

Conclusion:
Foam sclerotherapy is an effective alternative to surgery in this group of patients.

Keywords:
- Foam sclerotherapy
- Venous ulceration
- Healing rate
- Recurrence rate

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Keywords:
- Foam sclerotherapy
- Chronic venous ulceration
- Healing rate
- Recurrence rate
Early Venous Reflux Ablation study

450 PATIENTS
Venous ulceration <6 months
Superficial reflux
Early Venous Reflux Ablation study

450 PATIENTS
Venous ulceration <6 months
Superficial reflux

Compression

Compression + EVRA (<2 weeks)

Primary outcome: time to ulcer healing
Current Management

**BUT...**

- Not all patients are candidates
- Compliance issues
- Ulcers refractory to compression therapy
Aim

Is there a clinical benefit for using pharmacological agents as an adjunctive treatment for chronic venous ulcers?
Pentoxifylline

- Xanthine derivative
- Actual mechanism not fully understood although it has microcirculatory effects
  - Reduce platelet aggregation and leukocyte activation
  - Increase tissue oxygenation
  - Reduce blood viscosity

Gohel MS and Davies AH Phlebology 2010
Pentoxifylline

Cochrane Review 2012
- 12 RCTs (864 patients).
- Pentoxifylline is more effective than placebo in terms of complete ulcer healing or significant improvement.
- Pentoxifylline + compression is better than placebo + compression (RR 1.56, 95% CI 1.14 to 2.13).
- Pentoxifylline with NO compression is better than placebo or no treatment (RR 2.25, 95% CI 1.49 to 3.39).

Pentoxifylline

Economic modelling:
- a mean cost saving of GBP 98.09 (about USD 152) (95%CI - 49.21 to 245.00) per QALY gained if pentoxifylline was used (Iglesias 2006)

- Appears to be COST-EFFECTIVE

Aspirin

- n = 51; single institution RCT
- Aspirin 300 mg + compression therapy *versus* compression therapy alone
- 46% reduction in healing time in Aspirin group (12 weeks vs 22 weeks)
- BUT lack of placebo and information regarding blinding

Aspirin

Poor healing outcomes may be due to systemic inflammation

Impact of aspirin on VLU healing

Layton et al. Randomised trial of oral aspirin for chronic venous leg ulcers.
The Lancet 1994

del Río Solá et al. Influence of Aspirin Therapy in the Ulcer Associated With Chronic Venous Insufficiency.

Aspirin

ASPirin in Venous Leg Ulcer study

Clinical effectiveness of aspirin as an adjunct to 3-Layer compression therapy in healing chronic venous leg ulcers: a randomised double-blinded placebo-controlled trial [the ASPiVLU study]

Mesoglycan

- A sulphate polysaccharide extracted from porcine intestinal mucosa
- Composed of variable quantities of heparan sulphate, dermatan sulphate, electrophoretically slow-moving heparin and chondroitin sulphate
- Properties include reduce capillary permeability and inhibit neutrophil adhesion and activation
Mesoglycan

- Placebo controlled, double blind RCT; n = 183 (92 mesoglycan; 91 placebo)

- Mesoglycan 30 mg/day IM for 3 weeks followed by 100 mg/day PO + compression therapy versus placebo + compression therapy

- Estimated time to heal 75% patients in the mesoglycan group was 90 days compared to 136 days in the placebo group

Prostaglandin (PGE-1)

PROPOSED MECHANISMS OF ACTION

• reduction of the adhesiveness and platelet aggregation
• inhibition of the proliferation of the smooth muscle cells
• reduction of the haematic viscosity
• profibrinolytic effect
• inhibition of the chemiotaxis and the activation of white cells
• restoration of the equilibrium between the microvascular flow
  regulating system and the microvascular defense system, with a
• reduction of the endothelial permeability and inhibition of the
• vasoconstrictive activity of thromboxane A2, serotonin,
• leukotrienes, and endothelin
• stimulation of formation and growth of collateral circulation
Prostaglandin (PGE-1)

<table>
<thead>
<tr>
<th>M</th>
<th>20 days (%)</th>
<th>40 days (%)</th>
<th>60 days (%)</th>
<th>80 days (%)</th>
<th>100 days (%)</th>
<th>120 days (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGE-1 group</td>
<td>9 (22.5)</td>
<td>7 (42.5)</td>
<td>27 (67.5)</td>
<td>34 (85)</td>
<td>40 (100)</td>
<td>40/40 (100)</td>
</tr>
<tr>
<td>Placebo group</td>
<td>1 (2.6)</td>
<td>5 (13.1)</td>
<td>14 (36.8)</td>
<td>19 (50)</td>
<td>25 (65.8)</td>
<td>32/38 (84.2)</td>
</tr>
</tbody>
</table>

PGE-1, Prostaglandin E-1.
*Percentage of healed ulcers over all ulcers for each group.

◆ n=87

◆ PGE-1 treated group, 100% of ulcers had healed in ≤100 days whereas in the placebo group 84% of ulcers had healed (p<0.05).

Flavonoids

- Flavonoids are a diverse group of naturally-occurring venotonic compounds that address certain microcirculatory parameters involved in venous leg ulcer pathophysiology.

- Examples: micronised purified flavonoids fraction (MPFF) and hydroxyethylrutosides.
**Flavonoids**

**Cochrane Review 2013**

**MPFF**

- 5 RCTs (723 patients)

- With respect to number of ulcers completely healed - statistically significant effect in favour of MPFF (RR 1.36; 95% CI 1.07 to 1.74)

- ALTHOUGH the most rigorously conducted study (unpublished commercial trial) – NO ADDITIONAL BENEFIT with MPFF
Flavonoids

Cochrane Review 2013

_Hydroxyethylrutosides_

- 3 RCTs

- Ulcers completely healed - in favour of hydroxyethylrutosides (RR 1.70; 95% CI 1.24 to 2.34)

Flavonoids

Cochrane Review 2013

*Hydroxyethylrutosides*

- 3 RCTs

- Ulcers completely healed - in favour of hydroxyethylrutosides (RR 1.70; 95% CI 1.24 to 2.34)

Although the analysis overall in favour of flavonoids, all of the studies were poorly reported and had unclear risk of bias.

Sulodexide

• Antithrombotic and anti-fibrinolytic properties by factor Xa and thrombin inhibition

Sulodexide Arterial Venous Italian Study (SUAVIS)
• RCT: n = 230; Sulodexide versus Placebo
• Healing rate:
  – 2-month healing rate: 35% (sulodexide) vs 21% (placebo); p<0.018
  – 3-month healing rate: 52.5% (sulodexide) vs 32.7% (placebo); p<0.004

Sulodexide

• Pooled results have shown that Sulodexide may not have beneficial effects as an adjunct to ulcer healing in addition to conventional therapy (RR 0.16 95% CI 0.06 to 0.26)

Simvastatin as a novel therapeutic agent for venous ulcers: a randomized, double-blind, placebo-controlled trial

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Sample size

The sample size was computed using a two-sample comparison of means based on a previous study of 30 patients given 40 mg daily of simvastatin.\textsuperscript{32} In accordance with the results of this study, the SD was estimated as 8·6. Using a two-sided $\alpha$ of 0·05 and a power of 0·8, our calculations indicated that 29 patients were needed in each study arm. We aimed to recruit 64 patients to allow for a 10% dropout rate.

<table>
<thead>
<tr>
<th>Table 2 Total proportion of patients with complete healing and time to healing in both groups (available case analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total proportion healed, n (%)</td>
</tr>
<tr>
<td>Time to healing (weeks), mean ± SD</td>
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</table>
Conclusion

Pentoxifylline is the only treatment shown to significantly advance the rate of ulcer healing with a favourable cost-effective profile.

Statin possible benefit

Aspirin has shown early promise in a small randomised study and large confirmatory studies are awaited.
That's all Folks!
# Side Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Main side effects</th>
<th>Side effect incidence</th>
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</thead>
<tbody>
<tr>
<td>Pentoxifylline</td>
<td>Gastrointestinal disturbance&lt;sup&gt;22&lt;/sup&gt;</td>
<td>72%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Not stated&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Not stated</td>
</tr>
<tr>
<td>Sulodexide</td>
<td>Cutaneous rash, diarrhoea, epigastric pain, itching and headache&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Not stated</td>
</tr>
<tr>
<td>Mesoglycan</td>
<td>Skin rash, headache, pruritis, palpitations, congestive heart failure, orthostatic hypotension, episodes of fainting, superficial thrombophlebitis, bronchopneumonia*&lt;sup&gt;40&lt;/sup&gt;</td>
<td>8%</td>
</tr>
<tr>
<td>Prostaglandins and prostacyclin analogue</td>
<td>Diarrhoea and vomiting (one case), headache (2 cases), hypotension (1 case), and nausea (1 case)&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Total incidence: 11.36% (5/44)</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>Skin changes (including eczema), gastrointestinal disturbances (including diarrhoea) and hypertension&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Not stated</td>
</tr>
<tr>
<td>Thromboxane A2 antagonist (ifetroban)</td>
<td>No side effects reported&lt;sup&gt;53&lt;/sup&gt;</td>
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