Chronic Venous Disease

: Medical Treatments

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Supapong Arworn, MD

Division of Vascular and Endovascular Surgery
Department of Surgery, Chiang Mai University Hospital
Email: supapong.arworn@gmail.com

Vascular Surgery
Chiang Mai University

Venoactive Drugs (VADs)

- Heterogeneous group of products, of plant or synthetic in origin, which have effects on edema and on symptoms related to chronic venous disease.

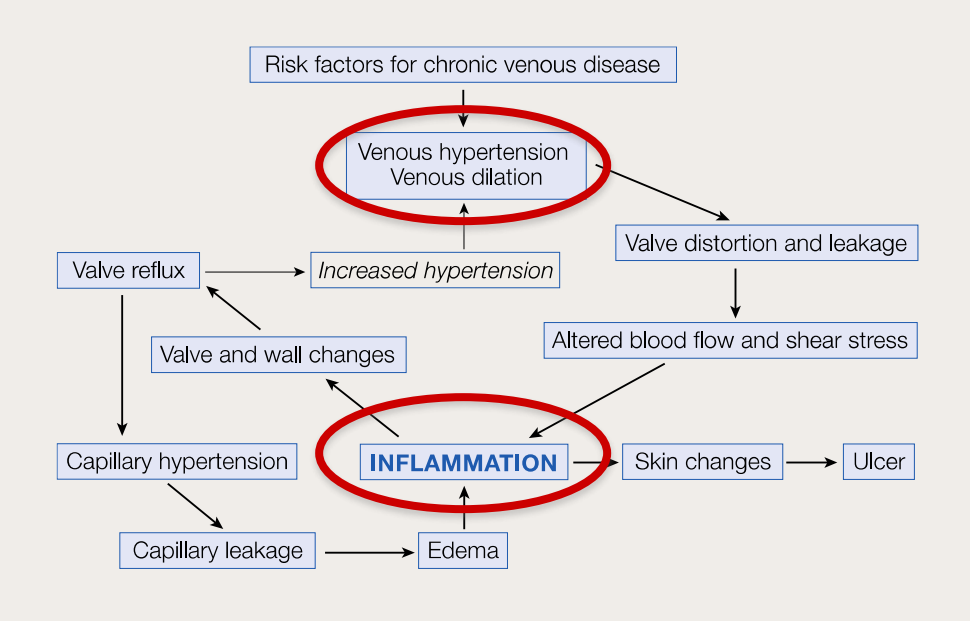
- Many names have been used to describe VAD: edema-protective agents, phlebotonics, venotonics, vasoprotectors, phlebotropics, and venotropics.

SOURCE : clinicalgate.com

Medical Treatment of CVD

Early Rx aimed at preventing VHT and inflammation → alleviate CVD symptoms + reduce the risk of ulcers

Treatment to inhibit inflammation may offer the greatest opportunity to prevent disease –related complications.



N Eng J Med 2006
Medicographia 2011

VADs : Modes of action

Decrease capillary permeability
Diminish release of inflammatory mediators
Improve venous tone

Non- venoactive drugs like pentoxifylline, reduce white cell activation, and acetylsalicylic acid inhibits platelet function and also has an anti-inflammatory effect

Venoactive Drugs (VADs)
: Substance & dosage

Group	Substance	Origin	Dosage (mg)	Number of doses/day
Benzyopyrones				
Alpha-benzopyrones	Coumarin	Melilot *(Melilotus officinalis)* Woodruff *(Asperula odorata)*	90 combined with troxerutin (540)	3
Gamma-benzopyrones (flavonoids)	Diosmin	*Citrus* sp *(Sophora japonica)*	300-600	1 or 2
	Micronized purified flavonoid fraction (MPFF)	*Rutaceae aurantiae*	1000	1 or 2
	Rutin and rutosides	*Sophora japonica*	1000	1 or 2
	0-(β-Hydroxyethyl)-rutosides (troxerutin, HR)	*Eucalyptus* sp *Fagopyrum esculentum*		
Saponins	Escin	Horse chestnut *(Aesculus hippocastanum)*	Initially 120, then 60	3
	Ruscus extract	Butcher's broom *(Ruscus aculeatus)*	2 to 3 tablets	2 to 3
Other plant extracts	Anthocyans	Bilberry *(Vaccinium myrtillus)*	116	2
	Proanthocyanidins	Maritime pine *(Pinus maritimus)*	100 to 300	1 to 3
		Grape pips *(Vitis vinifera)*	300 to 360	3
	Extracts of ginkgo	*Ginkgo biloba*	2 sachets (extracts of ginkgo, heptaminol, and troxerutin)	2
Synthetic products	Calcium dobesilate	Synthetic	1000 to 1500	2 to 3
	Benzarone	Synthetic	400 to 600	2 to 3
	Naftazone	Synthetic	30	1

Medicographia, Vol 33, No. 3, 2011

Venoactive Drugs (VADs) : Modes of action

Category	Drug	Effect on:					
		Venous tone	Venous wall and valve	Capillary leakage	Lymphatic drainage	Haemorheological disorders	Free radical scavengers
Flavonoids (gamma-benzopyrones)	Micronised purified flavonoid fraction	+	+	+	+	+	+
	Nonmicronised or synthetic diosmins*						
	Rutin and rutosides, O-(β-hydroxyethyl)-rutosides (troxerutin, HR)	+		+	+	+	+
	Anthocyans (Vitis vinifera)						+
	Proanthocyanidins (Vitis vinifera)			+			+
Alpha-benzopyrones	Coumarin			+	+		
Saponins	Horse chestnut seed extract; escin	+		+			+
	Ruscus extract	+		+			
Other plant extracts	Gingko extracts*						
Synthetic products	Calcium dobesilate	+		+	+	+	+
	Benzarone*						
	Naftazon*						

International Angiology Vol 33. No. 2. 2014

VADs for C_0-C_4

C1 Telangiectasia

<1mm in caliber

C1 Reticular vein

1-2mm in caliber

Varicose vein C2

Edema C3

Pigmentation C4

- RELIEF study, MPFF study,
- CVD C0s & MPFF study
- Cochrane 2010, ESVS guideline 2015
- International Angiology 2018

RELIEF study

: Reflux assEssment and quaLity of life improvement with micronized Flavonoids

23 countries, Patients = 5000 (Class 0-4)

Objectives - Reflux assessment

- Efficacy of MPFF, Rx duration 6 months

Results

- 57% of patients suffering from CVD (class 0-4) were reflux-free, which means that they were suffering from functional CVI.

- The clinical scores of all symptoms and signs had significantly decreased

Angiology 2002;53:245-56

MPFF study
: Therapeutic efficacy of Daflon

France, Patients = 11342, Female 87%

Objective - Efficacy of MPFF, Rx duration 6 months

Results

- Rx benefit of MPFF was evidence and significant
  - 1st months → 48%
  - 2nd months → 71%
- Reported side-effect 3.3%, GI disturbance

Tribune Medicale 1990;337:41-4

GSV reflux in patients with symptoms related to chronic venous disorders, but without visible signs (C0s), and its correction with MPFF treatment

Prospective study, Patients n = 41

Objectives
- Incidence of C0s
- Reflux study in the patient with C0s
- Efficacy of MPFF

Results

DUS - A total of 26/41 patients had no reflux in the morning, but presented with an evening GSV reflux.

Phlebolymphology 2015

GSV reflux in patients with symptoms related to chronic venous disorders, but without visible signs (C0s), and its correction with MPFF treatment

Prospective, Patients n = 41

Objectives -

-

-

Results

DUS - A total

but presented

Extent of GSV reflux at evening assessment (number of patients)			Type of GSV reflux at evening assessment (number of patients)	
Axial	2		Intervalvular	4
Segmental	Proximal	11	Commissural	22
	Medial	13		
Total		26		26

Phlebolymphology 2015

GSV reflux in patients with symptoms related to chronic venous disorders, but without visible signs (C0s), and its correction with MPFF treatment

Effect of MPFF - 2 months Rx

The evening reflux was eliminated in 22 of the 26 patients.

4 patients who had inter-valvular reflux, the extent of reflux slightly decreased.

Mean GSV diameter in mm (95% confidence interval)	Evening diameter	Difference between evening and morning
At baseline	6.33 (4.50-8.00)	0.82 (0.30-1.20)
At month 2 after MPFF treatment	5.50 (1.10-7.00)	0.37 (0.10-0.70)
P value	0.000008	0.000008

Phlebolymphology 2015

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Effect of MPFF

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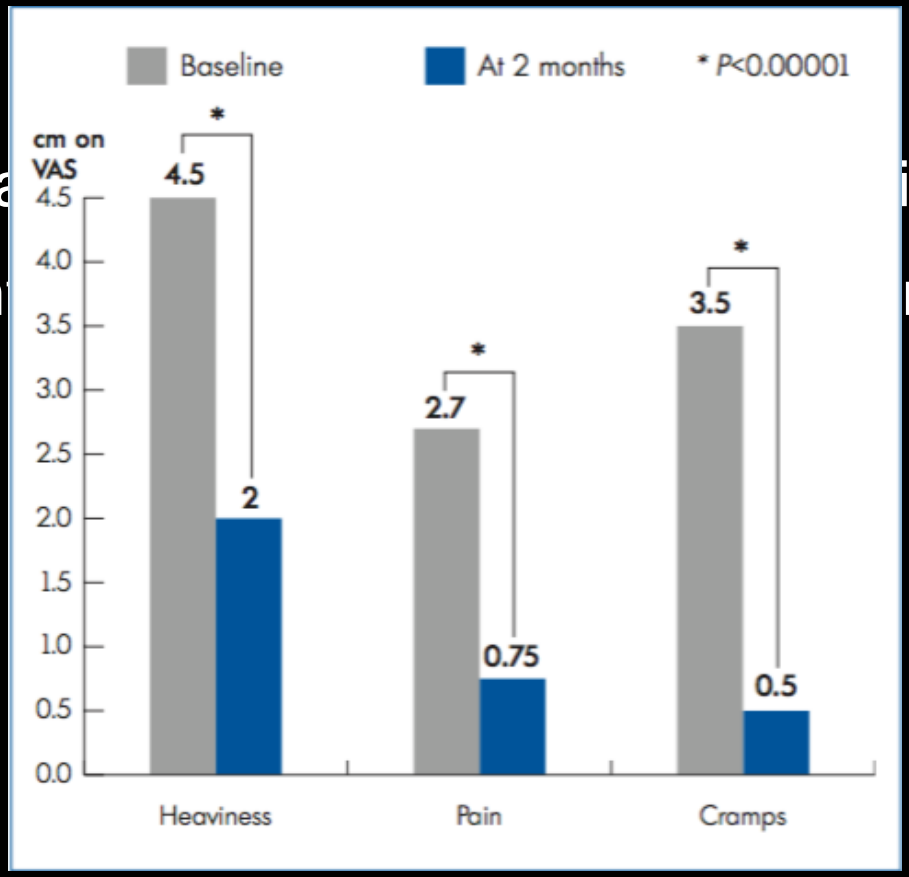


Phlebolymphology 2015

Horse chestnut seed extract for CVD

Generic name - Aescin

Classification – Antioedematous, anti-inflammatory

Pharmacologic actions

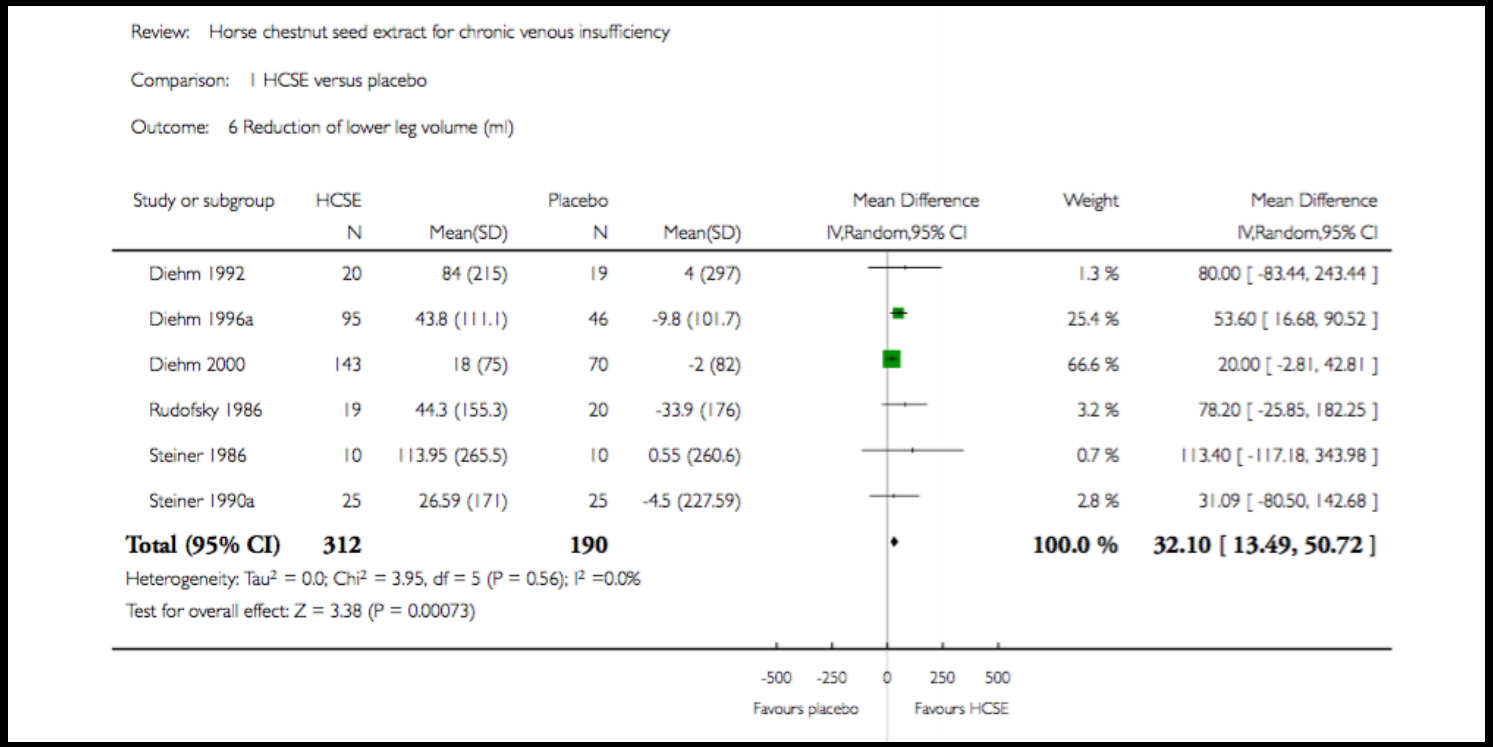
- Decrease capillary permeability
- Antibradykinin

Composition – sugar coat tablet + Aescin 20 mg

Indications
- Rx CVD
- Traumatic swelling
- Rx surgical wound

SOURCE: Madaus

Horse chestnut seed extract for CVD



Comparison HCSE versus placebo - Reduction of lower leg volume.
Study = 6 (yr1986-2000) patient = 312

SOURCE: Cochrance 2010

Editor's Choice — Management of Chronic Venous Disease

Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)

Recommendation 34

VADs should be considered as a treatment option for swelling and pain caused by chronic venous disease

Cochrane review 2005 (44 studies) - There was insufficient evidence to support the use of all VADs in the treatment of CVD. MPFF was the most effective at reducing symptoms of oedema and restless legs.

Eur J Vasc Endovasc Surg 2015

Levels of evidence for the effect of each VAD on individual symptoms/signs/QoL

Symptom/sign	MPFF	Ruscus	Oxerutins	HCSE	Calcium dobesilate
Pain (NNT) SMD	A (4,2) -0,25	A (5) -0,80	B -1,07	A (5,1)	B (1,4)
Heaviness (NNT) SMD	A (2,9) -0,80	A (2,4) -1,23	B (17) -1,00		A (1)
Feeling of swelling (NNT) SMD	A (3,1) -0,99	A (4) -2,27			
Functional discomfort (NNT) SMD	A (3,0) -0,87				B (4)
Leg fatigue (NNT) SMD	NS	B -1,16			
Cramps (NNT) SMD	B (4,8) -0,46	B/C	B -1,7		
Paresthesiae (NNT) SMD	B/C (3,5) -0,11	A (1,8) -0,86			B (2)
Burning (NNT) SMD	B/C -0,46	NS			
Pruritus/itching (NNT)		B/C	A(6,1)		
Tightness (NNT)	NS				
Restless legs (NNT)	NS				
Leg redness (NNT) SMD	B (3,6) -0,32				
Skin changes (NNT)	A (1,6)				
Ankle circumference (NNT) SMD	B -0,59	A -0,74	NS	A (4)	
Foot or leg volume SMD	NS	A -0,61	NS	A -0,34	A -11,4
Quality of life SMD	A -0,21				NS

International Angiology 2018

Recommendations based on magnitude of effect on venous symptoms

	MPFF	Ruscus	Oxerutins	HCSE
Pain	Strong	Strong	Strong	Strong
Heaviness	Strong	Strong	Strong	-
Feeling of swelling	Strong	Strong	-	-
Functional discomfort	Strong	-	-	-
Cramps	Strong	Weak	Strong	-
Leg redness	Strong	-	-	-
Skin changes	Strong	-	-	-
Edema	Strong	Strong	Weak	Strong
Quality of life	Strong	-	-	-
Paresthesiae	Weak	Strong	-	-
Burning	Weak	-	-	-
Leg fatigue	-	Strong	-	-
Pruritus	-	Weak	-	Strong

International Angiology 2018

VADs for Venous leg Ulcers

Healed ulcer C5

Active ulcer C6

- Therapeutic efficacy of MPFF in C6
- Sulodexide study
- ESVS guideline 2015 & International Angiology 2018

MPFF study
: Therapeutic efficacy in ulcer healing (CVI)

Study = RCT

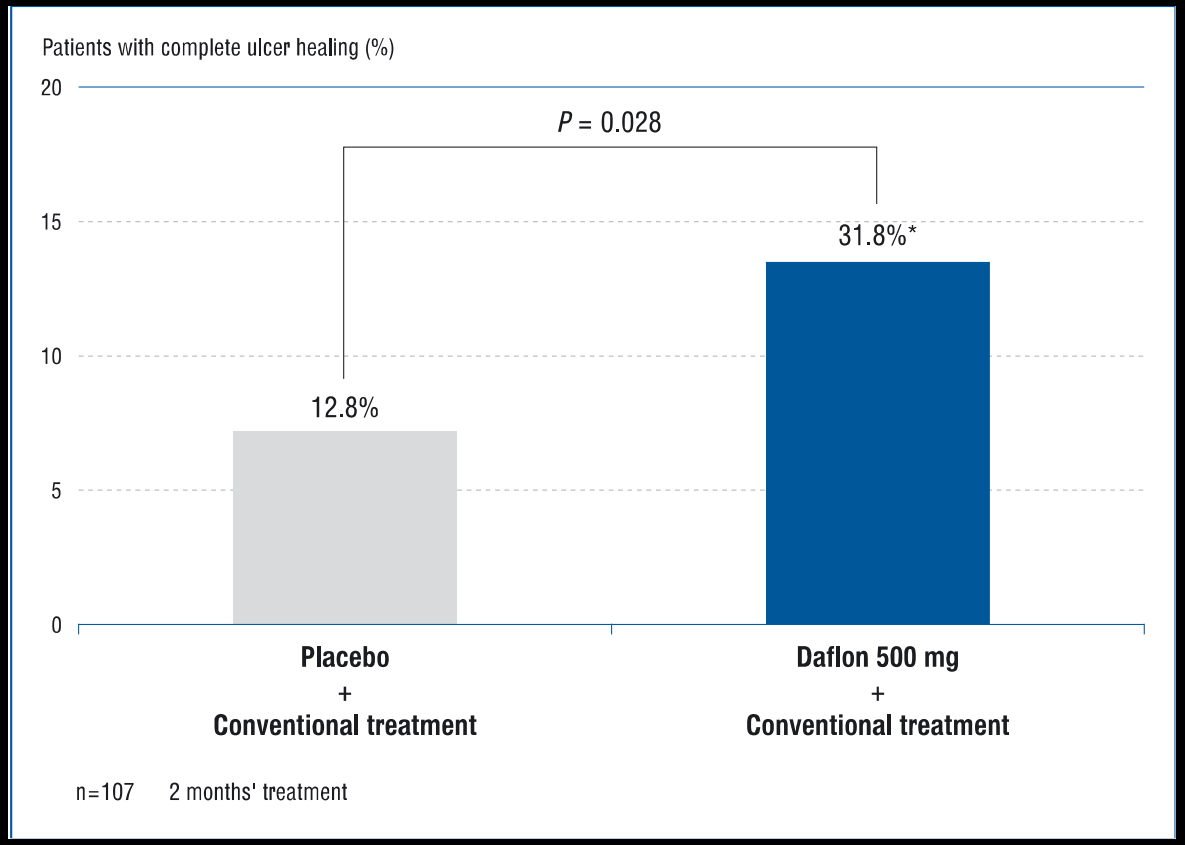
N = 107

Rx duration =2 month

Result

Complete healing of ulcers <10 cm was statistically higher in the MPFF group

– **32% vs 13%**



Phlebolymphology Vol 14. No. 2. 2007

MPFF study
: Therapeutic efficacy in ulcer healing (CVI)

Study = RCT

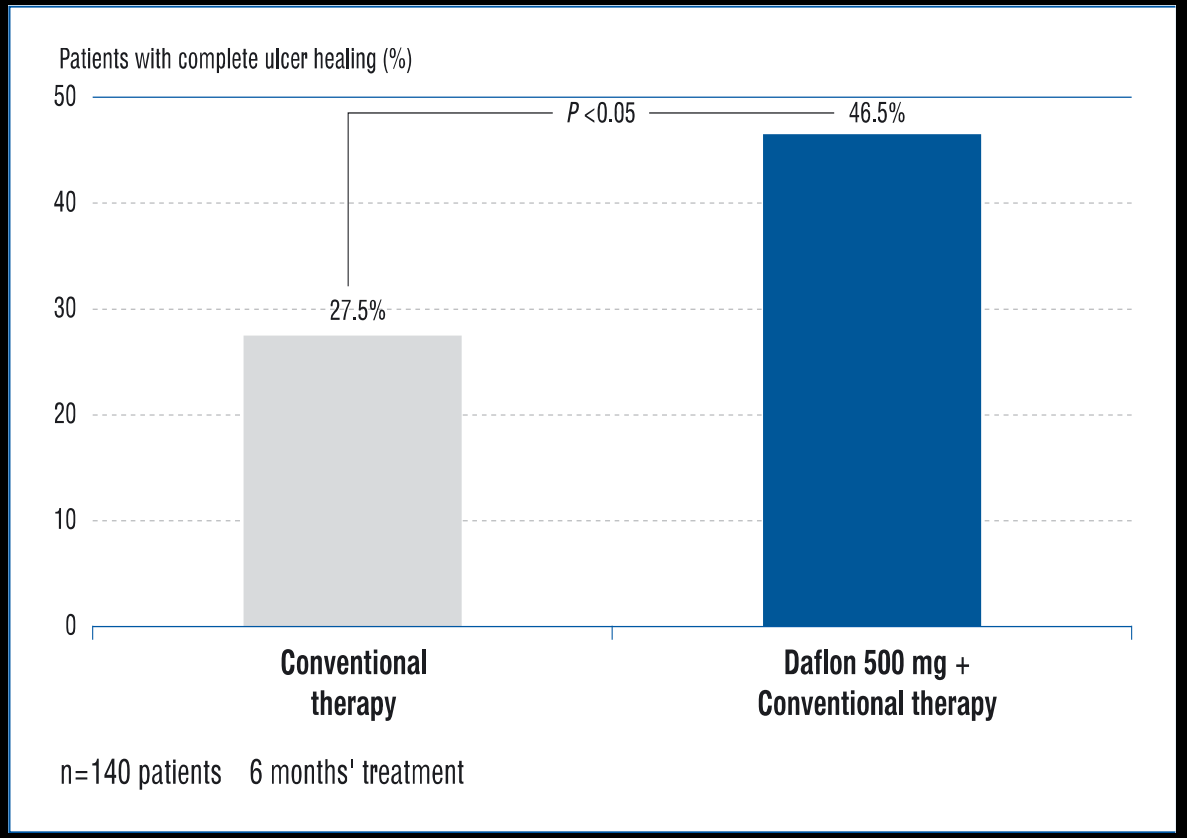
N = 140

Rx duration =6 month

Result

Complete healing of ulcers <10 cm was statistically higher in the MPFF group

47% vs 28%



Phlebolymphology Vol 14. No. 2. 2007

MPFF for treating venous leg ulcers.

Meta-analysis (5 RCT, 1996-2001), Patients n = 723

Objectives - Efficacy of MPFF

Rx duration = 6 months

Results

At 6 months, the chance of ulcer healing was 32% better in MPFF group and shorter time to healing, 16 vs 21 weeks.

The benefit of MPFF was found in the subgroup of ulcers between 5-10 cm^2, and in patients with ulcers of 6-12 month's duration

Angiology 2005

Sulodexide

Composition – Glycosaminoglycan
(obtain from porcine digestive mucosa)

Pharmacologic actions

- Decrease blood viscosity
- Antithrombotic effect → Rx microthrombosis
  Release of Tissue Factor Pathway Inhibitor (TFPI)
- Inhibit interleukin & MMP-9 → Rx inflammation

Int Angiology 2014

Randomised, double blind, placebo controlled study of Sulodexide in treatment of venous leg ulcers.

Prospective study, Patients n = 235

Objectives - Efficacy of Sulodexide vs placebo

Rx duration = 3 months

Results

2 months – Healing of ulcers was higher in the Sulodexide group **35% vs 20%** 3 months – **52% vs 33%**

In conclusion – Sulodexide associated with local treatment proved to be effective and well tolerate in the management of venous leg ulcers.

Thromb Haemost 2002

Sulodexide and phlebotonics in the treatment of venous ulcers.

Prospective study, Patients n = 70 (90 ulcers)

Objectives - Efficacy of Sulodexide + MPFF vs MPFF alone

Results

Ulcer size showed a faster reduction in study group (Sulodexide+MPFF) compare with the control group, 12 vs 21 weeks, $P<0.01$

LDS improved in both groups, but it's faster in the SDX group

In conclusion – The combination of SDX and MPFF was effective in accelerating ulcer healing, controlling pain and improving LDS.

International Angiology 2017

Sulodexide for treating venous leg ulcers.

Meta-analysis (4 RCT), Patients n = 463

Objectives - Efficacy of Sulodexide

Results

Sulodexide may increase the healing of venous ulcers, when used alongside local wound care, 49% vs 29%.

Cochrane Database 2016

Editor's Choice — Management of Chronic Venous Disease

Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)

Recommendation 35

Sulodexide and MPFF should be considered as an adjuvant to compression therapy in the patient with venous ulcer.

Eur J Vasc Endovasc Surg 2015

Effect of medications on the healing of leg ulcers :

	MPFF	Pentoxifylline	Sulodexide	Hydroxyethyl rutosides
Healing of leg ulcers	Grade A	Grade A	Grade A	Grade B

International Angiology 2018

Treating Associated Symptoms

Pain

- **VADs**
- Paracetamol, ibuprofen
- Rule out infection?

Leg swelling

- **VADs**
- Keeping your leg raised above hip level
  30 min, 3-4 times a day.
- Putting pillows or cushions under feet.
- Regular exercise

Itchy skin

- Corticosteroid cream or ointment
- Rule out cellulitis?
- Allergic to your dressing?

Key Points

VADs is indicated as a first line treatment of symptoms associated with any stage of CVD.

In more advanced disease stages, such as venous ulcer, VADs may be used in conjunction with compression Rx or venous intervention to increase ulcer healing rates.

Thank you for your attention