EVIDENCE BASED STATEMENT

DOMAIN 8, Statement 5

TOPIC: "RUTOSIDES EVIDENCE-BASED USE IN CHRONIC VENOUS DISEASE MANAGEMENT"

SEARCH TERMS & SOURCES

(rutosides) AND ((vein) OR (venous))

PubMed, Embase and Cochrane Library

INCLUSION CRITERIA

Indexed Journal, English Language, lower limb

Reviews, <10 y.

SEARCH RESULT BEFORE - AFTER SELECTION

42 (before) - 13 (after selection)

PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. Yildiz CE, Conkbayir C, Huseynov E, et al. The efficiency of O-(beta-hydroxyethyl)-rutosides in reducing the incidence of superficial venous insufficiency in patients with calf muscle pump dysfunction. Phlebology. 2017 Apr;32(3):179-184.

2. Belczak SQ, Sincos IR, Campos W, et al. Veno-active drugs for chronic venous disease: A randomized, double-blind, placebo-controlled parallel-design trial. Phlebology. 2014 Aug;29(7):454-60.

EVIDENCE BASED STATEMENT

Domain 8; Statement 5

IDENTIFIED REFERENCES

1. Pompilio G, Nicolaides A, Kakkos SK, Integlia D. Systematic literature review and network Meta-analysis of sulodexide and other drugs in chronic venous disease. Phlebology. 2021 Oct;36(9):695-709.
2. Kitchens BP, Snyder RJ, Cuffy CA. A Literature Review of Pharmacological Agents to Improve Venous Leg Ulcer Healing. Wounds. 2020 Jul;32(7):195-207.
3. Martinez-Zapata MJ, Vernooij RW, Simancas-Racines D, et al. Phlebotonics for venous insufficiency. Cochrane Database Syst Rev. 2020 Nov 3;11(11):CD003229.
4. Morling JR, Broderick C, Yeoh SE, Kolbach DN. Rutosides for treatment of post-thrombotic syndrome. Cochrane Database Syst Rev. 2018 Nov 8;11(11):CD005625.
5. Morling JR, Yeoh SE, Kolbach DN. Rutosides for prevention of post-thrombotic syndrome. Cochrane Database Syst Rev. 2018 Nov 8;11(11):CD005626.
6. Pikovsky O, Rabinovich A. Prevention and treatment of the post-thrombotic Syndrome. Thromb Res. 2018 Apr;164:116-124.
7. Martinez-Zapata MJ, Vernooij RW, Uriona Tuma SM, et al. Phlebotonics for venous insufficiency. Cochrane Database Syst Rev. 2020 Nov 3;11:CD003229. PMID: 27048768; PMCID: PMC7173720.
8. Yildiz CE, Conkbayir C, Huseynov E, et al. The efficiency of O-(beta-hydroxyethyl)-rutosides in reducing the incidence of superficial venous insufficiency in patients with calf muscle pump dysfunction. Phlebology. 2017 Apr;32(3):179-184.
9. Smyth RM, Aflaifel N, Bamigboye AA. Interventions for varicose veins and leg oedema in pregnancy. Cochrane Database Syst Rev. 2015 Oct 19;2015(10):CD001066.
10. Lemmens KJ, Herst PM, Housmans BA, et al. The contribution of the major metabolite 4'-O-methylmonoHER to the antioxidant activity of the flavonoid monoHER. Chem Biol Interact. 2015 Sep 5;239:146-52. doi: 10.1016/j.cbi.2015.07.004. Epub 2015 Jul 8. PMID: 26163455.
11. Boesten DM, von Ungern-Sternberg SN, den Hartog GJ, Bast A. Protective Pleiotropic Effect of Flavonoids on NAD^+ Levels in Endothelial Cells Exposed to High Glucose. Oxid Med Cell Longev. 2015;2015:894597.
12. Aziz Z, Tang WL, Chong NJ, Tho LY. A systematic review of the efficacy and tolerability of hydroxyethylrutosides for improvement of the signs and symptoms of chronic venous insufficiency. J Clin Pharm Ther. 2015 Apr;40(2):177-85.
13. Baldisserotto A, Vertuani S, Bino A, et al. Design, synthesis and biological activity of a novel Rutin analogue with improved lipid soluble properties. Bioorg Med Chem. 2015 Jan 1;23(1):264-71.
14. Ugusman A, Zakaria Z, Chua KH, et al. Role of rutin on nitric oxide synthesis in human umbilical vein endothelial cells. ScientificWorldJournal. 2014;2014:169370.
15. Kumazawa S, Kubota S, Yamamoto H, et al. Antiangiogenic activity of flavonoids from Melia azedarach. Nat Prod Commun. 2013 Dec;8(12):1719-20.
16. Lemmens KJ, van de Wier B, Vaes N, et al. The flavonoid 7-mono-O-(β-hydroxyethyl)-rutoside is able to protect endothelial cells by a direct antioxidant effect. Toxicol In Vitro. 2014 Jun;28(4):538-43.
17. Yoo H, Ku SK, Baek YD, Bae JS. Anti-inflammatory effects of rutin on HMGB1-induced inflammatory responses in vitro and in vivo. Inflamm Res. 2014 Mar;63(3):197-206.
18. Scallon C, Bell-Syer SE, Aziz Z. Flavonoids for treating venous leg ulcers. Cochrane Database Syst Rev. 2013 May 31;(5):CD006477.
19. Belczak SQ, Sincos IR, Campos W, et al. Veno-active drugs for chronic venous disease: A randomized, double-blind, placebo-controlled parallel-design trial. Phlebology. 2014 Aug;29(7):454-60.

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TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 8, Statement 5, TOPIC: "RUTOSIDES EVIDENCE-BASED USE IN CHRONIC VENOUS DISEASE MANAGEMENT"

Rutosides are derived from horse chestnut whose active component is escin. Escin demonstrated an anti-proteolytic activity on the capillary wall, leading to a fluid leakage counteraction. Its effect demonstrated to reduce pain, heaviness, cramps and swelling sensation.
Methodology biases related to the homogeneity of the study population, lack of blinding and different confounders.
[**Pompilio G, Nicolaides A, Kakkos SK, Integlia D. Systematic literature review and network Meta-analysis of sulodexide and other drugs in chronic venous disease. Phlebology. 2021 Oct;36(9):695-709**].

Rutosides benefit on ulcer healing has been recently questioned by a dedicated revision of the literature.
[**Kitchens BP, Snyder RJ, Cuffy CA. A Literature Review of Pharmacological Agents to Improve Venous Leg Ulcer Healing. Wounds. 2020 Jul;32(7):195-207**].
Some data suggest a potential short-term benefit of Rutosides in post-thrombotic syndrome symptoms, but a dedicated Cochrane analysis highlighted the need of proper data collection before recommending this drug use in the symptomatology preventive context.
The analysis provided no evidence to support the use of rutosides also in the treatment of post-thrombotic syndrome.

[**Morling JR, Yeoh SE, Kolbach DN. Rutosides for prevention of post-thrombotic syndrome. Cochrane Database Syst Rev. 2018 Nov 8;11(11):CD005626**].
A 2020 Cochrane included 28 studies on Rutosides concluding that rutosides probably improve oedema, volume of the leg and pain.
Very limited action was demonstrated ankle perimeter and ulcer healing. Very low evidence support its use for reducing heaviness, cramps, itching, and paraesthesia.
*[**Martinez-Zapata MJ, Vernooij RW, Simancas-Racines D, et al. Phlebotonics for venous insufficiency. Cochrane Database Syst Rev. 2020 Nov 3;11(11):CD003229**].

EVIDENCE BASED STATEMENT

Domain 8; Statement 5

STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 8, Statement 5

"Rutosides demonstrated to potentially reduce swelling and pain. Some studies suggest it can reduce symptoms after a deep venous thrombosis, but there is no high quality evidence which can suggests its use for post-thrombotic syndrome prevention."

4 SELECTED REFEREENCES

1. Pompilio G, Nicolaides A, Kakkos SK, Integlia D. Systematic literature review and network Meta-analysis of sulodexide and other drugs in chronic venous disease. Phlebology. 2021 Oct;36(9):695-709
2. Kitchens BP, Snyder RJ, Cuffy CA. A Literature Review of Pharmacological Agents to Improve Venous Leg Ulcer Healing. Wounds. 2020 Jul;32(7):195-207
3. Morling JR, Yeoh SE, Kolbach DN. Rutosides for prevention of post-thrombotic syndrome. Cochrane Database Syst Rev. 2018 Nov 8;11(11):CD005626
4. *Martinez-Zapata MJ, Vernooij RW, Simancas-Racines D, et al. Phlebotonics for venous insufficiency. Cochrane Database Syst Rev. 2020 Nov 3;11(11):CD003229

identified LITERATURE BIAS

Lack of homogenous study populations and blind assessment. Several confounders, including BMI.

SUGGESTED NEXT LINES OF RESEARCH

Properly conducted head to head evaluations