Kliiniline küsimus nr 11

Kas kõikidele kroonilise venoosse haavandiga patsientidele rakendada parema ravitulemuse saavutamiseks medikamentoosset ravi vs mitte:
- reoloogilised preparaadid (nt pentoksüfülliin, naftidrofürüül)
- venoaktiivsed preparaadid

Kriitilised tulemusnäitajad: ravisoostumus, ravi tulemuslikkus, haavandi paranemine, haavandi
retsidiivi teke, patsiendi elukvaliteet, patsiendi rahulolu, hospitaliseerimine, elulemus, üldsuremuse vähenemine, ravikulu

Süstemaatilised ülevaated

Kokkuvõte süstemaatilistest ülevaadetest

Reoloogilised preparaadid

Pentoksüfülliin

2012 Cochrane Collaborationi süstemaatiline ülevaade ”Pentoxifylline for treating venous leg ulcers.” 12 RCT-d 864 osalejaga. Pentoksüfülliin on oluliselt parem haavandi paranemise suhtes võrreldes platseeboga.

Naftidrofurüül

Süstemaatilisi ülevaateid ega RCT-sid ei leidunud.

Tsilostasool

Süstemaatilisi ülevaateid ega RCT-sid ei leidunud.

Prostaglandiinid

Süstemaatilisi ülevaateid ei leidunud. Kaks RCT-d – PGE-1 vs platseebo, 20 päeva infusioon – statistiliselt oluline erinevus PGE-1 kasuks haavandi paranemise suhtes. Iloprost vs platseebo, 3 nädalat infusiooni – statistiliselt oluline erinevus iloprosti kasuks haavandi paranemise suhtes. Mõlema uuringu korral oli valim väike (87 patsienti PGE-1 ja 98 patsienti iloprosti uuringus)

Atsetüülsalitsüülhape

Süstemaatilisi ülevaateid ei leidunud. 20 osalejaga RCT, milles näidati aspiriini efektiivsust kroonilise venoosse haavandi paranemises vs platseebo. Uuring madala kvaliteediga.
Väikesemahulises RCT-s (ITT 51 patsienti haavandiga, mille diameeter >2 cm ja kroonilise veenipuudulikkusega), ravigrupp sai 300 mg aspiriini, kontrollgrupp ei saanud ravi.
Koos graduaalse kompressioonraviga leidi, et aspiriini saavas grupis paranesid haavandid kiiremini (12 nädalaga ravigrupis vs 22 nädalat kontrollgrupis). Peamine näitaja oli haavandi suuruse muutus. Tegemist madala kvaliteediga uuringuga.

Venoaktiivsed preparaadid

MPFF (Daflon, Detralex, Mobiven)

2013 Cochrane Collaborationi süstemaatiline ülevaade „Flavonoids for treating venous leg ulcers“

723 patsiendi viiest madala kvaliteediga uuringust – statistiliselt oluline erinevus haavandi paranemises MPFF kasuks. Samas uuringute kallutatuse risk on suur. Avaldamata uuring 160 patsiendiga ei demonstreerinud MPFF kasu.

Hüdroksüetüülrutosiidid
2013 Cochrane Collaborationi süstemaatiline ülevaade „Flavonoids for treating venous leg ulcers“
3 madala kvaliteediga ja kallutatuse riskiga uuringut 279 patsiendiga näitasid statistiliselt olulist kasu HR kasutamiseks.

Hobukastani ekstrakt (estsiin)
Süstemaatilisi ülevaateid ega RCT-sid ei leidunud.

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusalli**
We included twelve trials involving 864 participants. The quality of trials was variable. Eleven trials compared pentoxifylline with placebo or no treatment. Pentoxifylline is more effective than placebo in terms of complete ulcer healing or significant improvement (RR 1.70, 95% CI 1.30 to 2.24). Pentoxifylline plus compression is more effective than placebo plus compression (RR 1.56, 95% CI 1.14 to 2.13). Pentoxifylline in the absence of compression appears to be more effective than placebo or no treatment (RR 2.25, 95% CI 1.49 to 3.39).More adverse effects were reported in people receiving pentoxifylline (RR 1.56, 95% CI 1.10 to 2.22). Nearly three-quarters (72%) of the reported adverse effects were gastrointestinal. Pentoxifylline is an effective adjunct to compression bandaging for treating venous ulcers and may be effective in the absence of compression. The majority of adverse effects were gastrointestinal disturbances.	Jull AB, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD001733. DOI: 10.1002/14651858.CD001733

Of the nine studies (1075 participants): five investigated Micronised Purified Flavonoid Fraction (MPFF), and four investigated hydroxyethylrutosides (HR). Meta-analysis involving 723 participants from five trials - four of which were characterised by poor reporting - showed more venous leg ulcers were healed in the MPFF groups than in the control groups (RR 1.36; 95% CI 1.07 to 1.74). However, the most rigorously conducted trial, which was at low risk of bias, did not show any additional benefit of MPFF (RR 0.94; 95% CI 0.73 to 1.22). Since this trial was unpublished, the possibility of publication bias in trials involving flavonoids must be acknowledged. Overall, the quality of reporting of trials on HR was also poor. Pooling three trials, all at unclear risk of bias, involving 279 participants showed a statistically significant effect in favour of HR with respect to number of ulcers healed (RR 1.70; 95% CI 1.24 to 2.34).	Scallon C, Bell-Syer SEM, Aziz Z. Flavonoids for treating venous leg ulcers. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD006477. DOI: 10.1002/14651858.CD006477.pub2.
BACKGROUND: Venous ulcers represent an important medical problem because of their high prevalence and consequent sanitary costs. In this study, we evaluated the effect of prostaglandin E-1 (PGE-1), a drug that improves district ischemia, on the healing of venous ulcers. **METHODS:** We performed a randomized, placebo-controlled, single blind study in which 87 patients who had venous leg ulcers homogeneous for dimensions and characteristics were treated for 20 days with an infusion of prostaglandin E-1 or placebo, in association with topical therapy. The dimension and the number of the ulcers were determined at the beginning of the treatment and then every 20 days up to 4 months, or until total recovery. The main outcome of the study was the recovery percentage of the ulcers at the end of the 120-day period of observation and the referred healing time. The reduction in the extension of ulcers from the baseline measurement to the last observation was also evaluated. **RESULTS:** The baseline characteristics of the treatment and control groups were similar. The reduction in the size of the ulcers was faster in the patients treated with PGE-1. In this group, 100% of the ulcers healed < or = 100 days, whereas in the placebo group, only 84.2% did so by the end of the 120-day observation period (P < .05). The estimated healing times of 25%, 50%, and 75% of the patients treated with PGE-1 were 23, 49, and 72 days, respectively, compared with 52, 80, and 108 for the patients in the placebo group. Only one serious event occurred in the treated group. **CONCLUSIONS:**	Efficacy of the treatment with prostaglandin E-1 in venous ulcers of the lower limbs Milio, Glauco et al. Journal of Vascular Surgery , Volume 42 , Issue 2 , 304 - 308

This study demonstrates the effectiveness of PGE-1 in reducing the healing time of venous ulcers, suggesting that venous ulcers should also be considered ischemic.	
We conducted a study using an intravenous (i.v.) infusion of iloprost in the treatment of venous ulcers to verify whether the association of i.v. iloprost + local therapy + elastic compression has a favorable effect when compared with traditional treatment with local therapy and elastic compression. **STUDY DESIGN:** We evaluated the effects of iloprost in 98 consecutive patients with noncomplicated venous ulcers of lower limbs subdivided into 2 groups: the first group (48 patients) received iloprost in saline solution for 3 weeks and the second group (50 patients) received a venous infusion of a saline solution. The patients were examined at baseline time 0 (first visit) and then after 15, 30, 45, 60, 75, 90, 105, 120, 135, and 150 days. **RESULTS:** In the first group, after 90 days, all the ulcers had healed, whereas in the second group only 50% of ulcers had healed after 105 days. At the end of the study, in the second group only 84.09% of ulcers had healed. The statistical analysis showed a significant difference between the first (iloprost group) and the second group (placebo group). Besides, in the first group the cicatrization of the ulcer happened in a shorter period (27.90% after 60 days; 41.86% after 75 days; and 100% after 100 days) whereas in the second group, at the end of the study, in 15.91% of patients the ulcers had not recovered. **CONCLUSION:** Iloprost can significantly reduce healing time for venous leg ulcers through several actions.	Ferrara F, Meli F, Raimondi F, Amato C, Bonura F, Mulè G. The treatment of venous leg ulcers, a new therapeutic use of iloprost.*Annals of Surgery* 2007;**246**(5):860-4.
The effect of oral aspirin on the healing rate of chronic venous leg ulcers was compared with that of placebo in a double-blind randomised trial. 20 subjects with chronic venous leg ulcers were randomised to daily enteric-coated aspirin 300 mg or placebo, and standardised compression bandaging. 4 months of treatment achieved ulcer healing in 38% of the patients receiving aspirin compared with 0% of those receiving placebo ($p < 0.007$). 52% of the aspirin-treated group showed significant reduction in ulcer size compared with 26% of placebo recipients ($p < 0.007$). Reduction inulcer surface area was significantly better in the aspirin-treated group at 2 ($p < 0.01$) and 4 months ($p < 0.002$) compared with that in the placebo group.	Lancet. 1994 Jul 16;344(8916):164-5. Randomised trial of oral aspirin for chronic venous leg ulcers. Layton AM1, Ibbotson SH, Davies JA, Goodfield MJ.
To determine the effect of aspirin on ulcer healing rate in patients with chronic venous insufficiency, and to establish	Ann Vasc Surg. 2012 Jul;26(5):620-9. doi:

prognostic factors that influence ulcer evolution. **METHODS:** Between 2001 and 2005, 78 patients with ulcerated lesions of diameter >2 cm and associated with chronic venous insufficiency were evaluated in our hospital. Of these, 51 patients (22 men, 29 women) with mean age of 60 years (range: 36-86) were included in a prospective randomized trial with a parallel control group. The treatment group received 300 mg of aspirin and the control group received no drug treatment; in both groups, healing was associated with standard compression therapy. During follow-up, held weekly in a blinded fashion, there was ulcer healing as well as cases of recurrence. Results were analyzed by intention-to-treat approach. Cure rate was estimated using Kaplan-Meier survival analysis, and the influence of prognostic factors was analyzed by applying the Cox proportional hazards model. **RESULTS:** In the presence of gradual compression therapy, healing occurred more rapidly in patients receiving aspirin versus the control subjects (12 weeks in the treated group vs. 22 weeks in the control group), with a 46% reduction in healing time. The main prognostic factor was estimated initial area of injury (P = 0.032). Age, sex, systemic therapy, and infection showed little relevance to evolution. **CONCLUSIONS:** The administration of aspirin daily dose of 300 mg shortens the healing time of ulcerated lesions in the chronic venous insufficiency (CVI). The main prognostic factor for healing of venous ulcerated lesions is the initial surface area of the ulcer.	10.1016/j.avsg.2011.02.051. Epub 2012 Mar 19. **Influence of aspirin therapy in the ulcer associated with chronic venous insufficiency.** del Río Solá ML[1], Antonio J, Fajardo G, Vaquero Puerta C.

Ravijuhendid

Kokkuvõte ravijuhendites leiduvast RNAO ei puuduta süsteemset ravi, seega seda edaspidi ei maini. Kõik kasutatud ravijuhendid soovitavad kasutada pentoksüfülliini koos kompressioonraviga. SVS soovitab kasutada MPFF-i kombinatsioonis kompressioonraviga pikaajalise haavandi korral. SIGN mainib, et puudub piisav tõenduspõhisus selle soovitamiseks. AWMA-s öeldakse, et vastunäidustuste puudumisel **võib** kasutada MPFF-i. Kõik ravijuhendid viitavad samadele uuringutele. Kõik ravijuhendid ütlevad, et puudub piisav tõestusmaterjal aspiriini kasutamiseks.

(chronic[All Fields] AND "varicose ulcer"[MeSH Terms]) AND ("pentoxifylline"[MeSH Terms] OR "pentoxifylline"[All Fields]) AND ((Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND ("2005/01/01"[PDAT] : "2015/03/31"[PDAT]))
Leitud 2, ei sobi

(chronic[All Fields] AND ("varicose ulcer"[MeSH Terms] OR ("varicose"[All Fields] AND "ulcer"[All Fields]) OR "varicose ulcer"[All Fields] OR ("venous"[All Fields] AND "leg"[All Fields] AND "ulcer"[All Fields]) OR "venous leg ulcer"[All Fields])) AND (("pharmacology"[MeSH Terms] OR "pharmacology"[All Fields] OR "pharmacologic"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]))
Ilma piiranguteta 59, 2 sobis

(((chronic[All Fields] AND ("varicose ulcer"[MeSH Terms] OR ("varicose"[All Fields] AND "ulcer"[All Fields]) OR "varicose ulcer"[All Fields] OR ("venous"[All Fields] AND "leg"[All Fields] AND "ulcer"[All Fields]) OR "venous leg ulcer"[All Fields])) AND (veno[All Fields] AND active[All Fields] AND drug[All Fields])) OR (veno[All Fields] AND active[All Fields] AND agent[All Fields])) OR "venoactive medication"[All Fields] AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2005/01/01"[PDAT] : "2015/03/31"[PDAT]))
Ühtegi tulemust

Tehtud lisaotsingud käsitsi.

(chronic[All Fields] AND "varicose ulcer"[MeSH Terms]) AND ("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) AND ((systematic[sb] OR Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp]) AND ("2005/01/01"[PDAT] : "2015/03/31"[PDAT]))
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