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REVIEW ARTICLE

Compression therapy after ankle fracture surgery: a systematic review

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Abstract
Purpose The main purpose of this systematic review was to investigate the effect of compression treatment on the perioperative course of ankle fractures and describe its effect on edema, pain, ankle joint mobility, wound healing complication, length of stay (LOS) and time to surgery (TTS). The aim was to suggest a recommendation to clinicians considering implementing compression therapy in the standard care of the ankle fracture patient, based on the existing literature.
Methods We conducted a systematic search of literature including studies concerning adult patients with unstable ankle fractures undergoing surgery, testing either intermittent pneumatic compression, compression bandage and/or compression stocking and reporting its effect on edema, pain, ankle joint mobility, wound healing complication, LOS and TTS. To conclude on data a narrative synthesis was performed.
Results The review included eight studies (451 patients). Seven studies found a significant effect on edema, two studies described a significant reduction in pain, one a positive effect on ankle movement, two a positive effect on wound healing, one a reduction in LOS and finally two studies reported reduction in TTS. A systematic bias assessment showed that the included studies had methodological limitations influencing the confidence in the effect estimate.
Conclusions Compression therapy has a beneficial effect on edema reduction and probably a positive effect on pain and ankle joint mobility, but with the methodological limitations in the included studies it is not possible to make a solid conclusion on the effect on wound healing, LOS and TTS.

Keywords Ankle fracture · Compression treatment · Edema · Pain · Wound complications · Length of hospitalization

Introduction

Ankle fractures are common with an incidence between 71 and 107/100.000 person years [1–3]. The edema that accompanies acute ankle fractures can be quite severe and is hypothesized to result in delayed surgery, pain, soft tissue complications and maybe also wound healing problems after surgery. The standard decongestion therapy following an ankle fracture is rest, ice and elevation, but this regime is not always sufficient to avert edema formation and skin blistering. Orthopedic surgeons have, therefore, looked to other medical fields in search for an efficient tool to prevent and treat edema. As a result compression treatment is gradually finding its way into the perioperative care following ankle fracture surgery, despite the lacking evidence of its effectiveness. Compression therapy is already widely used in prevention of deep venous thrombosis [4], edema management [5] and in wound care [6], where it is used to decongest the lower extremity, but to our knowledge a systematic review researching its use on patients with ankle fractures has not yet been performed.

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The aim of this systematic review was to investigate the effect of compression therapy on the perioperative course of an ankle fracture, with special focus on edema reduction, pain, ankle joint mobility, wound healing problems, length of stay (LOS) and time to surgery (TTS). The objective was to give an overview of the literature, making it easier for clinicians to decide whether or not to implement this regime in the standard care of the ankle fracture patient.

Methods

The PRISMA guideline (Preferred Reporting Items for Systematic Reviews and Meta-analysis) was used throughout this review. After completion of a study protocol, the review was registered in the PROSPERO database. (http://www.crd.york.ac.uk/PROSPERO). Registration number: CRD42016030165.

Search strategy

A literature search was performed in PubMed on 1 September 2015 using following search parameters and Boolean operators: [compression therapy OR "intermittent pneumatic compression" OR intermittent pneumatic compression (IPC)] AND (ankle fracture OR malleolar fracture) NOT "locking compression". English was chosen as language and we focused on human studies. Search in the databases Pedro, OTseeker, Cinahl, The Cochrane Database, Embase, and hand search through references was performed and did not result in any further articles. The search strategy is outlined in Fig. 1.

Eligibility criteria

Inclusion criteria were: age above 18 years, patients with malleolar fractures treated according to the ORIF principle (open reduction internal fixation) or minimal invasive surgery, studies reporting complications after ankle surgery; infection, edema, wound dehiscence, and wound necrosis. Patients treated with compression therapy, either IPC, compression bandage or compression stocking, before or/and after surgery. Excluding criteria were: duplicate results, biomechanical studies, case reports, comments and letters.

Study selection process

The study selection was carried out by two reviewers (RW and CR). To avoid any disagreements on eligibility, disagreements were discussed with a third reviewer (HG).

Outcome measures and definition

Data extraction was performed on the parameters shown in Table 1. An article only had to report on one of the above mentioned outcomes, to be included in the study.

Data collection and quality assessment

To perform a systematic data extraction, a data collection form was used (Table 2), including the following information: first author, year of publication, number of participants, age (range, median or mean), male/female ratio, length of follow-up, outcome (edema reduction, wound healing complications/SSI, pain, LOS, TTS and ankle joint mobility), evidence level assessed using the CEBM 'Levels of Evidence' (The 2011 Oxford CEBM Levels of Evidence) and compression type with mmHg applied. A systematic assessment of bias was done according to the Cochrane recommendations and Review Manager was used (RevMan. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to lay out a *risk of bias graph* and *risk of bias summary* table. To discuss the quality of the studies in a systematic manner, the GRADE principles were applied. Despite the intention to perform meta-analysis, forest, and funnel plot, this was not possible, due to the quality of the studies. Instead a narrative synthesis was performed to discuss, sum and conclude on the data.

Results

Search findings and studies selected

The search strategy resulted in identification of 248 articles. A review of titles was performed by two of the authors (RW and CR), resulting in 19 articles. Full text of these articles was reviewed by the same two authors resulting in 8 articles that met the inclusion criteria (Fig. 1).

Study characteristics

The main characteristics are summarized in Table 2. Fracture types are summarized in Table 3.

Edema reduction

Five of the six studies concerning compression treatments effect on edema show a significant reduction (Table 4). Rohner-Spengler et al. show a difference in preoperative edema reduction of 5% in the control group, compared to 23% in the compression bandage group and 0% in the impulse compression group. Postoperatively the difference

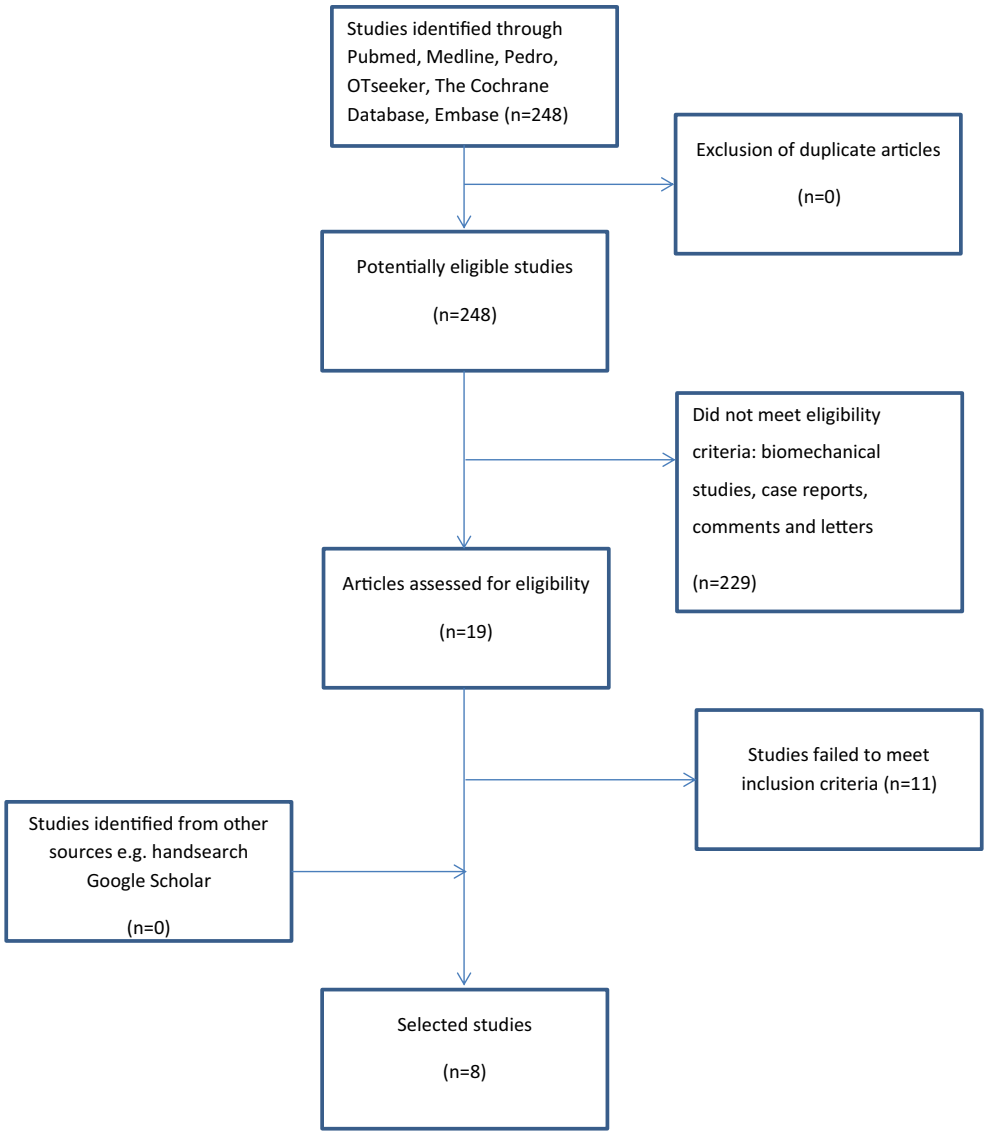


Fig. 1 Flow diagram showing results of literature search

Table 1 Outcome measures and definition

Parameter	Definition
Ankle fractures	Uni-, bi-, or trimalleolar fractures
Edema reduction	Loss of volume in the lower limb, measured either in percentage, centimeters or ratio
Wound healing problems	Surgical site infections, wound dehiscence, skin necrosis, visible osteosynthesis material or any other description of delayed healing
Compression therapy	Compression administered before or after surgery either by IPC, compression bandage or compression stocking. Because of great heterogeneity in how to use compression therapy in ankle fracture treatment, all studies using compression therapy was included, regardless treatment duration and type of compression device
Pain	Measured on VAS-scale or "yes/no"
Functional outcome	Measured using OMAS, AOFAS or degree of movement
Length of stay (LOS)	Time from hospitalization to discharge, measured in hours or days
Time to surgery (TTS)	Time from hospitalization to surgery, measured in hours or days

Table 2 Summary of findings

References	(*n*)	Age (years)	M:F	Follow-up	Outcome	CEMD level
Rohner-Spengler et al. [7]	58	37–44[a]	36:19[b]	52-week	Edema reduction: in bandage group: −23% ($p < 0.017$) after 2 days and −22% ($p < 0.017$) 2 days post-op. No difference after 6 weeks Ankle movement: no difference Days of hosp.: no difference Wound healing: no difference	2a
Sultan et al. [10]	90	46.4	36:54	24-week	Edema reduction: after 4 weeks edema is gone in intervention group with an ankle circumference ratio of 1.0 (95% CI 0.99–1.02) compared to control: 1.08 (95% CI 1.06–1.09) $p < 0.001$ OMAS: 12 weeks 88 points (95% CI 83–93) compared to control: 58 points (95% CI 52–64) $p < 0.01$. At 6 months 98 points (95% CI 96–99) compared to 67 points (95% CI 62–73) ($p < 0.001$) AOFAS: 12 weeks approx. 96 points compared to 80 in the control group ($p < 0.001$) Wound healing: wound inspection score[c] 1.55 (95% CI 1.19–1.90) in intervention group compared to 3.27 (95% CI 2.19–4.34) in the control group. $p < 0.009$ Pain: 97% in the intervention group had no pain, compared to 33% in the control group. $p < 0.001$	1b
Dodds et al. [15]	137	43.4	120:17	Till discharge	Time to surgery: control: 2 (0–10) days, intervention: 1 (1–3) day[d]. $p = 0.0025$ Length of stay: control: 4 (1–28) days, intervention 3 (2–7) days[d]. $p = 0.0008$ Surgical site infection: 11% in the control group compared with 3% in intervention group. $p =$ NA	3b
Keehan et al. [16]	24	50	9:3	Till discharge	Time to surgery: intervention group: 2.3 days. Control: 4.6 days. $p = 0.024$ Length of stay: 5.7 versus 9. $p = 0.116$	3b
Mora et al. [9]	24	31	18:6	Till surgery	Edema reduction: decrease in % intervention/control Day 1: 2.9/0.6 $p = 0.003$ Day 2: 4.4/1.7 $p = 0.001$ Day 3: 4.9/1.6 $p = 0.03$	2
Thordarson et al. [11]	25	NA	NA	Till surgery	Edema reduction: volume difference (IPPC-control) Day 1–2: −121 ml $p = 0.027$ Day 1–3: −63 ml $p = 0.049$	2b
Stöckle et al. [20]	60	33.9	44:16	6-day	Edema reduction: average decrease in %, cool packs/AV impulse Pre-OP: 10/53 $p =$ NA Post-OP: 45/74 $p =$ NA	2b
Airaksinen et al. [12]	34	43.7	14:20	5-day	Edema reduction: volume decrease intervention/control Day 5: 170 ml/15 ml $p < 0.001$ Ankle joint mobility: difference in increase intervention/control: Day 5: 11.9°/1° $p < 0.001$ Pain: drop in VAS-score intervention/control: 1.6/0.3 $p < 0.001$	2b

Ages are represented as means unless otherwise stated

M male, *F* female, *NA* not available

[a] Range in median age in postoperative group

[b] Ratio in postoperative group

[c] High score indicates poor healing or signs of infection

[d] Median values and range

Table 3 Fracture types

References	Fracture type
Rohner-Spengler et al. [7]	Isolated lateral malleolus: (OTA 44-A: 2, OTA 44-B: 28, OTA 44-C: 14) = 44 Tibia shaft (OTA 42-A: 1) = 1 Distal tibia (OTA 43-B: 3, OTA 43-C: 1) = 4 Talus (OTA 72-A: 1, OTA 72-B: 1, OTA 72-C: 1) = 3 Calcaneus (OTA 73-C: 2) = 2
Sultan et al. [10]	Weber A: 36 B: 42 C: 12. 30 undergoing ORIF
Dodds et al. [15]	Medial malleolus: 20. Lateral malleolus: 52. Bi-malleolar: 38. Trimalleolar: 24
Keehan et al. [16]	Weber B: 14. Weber C: 8. Isolated medial malleolus: 2
Mora et al. [9]	Weber A: 2. Weber B: 11. Weber C: 10. Isolated medial malleolus: 1
Thordarson et al. [11]	Closed weber B or C fractures, with relative stable fracture pattern
Stöckle et al. [20]	Ankle fractures: 29. Ankle ligament ruptures: 16. Calcaneal fractures: 8. Distal tibia fractures: 4. Metatarsal fractures: 1. Talus fracture: 1. Subtalar luxation: 1
Airaksinen et al. [12]	Fractures of the distal part of the lower leg, tri-malleolus or bi-malleolus

Table 4 Key outcomes regarding edema reduction, ankle movement and pain

Outcome	No of studies (patients)	Results
Edema reduction	6 (291)	
Rohner-Spengler et al. [7]	58	23%[a]
Mora et al. [9]	24	4.9%[a]
Stöckle et al. [20]	60	74%[a®]
Thordarson et al. [11]	25	121 ml[a]
Airaksinen et al. [12]	34	170 ml[a]
Sultan et al. [10]	90	Ratio: 1 (edema gone after 4 weeks)
Ankle movement	3 (182)	
Rohner-Spengler et al. [7]	58	No difference
Sultan et al. [10]	90	AOFAS: 16[b]. OMAS: 31[b]
Airaksinen et al. [12]	34	11.9°
Pain	2 (124)	
Sultan et al. [10]	90	Pain/no pain in intervention group: 97%/33%
Airaksinen et al. [12]	34	VAS drop (intervention group): 1.6

All differences are significant, except those marked ® (no p value available)

[a] Max values of reduction

[b] Gain in AOFA/OMAS point in intervention group

between groups is also significant, with a reduction of 22% in the compression bandage group, an increase of 7% in the control group and an increase of 46% in the impulse compression group. Six weeks postoperatively there is no difference between groups [7].

Stöckle et al. show a preoperative 10% reduction in the control group treated with cool packs, compared to 53% reduction in the group treated with intermittent impulse compression (IIC). Postoperatively the reduction is 45% in the cool pack group compared with 74% in the IIC group. No p value is calculated, but the authors conclude that ICC is the better treatment [8]. Mora et al. also report their results in *percentage reduction*, but the reduction is much smaller than Rohner-Spengler et al. and Stöckle et al. They compare a preoperatively administered cryo/cuff/IPC device plus elevation with elevation alone. At day 1 they report a reduction of 2.9% in the intervention group compared to 0.6% in the control group ($p = 0.003$). At day 2 the reduction is 4.4 and 1.7%, respectively ($p = 0.001$). At day 3 the reduction is 4.9 and 1.6%, respectively ($p = 0.03$) [9].

Another way to quantify edema reduction is by ratio. Sultan et al. compare an ankle injury stocking (AIS) to Tubigrip (Mölnlycke Health Care, Gothenburg, Sweden) and report edema reduction in a ratio, where 1 = no edema. At 4 weeks the mean circumference of the lower limb in the intervention group has returned to normal (ratio = 1) (95% CI 0.99–1.02), but in the control group it is 1.08 (95 CI 1.06–1.09) ($p < 0.001$) [10].

Thordarson et al. [11] and Airaksinen et al. [12] both choose to report edema reduction in milliliters. Thordarson et al. compare an intermittent pneumatic pedal compression (IPPC) with ice and elevation. Edema reduction is measured using the water displacement method. At day 1–2 they find a 88 ml reduction in the intervention group compared to a 33 ml increase in the control group ($p = 0.027$) and at day 1–3 the reduction is 31 ml compared to a 32 ml increase ($p = 0.049$). Airaksinen et al.'s study on edema reduction differs from the other studies, because the patients are enrolled in the study 6–12 weeks after ankle surgery, if they still have marked edema in the lower limb. The study compares 5 consecutive days of IPC therapy with no treatment. Volume reduction is measured in ml. In the intervention group the volume is reduced with 170 ml compared to 15 ml in the control group ($p < 0.001$).

Pain

Two of the three studies investigating pain, find a decrease in pain in the compression group. Airaksinen et al. use VAS to objectify pain and show that the score drops significantly in the IPC group from 3.6 to 2.0 vs 4.9 to 4.6 in the control group. Sultan et al. also show a significant difference with 97% in the control group experiencing pain compared to 33% in the compression group. Contradictory to this two other studies show that compression treatment results in pain, rather than relieving it; Rohner-Spengler et al. conclude that some patients who receive compression tend to have more pain than those in the control group, and the pain seems to come from the bandage treatment or IPC itself, resulting in several drop outs. The rest of the patients experienced the same level of pain as those in the control group. Stöckle et al. also describe two patients who have to stop IPC treatment because of pain.

Ankle joint mobility

Two of the three studies concerning ankle joint mobility are in favor of the treatment. Airaksinen et al.'s study shows improvement in ankle-range of motion after IPC use and reports an increase in 11.9° in the intervention group versus 1.0° in the control group. Sultan et al. report a significant improvement in OMAS [13] and AOFAS [14] score at all time during the 26-week follow-up. The improvement is attributed to the edema reduction. In contrast to these two findings, Rohner-Spengler et al. show that compression treatment in the form of a multilayer compression bandage significantly decreased ankle dorsiflexion on the third postoperative day, but the difference is gone 3 months and 1 year postoperatively.

Wound healing/surgical site infection (SSI)

Two out of the three studies reporting on wound healing/SSI fail to show an effect of compression treatment. Rohner-Spengler et al. show no difference between groups, and Dodds et al. show a drop from 11 to 3% regarding SSI, but do not report a p value [15]. The study by Sultan et al. points to a better wound healing with compression treatment compared with control. They use a wound inspection score indicating a significant better healing with a lower score. The compression group had a mean score of 1.55 (95% CI 1.19–1.90) compared with 3.27 (95% CI 2.19–4.34) in the control group.

Length of stay (LOS) and time to surgery (TTS)

Compression therapy shortens TTS in two out of three studies, but LOS was reduced in only one. Dodds et al. show a significant change in the median TTS from 2 days in the control group to 1 day in the intervention group. The total LOS shows a significant drop with a mean value of 4 days in the control group vs 3 days in the intervention group. Keehan et al. show that TTS is significantly shortened from 4.6 to 2.3 days in the intervention group. The average LOS was not significantly different [16]. Rohner-Spengler et al. reports no differences between group for either LOS or TTS.

Fracture types

Fracture types included are: 353 ankle fractures, 10 calcaneus fractures, 16 ligament ruptures, 9 tibia fractures, four talus fractures and one metatarsal fracture giving a total of 393 fractures. The rest is not accounted for, but include both ankle and lower leg fractures (Table 2).

Discussion

Edema reduction

Compression treatment seemingly reduces the edema after an ankle fracture, but there is no agreement among clinicians on a standardized way to ascertain lower leg volume. Different studies use different techniques to quantify swelling and the clinical consequence of a certain amount of edema reduction is unknown. When measuring a leg the result is prone to measurement uncertainty, since the circumference of the leg changes with the position of the leg and the amount of tightening of the measuring tool. Lower leg volume is affected by the circadian rhythm, the position of the body and physical activity prior to the measurements [17]. A certain asymmetry of the volume is probably

also to be expected due to dominance, making it unlikely that a small difference such as 7 mm should be of clinical importance. Another problem regarding the interpretation of edema reduction is that even though the reduction is statistically significant, it doesn't guarantee a clinical relevance. If the reduction is clinically relevant it would be expected to translate into an impact on the other outcomes looked at, which is not always the case.

Pain

Edema results in a tightening painful sensation of heaviness in the limb, so a reduction of edema could logically lead to a reduction in pain, but surprisingly two studies mention that compression is a painful treatment, resulting in drop outs. Airaksinen et al. show a statistically significant reduction of 1.6 VAS-units and this reduction is probably also clinically relevant. The minimal clinically important difference (MCID) in VAS after ankle surgery is unknown, but is 1.4 after shoulder arthroplasty [18] and 1.5 regarding radiating leg pain after back surgery [19].

Ankle joint mobility

No convincing effect is shown on ankle joint mobility, even though mobility is intuitively reduced when the skin envelope is swollen and tight. A reduction of edema should, therefore, improve range of motion, still only the high quality study by Sultan et al. shows an effect on mobility with a significant increase in OMAS and AOFAS from 4 to 26 weeks. Both tests assess outcomes scores after ankle surgery and include mobility and pain. OMAS is based on subjective outcome measures whereas AOFAS is an objective clinical score. The improved mobility is not backed up by Rohner-Spengler et al. who fail to reproduce this finding when investigating in ankle movement.

Wound healing/surgical site infection (SSI)

No convincing effect was shown on wound healing. Fluid imbibed tissue, impede micro circulation of blood which can delay or obstruct wound healing. A reduction of edema should logically lead to better wound healing, but only Sultan et al. show a significant reduction in wound healing problems, a tendency not reproduced in other studies. Rohner-Spengler et al. find no difference, and Dodds et al. report a difference without *p* value.

Length of stay (LOS) and time to surgery (TTS)

Because edema retards surgery, edema reduction should theoretically result in shortening of TTS, which is also shown in both studies looking at this endpoint [15, 16]. When TTS is reduced, a reduction of LOS would naturally expect to follow, but surprisingly only one study shows a slight reduction in LOS [15] and this is not reproduced in the other two studies looking at this end point [7, 16].

The strength of this review is the systematic literature search and the thorough selection procedure allowing only the more robust studies to be included, even though it resulted in a small material. Performing a systematic assessment of bias, also strengthen the discussion and

Table 5 Intervention type and duration of compression

References	Intervention type and duration
Rohner-Spengler et al. [7]	Ice gel packs (type not described), minimum 20 min per application, 4 times a day Multilayer compression bandage consisting of two layers of wool and two or three layers of short stretch bandage, 22 h of compression per day AV impulse system (Orthofix Vascular Novamedix, Andover, UK), 130 mmHg, at least 8 ± 2 h a day
Sultan et al. [10]	Ankle injury stocking (Advanced Therapeutic Materials Ltd, Coventry, West Midlands, UK), 10–25 mmHg, removed before surgery and refitted after. Aircast boot (DJO Global, Vista, CA, USA) <10 mmHg, worn until bony union
Dodds et al. [15]	AV impulse device (Covidien AG, Mansfield, MA, USA), 120 mmHg. Administered in the emergence department and continued until the time of surgery
Keehan et al. [16]	Orthofix AV impulse system[a], 130 mmHg. Administered in the orthopedic ward and continued until the time of surgery
Mora et al. [9]	Cryo/Cuff device with AutoChill pump[a], 30–35 mmHg. Applied during the day and turned off during the night, until the time of surgery
Thordarson et al. [11]	PlexiPulse (NuTech, San Antonio, TX, USA)[b], used full time until the time of surgery
Stöckle et al. [20]	AV impulse system (Novamedix Services Limited, Andover Hants, England), 130 mmHg. Used nearly continuously during the day, at night the patient was free to turn it off
Airaksinen et al. [12]	Ventipress model 24 (Ventipress Ltd., Lahti, Finland), 60 mmHg. Used 5 consecutive days for 75 min each day

[a] Manufacturer not listed

[b] mmHg not listed

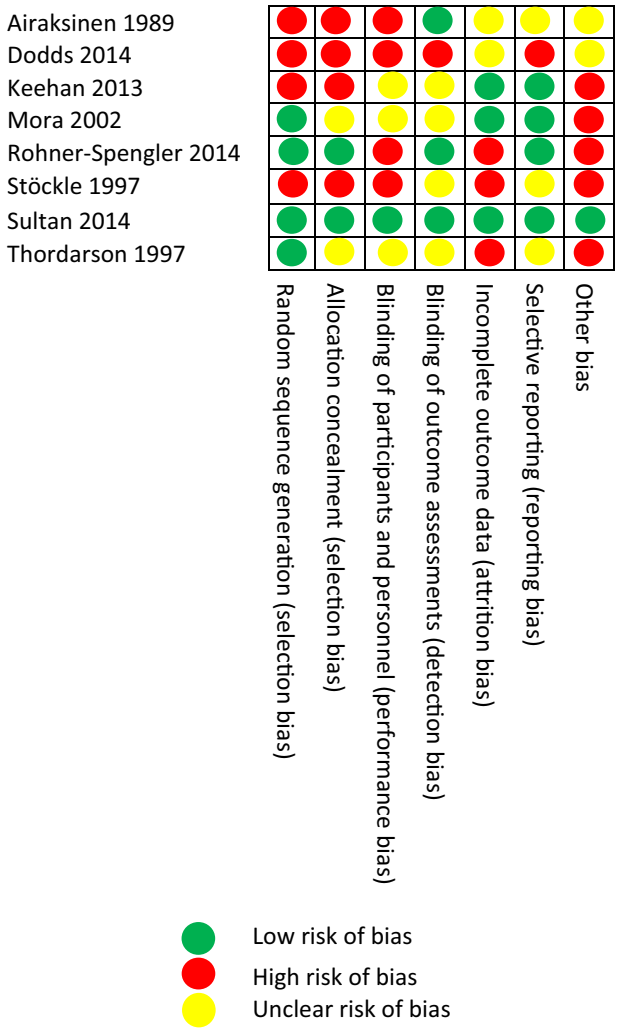


Fig. 2 Risk of bias summary

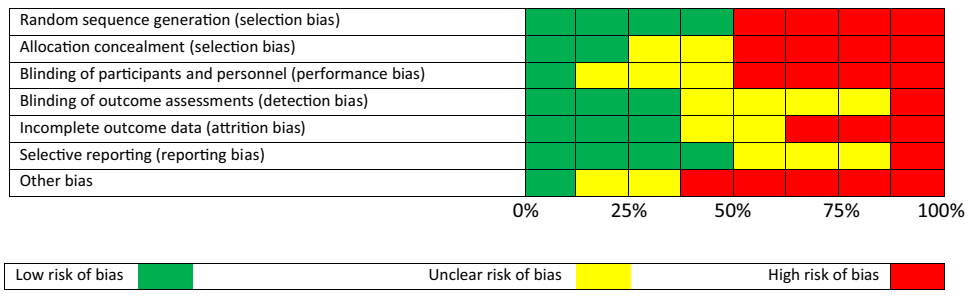
conclusion. The use of the PRISMA guidelines results in transparency and minimizes the risk of selection bias.

This study has several limitations; literature is scarce and heterogenic and most studies have small or very small sample sizes. Several studies exclude frail patients and several studies have historic controls or a control group that does not match the intervention group. Most studies do not report their power calculation. Some studies do not differentiate between primary and secondary outcomes. Follow-up is heterogenic and varies from "till surgery" to 12 months. Randomizing is not always done correctly. One study randomizes according to date and another according to date of birth. One study had to stop before planned due to financial problems and was thus underpowered.

When it comes to edema reduction, effect size differs widely from 0 to 56% [7, 9, 20]. The inconsistency can be explained by the difference in populations, intervention and outcomes and one could argue that this is sufficient explanation and that this as such should not lower our confidence in the results. On the other hand, the conducts of the studies are not of similar quality, and confidence intervals are seldom reported, making it difficult to compare studies.

Fracture types vary greatly (Table 3) including both distal tibia-, ankle-, foot and hind-foot fractures as well as ligamentous damage making comparison across studies difficult. Type of compression varies substantially; four studies use a foot-pump, two studies use foot/ankle/calf-pumps and one study uses a compression bandage and one a compression stocking (Table 5). The control treatment differs widely between studies, from nothing to elevation, elevation + ice, Tubigrip™ + Aircast® and continuous cryotherapy + elevation. Edema reduction is one of the most common outcomes reported in the studies, but it might be a surrogate outcome and it is uncertain if it truly relates to clinical relevant effects such as wound healing or range of motion. Since this correlation depends on an assumption, it weakens the conclusions. All the above mentioned parameters point towards a serious or very serious indirectness which lower the quality of evidence. Most studies have small or very small sample sizes and the total number of participants across studies is 451. Regarding wound healing complications, the number of events is very small which makes it unlikely that a small sample size is enough to detect a true difference across groups.

Fig. 3 Risk of bias graph



The studies are not fit for comparison in a funnel plot, because of the heterogeneity. Never the less, most studies in this review are small, positive studies. If a symmetrical distribution of studies is expected, one could expect the existence of small studies with negative or no results, that hasn't been published. Hence the risk of publication bias is present.

We performed a systematic assessment of bias in the individual studies according to the Cochrane recommendations (Figs. 2, 3), showing a tendency of poor reporting of bias in 6 out of 8 studies. All together 40% of the bias risk parameters were judged "high risk" 32% were judged "low risk" and 28% were judged "unclear risk". Despite including only the studies of the highest evidence level, the overall assessment yields a low or very low quality of the studies resulting in a reduction of our confidence in the effect estimate to *limited* or *very little confidence.*

In conclusion, a systematic reading of the literature gives weight to the postulate that compression therapy has a beneficial effect on edema reduction and probably also on ankle movement and pain. Because of methodological limitations in the included studies it is not possible to make a solid conclusion on the effect of wound healing, LOS and TTS. clinicians can implement this treatment if the goal is to diminish edema and can presumably expect to see a reduction in pain and an improvement in ankle movement, but it is still uncertain if compression has a positive effect on any of the other above mentioned parameters. Future studies in the field should provide a solid study design with emphasis on clinical relevant well defined endpoints.

Compliance with ethical standards

Conflict of interest R. Winge, L. Bayer, H. Gottlieb and C. Ryge declare that they have no conflict of interest.

This current research did not involve human participants and/or animals, since it is based on data from different literature databases. This is also the reason for which no "informed consent" was needed.

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