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REVIEW

Therapy modalities to reduce lymphoedema in female breast cancer patients: a systematic review and meta-analysis

Slavko Rogan[1,2] · Jan Taeymans[1,3] · Helena Luginbuehl[1] · Martina Aebi[1] · Sara Mahnig[1] · Nick Gebruers[4]

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Abstract The aim of the present study was to evaluate the effects of compression bandages, sleeves, intermittent pneumatic compression (IPC) and active exercise on the reduction of breast cancer-related lymphoedema (BCRL). A systematic literature search up to the year January 2016 was performed in CINAHL, Cochrane Register of Controlled Trials, Embase, International Clinical Trials Registry Platform (WHO), PEDro and PubMed. Inclusion criteria were (1) RCTs, (2) reported adequate statistics for meta-analysis, (3) English or German language. Exclusion criteria were (1) effects of drugs, hormonal, radiation and surgical procedures, (2) studies with children, (3) non-breast cancers, lower extremity oedema, (4) impact on fatigue only, diets or sexually transmitted diseases, (5) cost-analysis only and (6) non-carcinogenic syndromes or (7) prevention of breast cancer. After scoring the methodological quality of the selected studies, data concerning volume reduction of the oedema swelling were extracted. Thirty-two studies were included in this systematic review. Nine studies were selected for the RCT-based studies and 19 studies were included in the pre–post studies-based random-effects meta-analyses. All conclusions should be taken with precautions because of the insufficient quality of the selected papers. Exercise seems beneficial in reducing oedema volume in BCRL. IPC seems beneficial in helping to reduce the oedema volume in the acute phase of treatment. Compression sleeves do not aid in the volume reduction in the acute phase; however, they do prevent additional swelling.

Keywords Lymphoedema · Women · Mastectomy · Axillary dissection or breast cancer

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✉ Slavko Rogan
slavko.rogan@bfh.ch

Jan Taeymans
jan.taeymans@bfh.ch

Helena Luginbuehl
helena.luginbuehl@bfh.ch

Martina Aebi
martina.aebi@bfh.ch

Sara Mahnig
sara.mahnig@bfh.ch

Nick Gebruers
nick.gebruers@uantwerpen.be

1 Discipline of Physiotherapy, Bern University of Applied Sciences, Bern, Switzerland

2 Academy of integrative Physiotherapy and Training Education, Grenzach-Wyhlen, Germany

3 Faculty for Sports and Rehabilitation Science, Vrije Universiteit Brussel, Brussels, Belgium

4 Rehabilitation Sciences & Physiotherapy, University of Antwerp, Antwerp, Belgium

Introduction

Breast cancer-related lymphoedema (BCRL) is one of the most dreaded complications after treatment for breast cancer. The risk factors for BCRL are axillary clearance, radiation therapy, high BMI and post-operative infections [1–3]. The incidence of BCRL is related to the invasiveness of axillary lymph node extirpation, with less BCRL in sentinel node negative patients, and ranges between 12.5 and 49 % [3–6]. The pooled incidence for BCRL, taking into account the larger part of sentinel negative patients, is 16.6 % [3]. BCRL is now recognized as a chronic disease affecting most frequently the upper extremity, followed by the chest wall and breast [7]. This condition can develop directly after surgery or post-radiation therapy, although it can also occur months and even years later [4].

Women with BCRL complain of a reduced quality of life (QOL) [8] and tend to have higher rates of mental health problems [9], while shoulder stiffness and functional limitations in activities of daily living are also reported [10, 11]. Consequently, BCRL has implications on the ability to work, and hence lead to high direct and indirect monetary costs. After breast cancer treatment, women cannot return to work for 10.8 months on average, while in BCRL patients, this period is 12.9 months on average [12]. It is in the interest of the patient, the medical staff, the therapist and the insurance companies, to make the treatment as effective and as acceptable as possible.

The consensus document of the International Society of Lymphology for evaluation and managing peripheral lymphoedema [13] described the following treatment techniques for BCRL reduction: manual lymphatic drainage (MLD), compression bandaging, active exercises, and skin care. In the literature, this consensus treatment is referred to as complex decongestive therapy because the treatment is a combination of the mentioned treatment modalities. Two reviews and one meta-analysis evaluating the effectiveness of different treatment methods are available [14–16]. None of these reviews evaluated precisely the reduction of oedema after a comprehensive treatment or after an exercise intervention without MLD. Therefore, the aim of this present systematic review and meta-analysis was to evaluate the effect of compression and exercise modalities for the management of BCRL. The research question for the study was as follows: What are the effects of compression (bandages) and active exercise during the intensive phase of therapy in the reduction of lymphoedema in breast cancer patients?

Method

Study search

The methods used for this systematic review were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [17, 18]. This systematic literature search was conducted using multiple electronic databases from January 2015 until January 2016. The literature search was performed in CINAHL, Cochrane Register of Controlled Trials, and Physiotherapy Evidence Database (PEDro). The unpublished International Clinical Trials Registry Platform from the World Health Organization (WHO) was also searched. The reference list of all relevant studies was cross-referenced in order to find further literature. This systematic review and meta-analysis were registered at PROSPERO (CRD42014010700).

Study selection

Two independent reviewers (MA, SM) screened titles and abstracts for eligibility. The decision to read the full text was made based upon pre-defined eligibility criteria. Keywords and combination to the PICO-model were used for the search strategy:

Population (P): female or women; Intervention (I): lymphatic drainage or lymphtape or compression bandage or sleeve or intermittent pneumatic compression (ICP) or exercise; Comparator (C): Compression bandage against control intervention or compression bandage against exercise and Outcome (O): volume or oedema reduction.

Afterwards, three independent reviewers (SR, JT, NG) read the full text and selected the studies to include in the systematic review and meta-analysis if they (1) were RCTs, (2) reported mean and SD (or standard error) or mean change and SD (or standard error) or medians and interquartile range (3) were written in English or German language and (4) mentioned one of the following keywords in the title or abstract: lymphoedema, women, mastectomy, axillary dissection or breast cancer.

A study was excluded when the effect of (1) drugs, hormonal, radiation and surgical procedures was examined. The other exclusion criteria were studies with (2) children in the test groups, (3) non-breast cancers, (4) lower extremity oedema, (5) impact on fatigue only, (6) diets or sexually transmitted diseases, (7) cost-analysis only and (8) syndromes that are not carcinogenic nature or (9) investigation of the prevention of breast cancer.

Quality assessment

General study characteristics were extracted by two independent reviewers (MA, SM). The following information was included in this systematic review: study design, participants (N and age), intervention, outcomes and results.

The Cochrane Collaboration's Risk of Bias (RoB) tool [19] was used to assess the methodological quality of the included studies by two independent reviewers (MA, SM). The RoB criteria list covers six items that represent the aspects of internal validity. Each item was scored with "−" for no, with "+" for yes and with "?" if the information was unclear. A study was defined as having a low risk of bias if all criteria were fulfilled with yes. A study had a moderate risk of bias when one or more items were rated unclear, while a study was coded as high risk of bias if one or more key domains have been rated with no. Where discrepancies existed, a third reviewer (SR) intervened to obtain a consensus.

A meta-analysis was performed if two or more studies had measured and reported the same outcome. If more than one outcome variable was reported, the reviewers (SR, JT, NG) will decide, without knowledge of the results, which outcome variable should be pooled [20]. The decision was based on the reviewers' judgment. The main outcomes were reduction of oedema volume and reduction of arm volume.

The meta-analyses used a random-effects model. The effect sizes were expressed as standardized mean differences (SMDs). To explore the review questions, the following meta-analyses were conducted: (i) compression (bandage, sleeve, intermittent pneumatic pressure) versus control for reduction of oedema volume and (ii) exercise versus control for reduction of oedema volume. Furthermore, (iii) a subgroup one-arm pre–post-intervention effect analysis of compression and exercise on reduction of oedema volume was carried out.

Heterogeneity of treatment effects across the individual study estimates was investigated statistically using the Cochran's Q statistic and its corresponding degrees of freedom and p value. Higgins' I^2measure was used to determine how much of the observed variability can be explained by the true between-studies variability. Higgins' proposed benchmarking was used for the interpretation of these heterogeneity measures. An I^2 around 25 % indicates that the heterogeneity might not be important, while an I^2 around 50 % and I^2 around 75 % suggest that heterogeneity is moderate and substantially considerable, respectively [21].

For clinical interpretation of the findings based on the data from the included RCTs, the overall weighted standardized mean difference estimate of the meta-analysis was re-expressed in the original units using the "familiar instrument method" as proposed in the Cochrane handbook for systematic reviews of interventions [22]. For clinical interpretation of the findings based on the data from the included pre–post studies, the overall weighted standardized mean difference estimate of the meta-analysis was re-expressed in the original units using the "rule of thumb for effect sizes method" (i.e. Cohen's benchmarking of effect sizes) as proposed in the Cochrane handbook for systematic reviews of interventions [22].

Risk for publication bias was assessed by funnel plot inspection and the classic fail-safe N algorithm.

For all analyses, p values less than 0.05 were considered statistically significant. All calculations and plots were conducted using the CMA-2 software (Comprehensive Meta-Analysis 2nd version, Biostat, Englewood, NJ, USA).

Results

Flow of studies through this review

Figure 1 depicts the flow process of studies in this systematic review and meta-analysis. In total, 543 articles were found. After removing duplicates and reviewing 411 titles and abstracts, 121 original articles were read in detail. Overall, 32 studies were selected and included for the systematic review, while nine studies were selected for the RCT-based meta-analyses, and 19 studies were included in the pre–post studies-based meta-analyses.

Risk of bias

Table 1 shows the RoB assessment of the included studies. Most studies lacked concealed allocation and blinding and therefore showed a moderate to high risk of BIAS.

Study characteristics

The study characteristics are summarized in Table 2. Haghighat et al. [23] and Schmitz et al. [24] included more than 100 participants in their study. The other studies showed a sample size of less than 100 participants. The intervention method and outcome varied across all included studies.

Effect of intervention

Nine RCTs could be used to evaluate the effect of intermittent pneumatic compression (IPC), use of a sleeve or exercise vs. control on reduction of oedema (Fig. 2).

The meta-analysis for exercise yielded a SMD of −0.49 [95 % CI −0.86 to −0.11] ($p = 0.011$). The heterogeneity was low (Cochrane's $Q = 2.53$; df = 3; $p = 0.470$) with I^2 of 0 %. After re-expression in its original metric, the overall weighted effect size corresponded with a reduction of oedema volume of about 200 cm^3.

The meta-analysis for IPC showed a SMD of −0.54 [95 % CI −1.01 to −0.064] ($p = 0.026$). The heterogeneity was low (Cochrane's $Q = 1.36$; df = 1; $p = 0.244$) with I^2 of 26.3 %. After re-expression in its original metric, the overall weighted effect size corresponded with a reduction of oedema volume of about 400 cm^3.

The meta-analysis for the use of a sleeve showed an overall weighted SMD of −0.15 [95 % CI −0.44 to 0.14] ($p = 0.314$). The heterogeneity was low (Cochrane's $Q = 0.49$; df = 2; $p = 0.782$) with I^2 of 0 %. After re-expression in its original metric, the overall weighted effect size corresponded with a reduction of oedema volume of about 50 cm^3.

Nineteen studies could be included in a meta-analysis of effect sizes from pre–post-intervention studies and from multiple-armed RCTs, of which the arm of interest was extracted and used as an individual pre–post study. This allowed for the inclusion of bandage as an extra type of compression (Fig. 3).

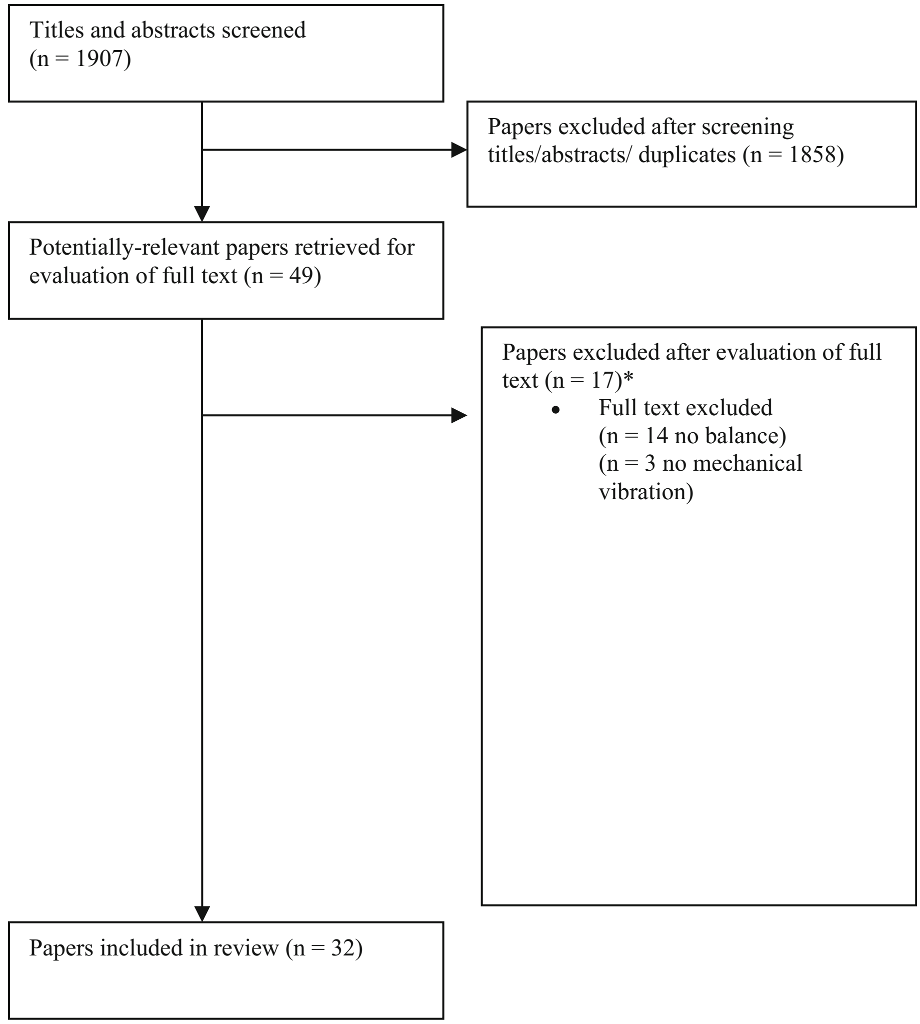

Fig. 1 Flow chart of this study

The meta-analysis for bandage showed a SMD of -0.33 [95 % CI -0.48 to -0.17] ($p < 0.0001$). The heterogeneity was low (Cochrane‘s $Q = 6.34$; df $= 7$; $p = 0.501$) with I^2 of 0 %. Using the rule of thumb for the re-expression of the SMDs, this overall weighted SMD would correspond with a small effect size.

The meta-analysis for exercise showed a SMD of -0.074 [95 % CI -0.28 to 0.13] ($p = 0.479$). The heterogeneity was low (Cochrane‘s $Q = 0.93$; df $= 4$; $p = 0.920$) with I^2 of 0 %. Using the rule of thumb for the re-expression of the SMDs, this overall weighted SMD would correspond with a small effect size.

The meta-analysis for intermittent pneumatic compression showed a SMD of 0.013 [95 % CI -0.25 to 0.28] ($p = 0.926$). The heterogeneity was low (Cochrane‘s $Q = 0.13$; df $= 2$; $p = 0.938$) with I^2 of 0 %.

The meta-analysis for sleeve showed a SMD of -0.26 [95 % CI: -0.519 to 0.001] ($p = 0.051$). The heterogeneity was low (Cochrane‘s $Q = 0.74$; df $= 2$; $p = 0.690$) with I^2 of 0 %. Using the rule of thumb for the re-expression of the SMDs, this overall weighted SMD would correspond with a small effect size.

Risk of publication bias was moderate. Figure 4 depicts the funnel plots for the meta-analyses based on RCTs and based on one-arm pre–post studies. No real critical funnel plot asymmetry was observed.

The “classic fail-safe N” algorithm revealed that 46 and 22 missing non-significant studies would be needed to bring the p value above the alpha level of 5 % in the RCT- and pre–post-based analysis, respectively.

Discussion

This systematic review and meta-analysis aimed at evaluating the effect of different compression modalities (such as the use of bandage, sleeve or intermittent pneumatic compression) and exercise for the management of BCRL. First, the results from RCT’s are discussed; second, the results of the pre–post designs are discussed.

Table 1 Overview of Risk of Bias (RoB)

Study	RCT	Allocation concealed	Blinding	Incomplete data adressed	Free of selective reporting	Free of other bias
Damstra et al. [37]	+	+	−	+	+	+
Dayes et al. [43]	+	−	+	+	+	+
Gautam et al. [47]	+	−	+	+	+	+
Godoy et al. [49]	+	−	−	?	−	−
Haghighat et al. [23]	+	−	−	+	+	+
Johansson et al. [45]	−	−	−	+	+	−
Johansson et al. [39]		−	−	+	+	−
Johansson et al. [35]	−	−	−	+	+	−
Johansson et al. [48]	+	−	−	+	+	−
Kasseroller and Brenner [40]	+			−	+	−
Kim et al. [50]	+		−	+	+	+
King et al. [41]	+	?	−	+	−	−
Kozunaglu et al. [51]	+	−		+	+	−
Letellier et al. [52]	+	−		+	+	−
Loudon et al. [53]	+	+	−	+	+	−
Maher et al. [54]	+	−	−	+	+	−
Maldonado et al. [42]	+	−	−	+	+	+
Malicka et al. [27]	+	−	−	+	+	−
Malicka et al. [55]	+	−	−	+	+	−
McKenzie et al. [28]	+		−	+	+	−
Partsch et al. [38]	+	−	−	+	+	−
Pilch et al. [56]	+	−	−	+	+	−
Randheer et al. [57]	−	−	−	−	+	+
Ridner et al. [44]	+	−	−	+	+	+
Ridner et al. [58]	+	+	+	+	+	+
Schmitz et al. [59]	+	+	−	+	+	+
Sitzia et al. [60]	+	+	−	+	+	+
Stout et al. [33]	−	−	−	+	+	−
Szuba et al. [61]	+	?	−	+	+	−
Tsai et al. [62]	+	+	−	−	+	+
Uzkeser et al. [63]	+	?	+	+	+	+
Vale et al. [34]	−		−	+	+	+

Four RCT's reported on the effects of exercise [25–28]. Unfortunately, the exercise programs cannot be compared due to the large variation in protocol. Despite the different protocols (Yoga, Nordic Walking, Resistance training), all protocols favoured lymphoedema volume reduction. On recalculating, exercise resulted in a volume reduction of 200 ml. These results add to the knowledge that exercise is beneficial in the treatment of BCRL and does not aggravate lymphoedema [29, 30].

Two RCT's reported from a sample of BCRL patients that additionally received IPC to the consensus treatment [23, 31]. Both IPC protocols were comparable, and a recalculation of the effect of IPC demonstrated that IPC was able to reduce lymphoedema volume to 400 ml in the intensive phase. Unfortunately the effect of IPC cannot be maintained in the maintenance phase as is demonstrated in another meta-analysis [32]. Therefore, these results should be interpreted with precaution. IPC lacks the ability to be a standalone therapy since it only stimulates the lymphatic drainage in working collectors. Therefore, IPC has a limited effect on the resorption of the interstitial oedema fluid.

Three RCT's reported on the effect of a compression sleeve in the intensive phase [33–35]. In two studies, the compression sleeve was additional to exercises [34, 35], and in one study, the compression was the only treatment provided when arm volume started to increase in

Table 2 Study characteristics

Study	Participants (Groups, N) mean age ± SD or (range)	Protocol group A	Protocol group B	Outcomes results
Damstra et al. [37]	LPB: N: 18 60.5 (45–84 years) HBP: N: 18 61.2 (50–73 years)	LBP: bandages with low interface pressure (20–30 mmHg) over 2 h and new bandage over 24 h	HBP: bandages with high interface pressure (44–58 mmHg) over 2 h and new bandage over 24 h	Inverse water volumetry: LBP: reduction after 2 and 24 h ($p < 0.01$) HBP: reduction after 24 h ($p < 0.01$)
Dayes et al. [43]	CDT: N: 57 61 (36–86 years) CON: N: 46 59 (41–76 years)	CDT: 1 h MLD, compression bandage, skin care, exercise	CON: elastic compression garments and glove over 12 h/day	Arm circumferences: after 6 weeks CDT: mean reduction excess arm volume 29 % CON: mean reduction excess arm volume 22.6 %
Gautam et al. [47]	IG: N: 32 45.6 ± 6.98 years	Upper-limb exercise over 5 days/week		Circumferential measurements and volumetric method; decrease of upper-limb circumference ($p = 0.001$) and volume ($p = 0.001$)
Godoy et al. [49]	CPG: N: 20 WCPG: N: 20	CPG: exercise 2×/week, compression sleeve, active exercise device	WCPG: exercise 2x/week, active exercise devise	Volumetric method CPG: 24.6 ml reduction ($p < 0.0004$) after 1 h WCPG: non-significant reduction of 9.7 ml after 1 h
Haghighat et al. [23]	CDT: N: 56 53.4 ± 11.4 years IPC: N: 56 52.7 ± 10.8 years	CDT: 45 min MLD, compression bandages, exercise	ICP: trunk lymphatic drainage (10–15 min), four chamber pneumatic sleeve and intermittent pneumatic compression pump set at 40 mmHg for 30 min	Water displacement method group differences ($p = 0.036$) between CDT (−43.1 %) and IPC (−37.5 %).
Johansson et al. [45]	MLG + IPC: N: 12 64 (52.5–69.5 years) IPC: N: 12 57.5 (47.5–69.5 years)	MLG + IPC: MLD with pneumatic compression	IPC: pneumatic compression	Volume displacement MLG + IPC: 75 ml reduction ($p < 0.001$) IPC: 28 ml reduction ($p = 0.03$)
Johansson et al. [39]	MLG + CB: N: 20 58 ± 12 years CB: N: 18 64 ± 12 years	MLG + CB: MLD and compression bandage	CB: compression bandage	Volume displacement MLG + CB: reduction of 47 ml ($p < 0.001$) IPC: reduction of 20 ml ($p = 0.03$)
Johansson et al. [35]	N: 31 55.3 ± 7.3 years EG: not specified EG + CB: not specified	EG: standardized exercise program [64]	EG + CB: try compression bandages during standardized exercise program [64]	Volume displacement EG: increased total arm volume after exercise ($p < 0.05$) EG + CB: increased total arm volume after exercise ($p < 0.05$)
Johansson et al. [48]	IG: N: 23 58 ± 8 years	IG: Compressive sleeve (compression grade 23–32 mmHg) and isometric exercise		Water displacement IG: Lymph absolute volume reduction of 21 ml ($p = 0.03$).
Kasseroller and Brenner [40]	IG: N: 41 57.4 ± 8.9 years	MLD + CPG: MLD from Monday to Friday + conventional low-stretch compressive bandage every 7 days	MLD + alginate CPG: MLD fom Monday to Friday + alginate semi-rigid bandage on Friday	Volume difference MLD + CPG:Total arm volume arm decreases of 264.5 ml (8.5 %). MLD-alginate CPG: Total arm volume arm decreases of 322.5 ml (10.5 %).
Kim et al. [50]	AED: N: 20 50.5 ± 10.6 years NAEG: N: 20 50.9 ± 9.2 years	AEX: MLD + compression therapy + remedial exercise + active exercise 1x/day over 14 days	NAEX: MLD + compression therapy + remedial exercise 1x/day over 14 days	Arm circumference AEX: reduction in the proximal arm ($p < 0.05$). NAEX: reduction in the proximal arm ($p < 0.05$).

Table 2 continued

Study	Participants (Groups, N) mean age ± SD or (range)	Protocol group A	Protocol group B	Outcomes results
King et al. [41]	CBG: N: 10 57 (44–69 years) CPG: N: 10 64. 5 (52–76 years)	CBG: CDT from Monday to Friday over 2 weeks and compression glove.	CPG: CDT from Monday to Friday over 2 weeks and compressive bandage.	Volumetric measurement CBG: median reduction of 50 ml after 3 months CPG: median reduction of 97.5 ml after 3 months
Kozunaglu et al. [51]	CPG: N: 24 51.2 ± 10.3 years LLG: N: 23 45.4 ± 9.9 years	CPG: 2 h of compression therapy (pressure 60 mmHg) for 4 weeks	LLG: 20 min low laser therapy (2800 Hz, 1.5 J/cm^2) 3x/week for 4 weeks	Arm circumference; arm circumference differences between groups ($p = 0.030$) after 4 months
Letellier et al. [52]	ALG: N: 13 56.4 ± 9.8 years CG: N: 12 53.4 ± 9.4 years	ALG: aqua exercise 60 min weekly + exercise of a DVD [65] over 25–30 min over 12 weeks	CG: DVD exercise [65] over 12 weeks	Water displacement ALG: Volume reduction of 1.1 % ($p = 0.300$) CG_ Volume reduction of 0.4 % ($p = 0.908$)
Loudon et al. [53]	EG: N: 15 55.1 (±2.5 years) CG: N: 13 60.5 (±3.6 years)	EG: Yoga weekly 90 min (DVD) + MLD + compression sleeve	CG: MLD + compression sleeve + self massage + skin care	Arm circumference between groupo changes ($p = 0.032$), to the significant increase in the EG (25.72 ml) after 12 weeks
Maher et al. [54]	IG: N: 15 60 ± 12 years EG: N: 15 46 ± 10 years	IG (Oedema patient): MLD	EG: (without oedema): MLD	Arm volume by perometry IG: acute effects: oedema increases by median of 32.8 ml EG: acute effects: oedema increases by median of 0.08 ml
Maldonado et al. [42]	CPG: N: 10 ASCG: N: 10	CPG: compression sleeve of 15 - 20 mmHg during 4 weeks, then to discontinue for the following 4 weeks and than again to use for 4 weeks.	ASCG: only stem cell mobilization	Volume measurement based on circumference
Malicka et al. [27]	EG: N: 23 63.6 ± 6.8 years CG: N: 15 63.8 ± 9.2 years	EG: Nordic walking (40 min) over 8 weeks.	CG: rehabilitation programme (no physical activity)	Volume measurement based on circumference No significant differences in both groups
Malicka et al. [55]	CPG: N: 14 60.1 ± 6.3 years CG: N: 15 59.5.8 ± 5.7 years	CPG: Kinesiotaping	CG: no anti-oedema treatments	Volume measurement based on circumference CPG: differences between pre- and post-measurements ($p = 0.0009$) CG: no significant difference
McKenzie et al. [28]	EG: N: 7 56.4 ± 10.4 years CG: N: 7 56.9 ± 20.6 years	EG: sleeve and resistance exercise over 8 weeks	CG. activity of daily living	Circumferences (cm) No significant reduction in both groups
Partsch et al. [38]	CPGL: N: 18 adults CPGH: N:18 adults	CPGL: multi-component short stretch bandages between 20 and 30 mmHg	CPGH: multi-component short stretch bandages between 44 and 58 mmHg	Water volumetry No significant reduction in both groups
Pilch et al. [56]	ICP 1: N: 17 57.6 ± 9.6 years ICP 2: N: 9 58.0 ± 7.6 years ICP 3: N: 11 60.1 ± 12.7 years ICP 4: N: 20 55.3 ± 10.0 years	ICP 1: one-to-one cycle of compression and intercall (90 s-: 90 s) with a single chamber sleeve ICP 2: one-to-one cycle of compression and intercall (90 s-: 90 s) with a three chamber sleeve	ICP 3: three-to-one cycle of compression and intercall (45 s -: 15 s) with a single chamber sleeve ICP 4: three-to-one cycle of compression and intercall (90 s -: 90 s) with a three chamber sleeve	Volume measurements before and after 5 weeks reductions in relative oedema found in all groups after 5 weeks ($p < 0.05$)

Table 2 continued

Study	Participants (Groups, N) mean age ± SD or (range)	Protocol group A	Protocol group B	Outcomes results
Randheer et al. [57]	CDT: N: 25 52 (30–76 years)	CDT: MLD for 45 min, compression bandage, skin care and isotonic exercise over 4 weeks		Volume measurement based on circumference and volumetry 224.7 ml volume reduction ($p < 0.001$)
Ridner et al. [44]	PCG1: N: 21 50.8 ± 8.1 years PCG2: N: 21 56.9 ± 8.1 years	PCG1: pneumatic compression treatment to truncal/chest/arm (9.0 ± 4.2–13.7 ± 4.9 mmHg) over 36 min	PCG2: pneumatic compression treatment to arm (9.0 ± 4.2–13.7 ± 4.9 mmHg) over 36 min	Volume measurement based on circumference No significant changes in both groups
Ridner et al. [58]	MLG: N: 16 67.5 ± 10.3 years LLG: N: 15 66.4 ± 11.3 years MLG + LLG: N: 15 66.0 ± 10.2 years	MLG: MLD for 40 min and bandages	LLG: 20 to 30 s per point MLG + LLG: 20 min low laser therapy, followed by 20 min of MLD.	Volume measurement based on circumference oedema reductions in all groups ($p < 0.001$)
Schmitz et al. [59]	EG: N: 71 56 ± 9 years CG: N: 70 58 ± 10 years	EG: start with 13 weeks of 90 min supervised weight-lifting (2x/week) then unsupervised exercise for 39 weeks	CG: participants were asked not to change their exercise level during study period	Interlimb volume difference (%) No significant differences between the two groups
Sitzia et al. [60]	MLG: N: 15 68.0 ± 10.8 years SLD: N: 13 75.0 ± 10.2 years	MLG: MLD (40 to 80 min) + bandaging	SLD: less complex technique based on the principle of MLD (appr. 20 min) + bandaging	Volume measurement based on circumference MLG: % change in excess limb volume was 33.8 % SLD: % change in excess limb volume was 22 %
Stout et al. [33]	MLG: N: 43 55.3 ± 12.1 years CG: N: 53 53.4 ± 12.3 years	MLG: light-grade compression garments worn daily (20 to 30 mmHg)	CG: no lymphatic oedema	Volume measurements with Perometer MLG: Limb volume decreases of 46 ml (± 103 ml/4.1 %) CG: Limb volume decreases of 2.3 ml (± 103 ml/0.7 %)
Szuba et al. [61]	IPC: N: 12 68.8 ± 9.11 years MLG: N: 11 65.0 ± 10.8 years	IPC: daily MLD (30 min at 40–50 mmHg) + compression bandage	MLG: daily MLD + compression bandage	Water displacement volumetry at baseline and follow-up (day 30) Reduction of oedema in IPC = 45.3 % and MLG = 26.0 % ($p < 0.05$)
Tsai et al. [62]	MLG: N: 21 KMLG: N: 20 54.6 (36–75 years)	MLG: MLD (30 min), skin care, 60 min PCT (at 40 mmHg), bandaging (20 min) and exercise (20 min) 5x/week	KMLG: MLD (30 min), skin care, 60 min PCT (at 40 mmHg), Kinesiotaping and exercise (20 min) 5x/week	Arm volume (ml: Water Displacement Volumetry) and Circumference after 4 weeks and 3-month follow-up. Reduction of water displacement and circumference in the MLG after 4 weeks ($p < 0.05$)
Uzkeser et al. [63]	MLG: N: 15 56 (37–75 years) PCG: N: 16 55 (42–75 years)	MLG: MLD, skin care, compression bandage, compression garments and exercise, 5x/week (3 weeks)	PCG: MLD, skin care, 45 minPCT (at 40 mmHg), and exercise, 5x/week (3 weeks)	Volume measurement based on circumference after 3 weeks and 7 weeks. MLG: after 3 weeks: −630 ml ($p = 0.001$) and after 7 weeks: −510 ml (Pp = 0.005) PCG: −500 ml after 3 weeks ($p = 0.001$) and after 7 weeks: −500 ml ($p = 0.016$).

Table 2 continued

Study	Participants (Groups, N) mean age ± SD or (range)	Protocol group A	Protocol group B	Outcomes results
Vale et al. [34]	CPG: N: 9 EG: N: 9 57.8 (34–78 years)	CPG: 4 periods of exercise (12 min) with 3-min breaks inbetween + compression sleeve (60 %:40 % cotton-polyester textile: Gorgurão)	EG: 4 periods of exercise (12 min) with 3-min breaks inbetween	Lymphoedema volume at baseline and immediately after intervention CPG: decreased volume ($p = 0.001$)

F female, *M* man, *AEG* active exercise group, *ALG* aqua lymphatic group, *ASCG* autologous stem cell group, *CON* control group, *CB* compression bandage, *CBG* compression bandage group, *CBGL* compression bandage group low pressure, *CBGH* compression bandage group high pressure, *CDT* complex decongestive therapy, *CPG* compression group, *EG* exercise group, *IPC* intermittent pneumatic compression, *KMLG* Kinesiotape manual lymphatic group, *LLG* low laser group, *MLD* manual lymph drainage, *MLG* manual lymphatic group, *NAEG* nom active exercise group, *PCG* pneumatic compression group, *WCPG* without compression Group, *h* hour

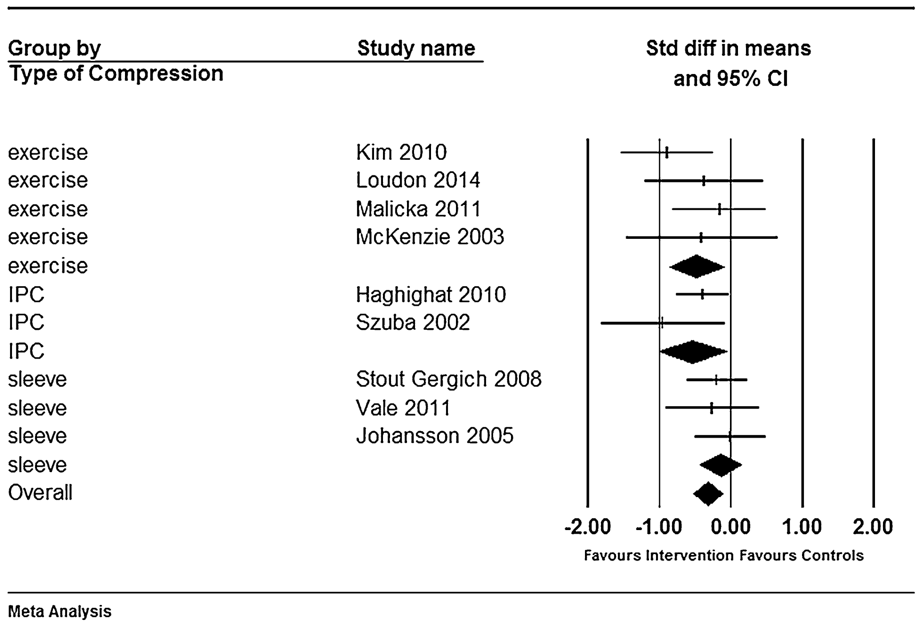

Fig. 2 Forest plot presenting the effects of intermittent pneumatic compression (IPC), use of a sleeve and exercise on the reduction of lymphoedema in patients with breast cancer based on the RCT-designed studies. Values on *x*-axis denote standardized mean differences. The *diamond* illustrates the 95 % confidence interval of the pooled effects. The *horizontal line* at the diamond illustrates the 95 % prediction intervals indicating that 95 % of the future studies will lie within this interval

comparison to pre-operative volume [33]. The effect on oedema volume reduction was limited to 50 ml. These results were to be expected since a compression sleeve is not a treatment modality to reduce volume but to maintain the leanest volume. Therefore, a sleeve should not be used in the intensive phase unless the sleeve is provided very early after onset of lymphoedema, as was the case in the study of Stout-Gergich [33]. In the treatment of severe lymphoedema, a compression sleeve should be provided by the start of the maintenance phase to limit the risk of volume increase. In a large cohort study, it was demonstrated that patients who adhere to wearing the compression sleeve have the lowest risk for regaining oedema volume [36].

For the pre–post results, we were able to extract data concerning the use of bandages, IPC, compression sleeve and exercises. These results were based on a comparison between baseline measurements and measurements taken at the end of the intervention; therefore, no control group is available. Again, all interventions relate to the intensive phase of BCRL treatment.

Eight samples from five studies were selected to demonstrate the effect of compression bandages [37–41]. Overall, it was shown that bandaging has the ability to decrease the oedema volume in the intensive phase. As demonstrated by the different samples, therapists need to be aware that the pressure provided by the bandages must be optimal [37, 38]. Compression bandaging reduces volume more and faster when compared to wearing a compression sleeve in the intensive phase of the consensus treatment [41].

Continuing with the results concerning compression sleeve, we were able to extract data from three studies [41–43]. Comparable to the results from the RCT's,

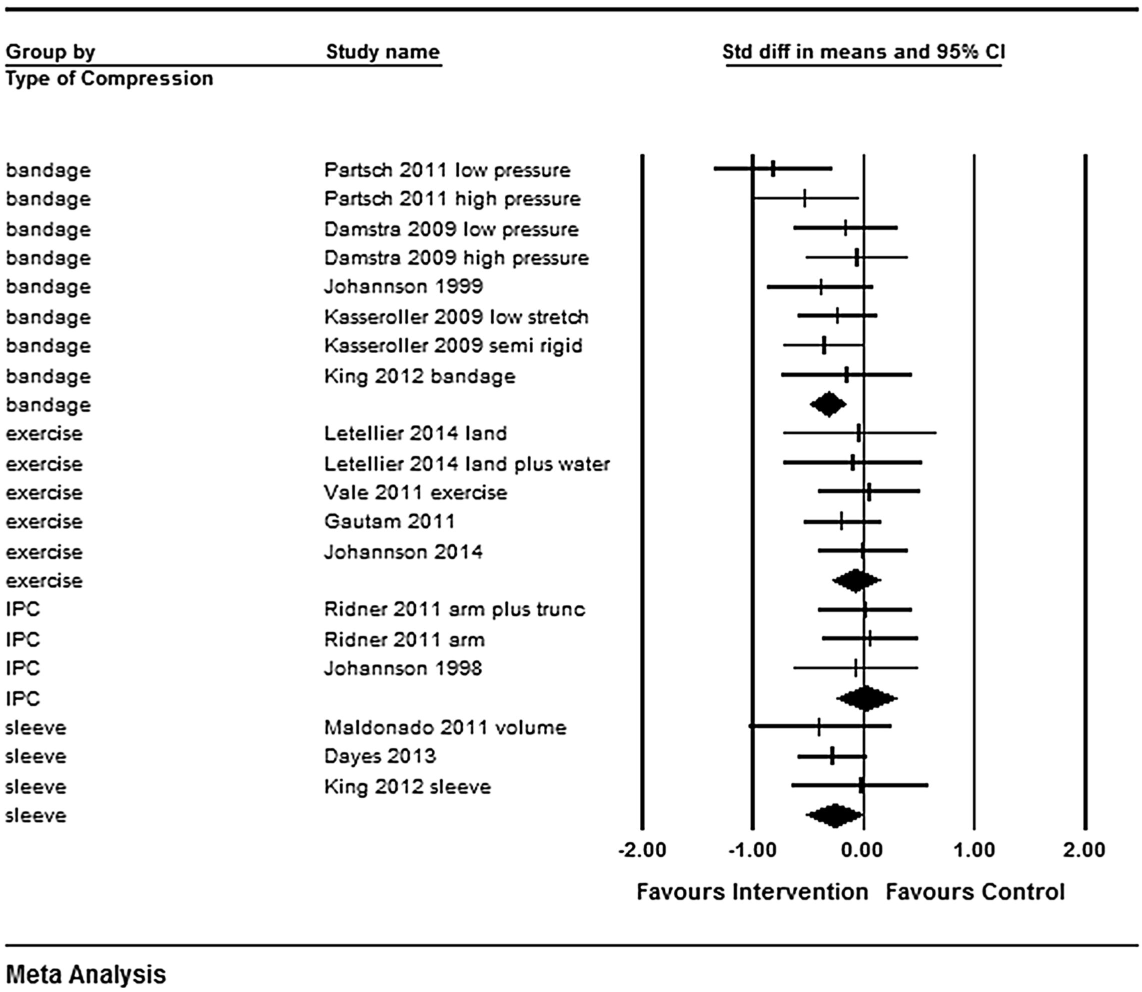

Fig. 3 Forest plot presenting the effects of bandage, intermittent pneumatic compression (IPC), use of a sleeve and exercise on the reduction of lymphoedema in patients with breast cancer based on the (uncontrolled) pre–post-intervention data. Forest plot of the effects of WBV plus exercise compared to exercise on TUG. Values on *x*-axis denote standardized mean differences. The *diamond* illustrates the 95 % confidence interval of the pooled effects. The *horizontal line* at the *diamond* illustrates the 95 % prediction intervals indicating that 95 % of the future studies will lie within this interval

compression sleeves had a low effect on volume reduction in the intensive phase. The small reduction of volume by wearing a compression sleeve is due to the increased interstitial pressure, limiting filtration. (ref: http://www.woundsinternational.com/media/issues/212/files/content_177.pdf) As stated before, compression sleeves are more appropriate in the maintenance phase.

In contrast to the results from the RCT's, IPC [44, 45] as well as exercise [34, 46–48] effect sizes from the pre–post-designed studies showed no benefit on volume reduction. Especially for IPC, the results demonstrated a very low effect size, confirming that IPC is not a standalone therapy. For exercises, however, it is a mixed story. Low effect sizes were found in the study that did not include compression during exercise. [34] The studies that did combine exercise and compression demonstrated a better result: Gautam et al. [47] demonstrated a 122 ml reduction during exercise.

Unfortunately, the research question "what are the effects of compression bandages and active exercise on the reduction of lymphoedema volume in breast cancer patients during the intensive phase?" could not be answered conclusively. This conclusion is based upon the many encountered limitations in the selected papers. Therefore, several limitations of the current systematic review and meta-analysis need to be discussed. Overall, we were confronted with a low number of studies that reported on the outcomes selected for this meta-analysis and unfortunately most of them had but poor to moderate methodological quality. Due to the consensus treatment proposed by the ISL, it is difficult to select studies that scope only one treatment modality. Recently, two

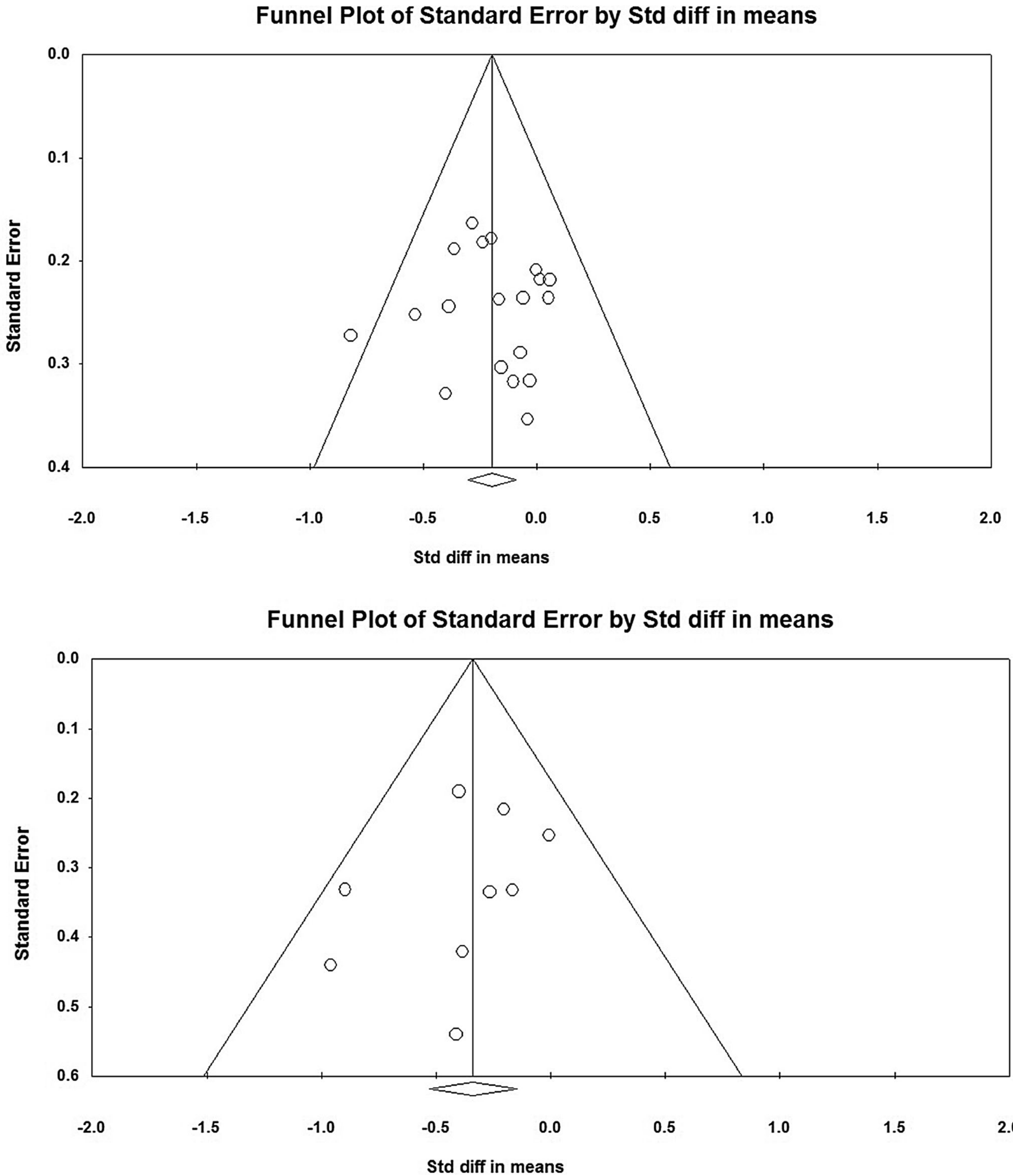

Fig. 4 Funnel plots for the meta-analyses based on RCTs (*left*) and based on one-arm pre–post studies (*right*)

Cochrane reviews were published concerning the added value of MLD in the consensus treatment demonstrating likewise difficulties [14, 15]. In studies reporting from the consensus treatment, no information about the separate effects of the different modalities are reported. Many of the selected studies provided a general treatment based upon the consensus treatment and added the treatment modality of interest to the experimental group [23, 25, 43]. Besides the low number of studies, sample sizes of the selected studies were also low (n ranged from 7 to 56 patients). Furthermore, a risk of publication bias cannot be excluded. However, we believe that this risk is limited since a rigorous search was performed in different databases, and no real critical asymmetry was observed in the funnel plots.

Conclusion

This systematic review and meta-analysis showed some evidence that active exercising may reduce oedema volume in BCRL. IPC seems beneficial in helping to reduce the oedema volume in the acute phase of treatment, while compression sleeves do not aid in the volume reduction in the acute phase but they do prevent additional swelling. All conclusions should be taken with precautions because of the insufficient quality of the selected papers.

Compliance with ethical standards

Conflict of interests The authors report no conflicts of interest.

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