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Title: The Effectiveness of Cryo or Compression Therapy in Preventing Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review and Network Meta-Analysis

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Clinical Question Box

Is Cryotherapy or Compression Therapy Recommended for Preventing Chemotherapy-Induced Peripheral Neuropathy (CIPN) in Patients Undergoing Cytotoxic Regimens?

Various cryo- and compression therapy interventions have been evaluated for the prevention of CIPN. Although the certainty of evidence remains low, cryotherapy—particularly continuous cooling and the use of frozen gloves—is strongly suggested for CIPN prevention due to its demonstrated efficacy. For patients who cannot tolerate cryotherapy, the use of surgical gloves may be considered, although the recommendation is supported by limited evidence.

Abstract

Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is a common, dose-limiting adverse effect of neurotoxic chemotherapy agents. Despite its prevalence and clinical significance, effective preventive strategies are limited. Cryo- and compression therapy have emerged as promising non-pharmacological interventions.

Methods: A comprehensive literature search was performed across PubMed, Embase, Cochrane Library, and Web of Science up to March 31, 2025. Eligible studies included randomized controlled trials and self-controlled trials assessing the preventive efficacy of cryotherapy-related interventions in adult cancer patients undergoing neurotoxic chemotherapy. The primary outcome was the incidence of CIPN. A frequentist random-effects network meta-analysis was conducted to estimate odds ratios (ORs).

Results: A total of 13 studies involving 865 patients were included in the analysis. Cryotherapy was found to be associated with a significant reduction in CIPN incidence compared to usual care (OR: 0.32, 95% CI: 0.17–0.60), followed by compression therapy (OR: 0.44, 95% CI: 0.21–0.94). Among the specific modalities evaluated, continuous cooling (OR: 0.25, 95% CI: 0.07–0.93) and frozen gloves (OR: 0.28, 95% CI: 0.12–0.68) showed the highest preventive efficacy. The surface under the cumulative ranking curve (SUCRA) values supported these findings, with cryotherapy ranked as the most effective intervention overall (SUCRA = 0.873), particularly continuous cooling (0.734) and frozen gloves (0.714).

Conclusion: Cryotherapy, especially continuous cooling and frozen gloves, emerged as the most effective non-pharmacological intervention for preventing CIPN. Compression therapy also showed potential as an alternative, though the certainty of evidence remains low.

Keywords: chemotherapy-induced peripheral neuropathy, CIPN, cryotherapy, compression therapy, cryocompression, meta-analysis

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent and often dose-limiting side effect associated with various chemotherapeutic agents, particularly taxanes, platinum-based compounds, vinca alkaloids, and proteasome inhibitors.[1] An estimated 41.2% of chemotherapy patients develop symptoms that may persist over time.[2] The incidence rates vary depending on the specific agent, cumulative dose, patient age, comorbidities, and presence of preexisting neuropathy.[3] In some studies, the prevalence of CIPN has been reported to range from 19% to over 85% within the first month following chemotherapy completion.[4,5] The clinical manifestations of CIPN are diverse and typically include numbness, tingling, burning sensations, and pain, predominantly in the hands and feet.[6] These sensory disturbances can persist for months or even years, substantially impairing patients' quality of life, physical functioning, and emotional well-being.[7] Beyond personal discomfort, the burden of CIPN extends to healthcare systems and society at large. The symptoms often lead to treatment delays, dose reductions, or even discontinuation of chemotherapy, potentially compromising oncologic outcomes.[8] Moreover, chronic CIPN contributes to long-term disability and increased medical costs due to the need for supportive care, rehabilitation, and pharmacological interventions. Despite its high prevalence and significant impact, there is a lack of effective, evidence-based strategies for the prevention of CIPN, highlighting a critical unmet need in oncology supportive care.[9]

Various pharmacological and non-pharmacological interventions have been proposed for preventing or mitigating CIPN.[10] Pharmacological treatments, including duloxetine, gabapentin, and antioxidants, have shown limited and inconsistent effectiveness in clinical trials.[11] Furthermore, the potential for adverse effects associated with these agents has curtailed their widespread adoption for CIPN prevention.[12] As a result, non-pharmacological strategies have

gained attention due to their favorable safety profiles and feasibility in clinical practice. Among the non-pharmacological modalities, physical therapy, acupuncture, limb hypothermia, and compression interventions are promising candidates.[13] Cryotherapy, which involves the application of cold (via frozen gloves, socks, or gel packs) to peripheral extremities during chemotherapy infusion, aims to reduce local blood flow and thereby limit the exposure of peripheral nerves to neurotoxic agents.[14] Similarly, compression therapy involves using garments or surgical gloves one size smaller than the limb to apply pressure, potentially inducing transient vasoconstriction and achieving a comparable pharmacokinetic effect.[15] These interventions are relatively simple, low-cost, and well-tolerated by most patients, making them attractive options for routine clinical use.

Recent randomized controlled trials and observational studies have explored the effectiveness of cryotherapy and compression therapy in preventing CIPN, particularly among patients receiving Taxane- or platinum-based chemotherapy.[16,17] While many studies have reported significant alleviation of symptoms, others revealed inconclusive or negative findings due to variations in study design, treatment protocols, and outcome measures.[18,19] Previous meta-analyses have often examined these interventions separately, lacking integrated comparisons.[14,15] To bridge this gap, we conducted a systematic review and network meta-analysis (NMA) to evaluate the comparative efficacy of cryotherapy and compression therapy. By leveraging direct and indirect evidence, our NMA offers a comprehensive assessment to support clinical decision-making and guide future research in supportive oncology care.

Methods

Protocol and Registration

This systematic review and network meta-analysis (NMA) were conducted according to the PRISMA-NMA guidelines.[20,21] The protocol was prospectively registered in the University Medical Information Network (UMIN000057786).[22]

Eligibility Criteria

The inclusion criteria comprised RCTs that met the following conditions: (1) evaluated the preventive effects of cryotherapy, compression therapy, or cryocompression therapy on CIPN; (2) enrolled adult patients (aged ≥18 years) receiving neurotoxic chemotherapy; (3) assessed CIPN occurrence as an outcome of the intervention; and (4) included self-controlled designs, which were considered acceptable. Studies were excluded if they met any of the following criteria: (1) the intervention was not intended for prevention; (2) the study was not a randomized controlled trial; or (3) the data were not comparable.

Information Sources and Search Strategy

A comprehensive literature search of the PubMed, Embase, Cochrane Library, and Web of Science databases was conducted, with the final search updated on March 31, 2025. The search strategy utilized a combination of keywords related to "chemotherapy-induced peripheral neuropathy"and "CIPN" to identify the target patient population; terms such as "cryotherapy," "cold," "compression," "cryocompression," "hypothermal," and "surgical gloves" to capture relevant interventions; and the keyword "randomized" to identify randomized controlled trials (Table S1). No language restrictions were applied during the search.

Study Selection

Data were extracted by H.C. and K.H. using a standardized form and cross-checked for consistency, with any discrepancies resolved by consensus. Collected information included study characteristics (author, year, country, design, and sample size), patient characteristics (cancer type, age, chemotherapy regimen), intervention details (type of cryotherapy or compression, temperature, duration, and timing), and outcomes such as the incidence of CIPN. Titles and abstracts were independently screened for eligibility. Full texts of potentially relevant articles were assessed for inclusion. Discrepancies were resolved through discussion or consultation with a third reviewer (M. K.).

Outcome

Due to variations in scoring scales across different CIPN assessment tools, the outcome of CIPN was primarily defined as a Common Terminology Criteria for Adverse Events (CTCAE) grade greater than 1 to allow inclusion of a broader range of studies. For continuous outcome measures such as the Functional Assessment of Cancer Therapy–Neurotoxicity (FACT-NTX), CIPN was defined as a ≥10% increase or an absolute increase of ≥6 points. Cryotherapy interventions included continuous cooling (hilotherapy), ice bags, or frozen gloves. CIPN incidence was regarded as the primary outcome.

Summary Measures

The incidence of CIPN was estimated using odds ratios (ORs) with 95% confidence intervals (CIs). A frequentist random-effects network meta-analysis was conducted to account for between-study heterogeneity, and consistency assessed using node-splitting and global inconsistency tests. Surface Under the Cumulative Ranking (SUCRA) probabilities were

calculated to rank the relative efficacy of each intervention. Analyses were performed using the meta and netmeta packages in R (version 4.4), where meta facilitated pairwise meta-analysis and netmeta supported the network meta-analysis, including random-effects models and the calculation of SUCRA values.

Assessment of Inconsistency

Inconsistency in the network was assessed using both local (node-splitting) and global (design-by-treatment interaction) methods. Inconsistency was considered significant if the p-value was <0.05. The risk of bias was independently assessed by two reviewers using the Cochrane Risk of Bias 2.0 tool, with each domain rated as low risk, some concerns, or high risk. The results were summarized in a risk-of-bias table. Publication bias and small-study effects were evaluated using comparison-adjusted funnel plots and Egger's test. The certainty of evidence across the network was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for NMA.

Results

Study Selection and Characteristics

After searching the databases, 815 studies were identified. Subsequently, 95 duplicate records were removed, followed by the exclusion of 604 and 44 articles during the first and second screenings, respectively (Figure S1). Finally, 13 studies comprising 865 patients were included in the NMA to evaluate the efficacy of various interventions in preventing CIPN (Table 1).[23-35] These studies were conducted between 2018 and 2024, comprising eight RCTs and five self-controlled trials from multiple countries, including the USA, Japan, Belgium, the Netherlands, China, Thailand, and Singapore. Sample sizes ranged from 36 to 194 participants, with mean ages between 50.5 and 65 years. Most studies focused on taxane-based chemotherapy, while a few involved platinum or Oxaliplatin regimens. Cancer types primarily included breast, gynecologic, and digestive cancers. CIPN was assessed using various criteria, including CTCAE ≥ Grade 2, NTX ≥ 6-point increase, and GOG-NTX >10% increase. Follow-up durations ranged from 12 weeks to 9 months. Interventions mainly involved physical cooling methods such as frozen gloves, compression garments, surgical gloves, ice bags, or continuous cooling, with most studies comparing these strategies to usual care as control groups.

Summarized Efficiency in CIPN Prevention

The network graph illustrating studies involving compression, cryotherapy, and cryocompression is presented in Figure 1A. Seven studies compared cryotherapy with usual care. The direct comparisons are shown in Figure 2A. Among all interventions, cryotherapy demonstrated the greatest efficacy, with an OR of 0.32 (95% CI: 0.17–0.60), followed by compression therapy with an OR of 0.44 (95% CI: 0.21–0.94), and cryocompression with an OR of 0.53 (95% CI: 0.20–1.43).

The results of the NMA are summarized in Table 2. Although cryotherapy was not significantly more effective than compression or cryocompression, it was confirmed to be significantly more effective than the placebo. The ranking of treatment efficacy is illustrated in Figure S2. Cryotherapy had the highest probability of being the most effective treatment (SUCRA = 0.873), followed by Compression (0.589) and Cryocompression (0.498). The Control group ranked the lowest (0.039).

Detailed Efficiency in CIPN Prevention

The network graph illustrating studies involving compression, cryotherapy, and cryocompression is presented in Figure 1B. Five studies compared frozen gloves with usual care, and two studies compared surgical gloves. The direct comparisons are shown in Figure 2B. Among all interventions, continuous cooling demonstrated the greatest efficacy, with an OR of 0.25 (95% CI: 0.07–0.93), followed by frozen gloves with an OR of 0.28 (95% CI: 0.12–0.68), ice bags with an OR of 0.38 (95% CI: 0.06–2.50), surgical gloves with an OR of 0.41 (95% CI: 0.14–1.21), compression gloves with an OR of 0.45 (95% CI: 0.08, 2.60), and surgical gloves with ice bags with an OR of 0.58 (95% CI: 0.12, 2.80).

The results of the NMA are summarized in Table 3. Although continuous cooling and frozen gloves did not show statistically significant superiority over other therapies, they were confirmed to be significantly more effective than placebo, as indicated by the previously presented ORs. Treatment efficacy ranking is illustrated in Figure S3. Among the interventions assessed, continuous cooling had the highest SUCRA value (0.734), followed closely by frozen gloves (0.714), suggesting superior efficacy in preventing CIPN. Ice bags (0.554), surgical gloves (0.522), and compression gloves (0.493) showed moderate rankings. Surgical gloves with ice (0.369) were less effective, and the control group had the lowest SUCRA value (0.115).

Sensitivity Analysis of CIPN Prevention

A sensitivity analysis including all RCTs was conducted, with the network graph presented in Figure S4. Four studies compared frozen gloves with usual care. Among all interventions, frozen gloves demonstrated the greatest efficacy, with an OR of 0.22 (95% CI: 0.05–1.06), followed by surgical gloves (OR: 0.29; 95% CI: 0.02–4.42), compression gloves (OR: 0.40; 95% CI: 0.03–5.23), ice bag (OR: 0.48; 95% CI: 0.01–16.47), continuous cooling (OR: 0.50; 95% CI: 0.03–7.40), and surgical gloves with ice bags (OR: 0.78; 95% CI: 0.01–64.72). The results of the NMA are summarized in Table S2. No treatment demonstrated clearly superior efficacy over the others. The ranking of interventions is illustrated in Figure S6. Among the assessed treatments, frozen gloves had the highest SUCRA value (0.705), followed by surgical gloves (0.594), compression gloves (0.543), continuous cooling (0.496), ice bag (0.495), surgical gloves with ice (0.392), and control (0.275).

Bias and Certainty of evidence

The risk of bias is presented in Figure S4. Three studies were assessed as having a low risk of bias, while the remaining five were judged as having some concerns or a high risk of bias. For summarized therapy, no significant inconsistency was found ($p = 0.08$), and Egger's test also indicated no bias ($p = 0.12$). For detailed treatment, significant inconsistency was observed overall ($p = 0.01$), mainly due to between-design heterogeneity ($p = 0.02$), while within-design heterogeneity was not significant ($p = 0.12$). Egger's test showed no publication bias ($p = 0.23$). The certainty of evidence assessed by GRADE was low for the suggestion that continuous cooling or frozen gloves are effective, primarily due to the risk of bias and imprecision.

Discussion

This NMA synthesized evidence from 13 studies to compare the effectiveness of cryotherapy, compression therapy, and cryocompression in preventing CIPN. Our findings indicated that cryotherapy, particularly continuous cooling and frozen gloves, demonstrated the highest efficacy in reducing the incidence of CIPN, followed by compression therapy. These findings are consistent with previous meta-analyses that evaluated cryotherapy and compression therapy separately, but our integrated network analysis provides a more comprehensive comparison of various physical interventions.[36,37] Notably, the SUCRA values ranked continuous cooling and frozen gloves highest, highlighting their potential as first-line non-pharmacological interventions. A recently published article also confirms this finding.[38] This study builds upon earlier research by directly and indirectly comparing and evaluating newer modalities such as cryocompression.

These findings have significant clinical implications, particularly considering the limited effectiveness and adverse effects of pharmacological agents used to prevent CIPN.[39] Cryotherapy and compression therapy are simple, cost-effective methods that are generally well tolerated. Although there were concerns about cold sensitivity, especially with oxaliplatin, most patients managed the side effect well, and some even reported a reduction in throat discomfort.[40] Hilotherapy, which uses milder cooling around 10 ℃, is usually better tolerated than traditional cryotherapy, which involves using frozen gloves or ice packs that reach temperatures below-20 ℃.[26] However, practical issues exist, such as limited mobility, difficulty with IV insertion due to cold-induced vessel constriction, and the need for multiple glove changes, freezers, and additional nursing support. Patients with Raynaud's or peripheral vascular disease may not be eligible.[41] These logistical demands can affect chemotherapy workflows, as seen with scalp

241 cooling. Although there is a theoretical concern that cooling could create areas for cancer to spread,
242 current evidence does not show higher relapse rates. Given the impact of chemotherapy-induced
243 nerve damage, integrating these non-drug approaches may improve outcomes. Further studies are
244 needed to confirm long-term safety and effectiveness and to standardize treatment protocols.

245 Although cryocompression combines the effects of both cryotherapy and compression,
246 current evidence does not consistently demonstrate its greater efficacy over either modality used
247 independently. One possible reason is that the simultaneous application of cold and compression
248 may not result in additive benefits; instead, it may alter the physiological response in ways that do
249 not significantly enhance efficacy.[42] The small sample size may be another reason
250 cryocompression's efficiency in preventing CIPN is not identified. A recent study revealed the
251 possibility of cryocompression. [43] Variability in protocols across studies, including differences in
252 pressure levels, temperature settings, and application duration, also complicates direct
253 comparisons and may contribute to the absence of clear benefits. Therefore, while
254 cryocompression appears promising in theory, further well-controlled trials are needed to clarify
255 its comparative advantages.

256 Several limitations should be acknowledged. First, the included studies displayed
257 substantial variation in assessment methods, intervention protocols, dropout rates, and follow-up
258 durations, which may affect the applicability of our findings. Second, definitions of “usual care”
259 differed across studies and were often inadequately described, complicating comparisons between
260 interventions and control groups. Third, some studies exhibited a risk of bias, and the overall
261 certainty of evidence, as evaluated using GRADE, was low, which limits the confidence in our
262 conclusions. Fourth, while we incorporated both randomized controlled trials and self-controlled
263 studies to include as much relevant data as possible, this variation in study design may have

introduced inconsistency. Lastly, adverse events and dropout rates were inconsistently reported, precluding a comprehensive summary of safety and treatment adherence.

Conclusion

This NMA suggests that cryotherapy, particularly continuous cooling and frozen gloves, may be among the more effective non-pharmacological options for preventing CIPN; however, the certainty of evidence is low. Compression therapy also showed potential benefit and might be considered when cryotherapy is not feasible. Given the limitations in the current evidence base, these findings should be interpreted with caution. Further high-quality, adequately powered trials are needed to confirm these results and guide clinical implementation.

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Data Availability: The corresponding author shall make the datasets available upon reasonable request.

Ethical Statement: Institutional Review Board approval was waived due to the nature of the meta-analysis.

Conflict of Interest: The authors report no conflicts of interest in this work.

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Table 1: Characteristics and Background of Enrolled Studies

Author year	Country	CIPN Criteria	Design	Cases	Age (years)	FU	Regimen	Cancer type	Detailed Intervention
Accordino 2024	USA	NTX: ≥6-point increase	RCT	63	54.4 (14.2)	12w	Taxane	B	Frozen glove (–25 to –30°C) vs. compression garment glove vs. control group
Brunner 2024	Netherlands	CTCAE ≥ Grade 2	RCT	194	54.8 (12)	9m	Taxane	B&G	Surgical gloves and ice bags vs. ice bags
Chitkumarn 2022	Thailand	GOG-NTX: >10% increase	RCT	79	56.5 (12.2)	12w	Taxane	G	Frozen gloves (gel pack) vs. control group
Coolbrandt 2023	Belgium	CTCAE ≥ Grade 2	RCT	77	63.3(10.8)	24w	oxaliplatin	D	Continuous cooling vs. usual care
Guo 2024	China	CTCAE ≥ Grade 2	RCT	80	51.5 (10.7)	18w	Taxane	B	Surgical gloves vs. control group
Ng 2020	Singapore	CTCAE ≥ Grade 2	RCT	38	55.1(7.8)	9m	Paxtel	B	Frozen glove (-25-30°) vs. usual care
Ruddy 2019	USA	CTCAE ≥ Grade 2	RCT	42	51.5 (11.7)	6m	Taxane	B	Ice bags vs. control group
Shigematsu 2023	Japan	NTX: ≥6-point increase	RCT	38	N/A	12w	Taxane	B	Frozen glove (–20°C) vs. control group
Anastasio 2023	USA	CTCAE ≥ Grade 2	Self-control	69	65 (10.1)	22w	Taxane / Platinum	G	Surgical gloves with ice bags vs. control group
Coolbrandt 2022	Belgium	CTCAE ≥ Grade 2	Self-control	62	53.1(11.3)	24w	taxane	B	Frozen glove (–25 to –30°C) vs. continuous cooling
Hanai 2018	Japan	CTCAE ≥ Grade 2	Self-control	36	56 (13.8)	12w	Taxane	B	Frozen glove (–25 to –30°C) vs. control group
Kanbayashi 2020	Japan	CTCAE ≥ Grade 2	Self-control	38	57.6 (11)	12w	Taxane	B	Surgical gloves and frozen glove (–25 to –30°C) vs. control group
Kotani 2021	Japan	CTCAE ≥ Grade 2	Self-control	49	50.5 (12)	12w	Taxane	B	Surgical gloves vs. control group

CTCAE: Common Terminology Criteria for Adverse Events; GOG-NTX: Functional Assessment of Cancer Therapy‐Gynecologic Oncology Group‐Neurotoxicity; NTX: Functional Assessment of Cancer Therapy‐Neurotoxicity; RCT: randomized control trail; CIPN: Chemotherapy-Induced Peripheral Neuropathy; N/A: not available; FU: follow-up; m: months, w: weeks; B: breast cancer; G: Gynecologic Cancer; D: digestive system cancer; vs: versus

Table 2: Network meta-analysis comparing different interventions in the prevention of CIPN.

Cryotherapy			
0.71 [0.31; 1.64]	**Compression**		
0.60 [0.19; 1.60]	0.84 [0.26; 2.73]	**Cryocompression**	
0.32 [0.17; 0.60]	0.44 [0.21; 0.94]	0.53 [0.20; 1.43]	**Usual Care**

435 Table 3: Network meta-analysis comparing detailed interventions in the prevention of CIPN

Continuous cooling						
0.90 [0.25; 3.26]	**Frozen gloves**					
0.66 [0.07; 6.46]	0.73 [0.09; 5.83]	**Ice bag**				
0.62 [0.12; 3.14]	0.69 [0.20; 2.34]	0.94 [0.11; 8.19]	**Surgical gloves**			
0.56 [0.07; 4.50]	0.62 [0.11; 3.58]	0.85 [0.07; 11.01]	0.90 [0.12; 6.67]	**Compression gloves**		
0.43 [0.06; 3.32]	0.48 [0.08; 2.91]	0.66 [0.14; 2.99]	0.70 [0.10; 4.69]	0.77 [0.07; 8.10]	**Surgical gloves with ice**	
0.25 [0.07; 0.93]	0.28 [0.12; 0.68]	0.38 [0.06; 2.50]	0.41 [0.14; 1.21]	0.45 [0.08; 2.60]	0.58 [0.12; 2.80]	**Control**

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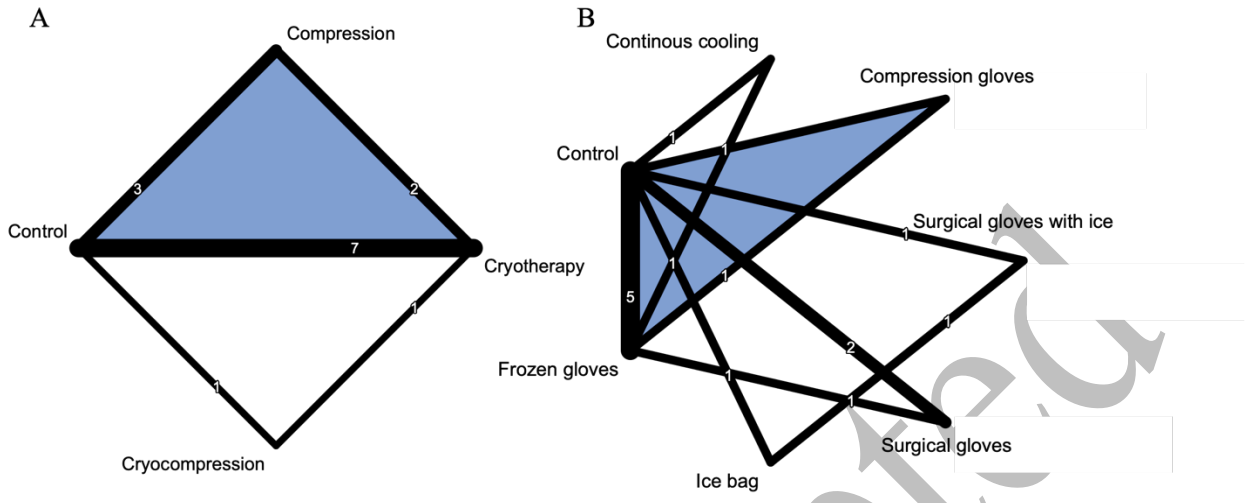
438 Figure 1. Network Graph of Enrolled Studies



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440 A: Summary of therapies; B: Detailed description of each therapy

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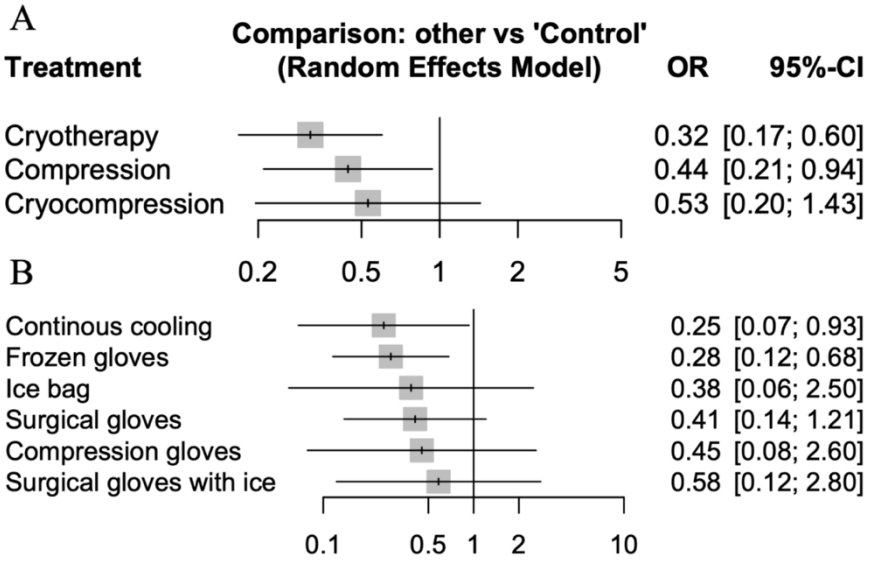
443 Figure 2. Direct Comparisons of Interventions Versus Control



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