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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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CRYOTHERAPY FOR THE PREVENTION OF TAXANE-INDUCED PERIPHERAL NEUROPATHY IN BREAST CANCER: A PROSPECTIVE MULTICENTER STUDY

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Abstract.

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting toxicity of taxane-based chemotherapy in breast cancer. Cryotherapy using cooling gloves and socks has been investigated as a preventive strategy, although evidence remains inconsistent. This study evaluated the effect of preventive cryotherapy on neuropathy-related pain and symptom burden in patients receiving taxane-containing chemotherapy.

Methods: This prospective multicenter controlled study included patients with stage I–IV breast cancer treated with taxane-based chemotherapy between March 2023 and September 2025. Patients either received cryotherapy during chemotherapy infusion or standard treatment without cryotherapy. Outcomes were assessed using the Edmonton Symptom Assessment System (ESAS) and EORTC QLQ-CIPN20 questionnaire. The primary outcome was final ESAS pain score. Secondary outcomes included clinically meaningful pain (ESAS ≥4), change in pain from baseline, neuropathy-related extremity pain, overall symptom burden, and functional impairment.

Results: A total of 190 patients were included (95 cryotherapy; 95 control) in the final analysis. No statistically significant difference was observed in adjusted final ESAS pain scores between groups, although a trend toward higher pain scores was observed in the cryotherapy group. Clinically meaningful pain (ESAS ≥4) was more frequent in the cryotherapy group (20.0% vs 8.4%; p = 0.022). Adjusted analyses demonstrated higher neuropathy-related extremity pain scores in the cryotherapy group. No significant differences were observed in overall symptom burden or functional impairment.

Conclusion: Preventive cryotherapy did not demonstrate a significant reduction in neuropathy-related pain in patients receiving taxane-based chemotherapy. Neuropathy-specific outcomes suggested higher extremity pain in patients undergoing cryotherapy. Further randomized studies with standardized protocols are warranted.

Key words. Cryotherapy, chemotherapy-induced peripheral neuropathy, taxane.

Introduction.

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and represents a major global health challenge. Advances in early detection and systemic therapies have significantly improved survival outcomes, leading to an increasing number of patients receiving systemic treatment. Among available chemotherapeutic agents, taxanes such as paclitaxel and docetaxel are widely used in the treatment of breast cancer across different disease stages due to their proven efficacy in improving oncologic outcomes [1].

Despite their therapeutic benefits, taxane-containing chemotherapy regimens are frequently associated with chemotherapy-induced peripheral neuropathy (CIPN), a dose-limiting toxicity that may significantly impair patients' quality of life [2]. CIPN predominantly affects sensory nerves and is commonly characterized by symptoms such as numbness, tingling, burning sensations, and neuropathic pain in the extremities [3]. The incidence of taxane-induced peripheral neuropathy varies depending on the specific drug and regimen, with reported rates ranging from approximately 42–70% for paclitaxel and 20–58% for docetaxel [4]. In many patients, these symptoms may persist long after the completion of chemotherapy and can interfere with daily functioning and psychological well-being [5]. Importantly, severe neuropathy may necessitate dose reductions, treatment delays, or discontinuation of chemotherapy [2].

Among the manifestations of CIPN, neuropathic pain represents a particularly distressing symptom for patients undergoing taxane therapy. Painful peripheral neuropathy may present as burning, electric shock-like sensations, hypersensitivity to touch, or persistent discomfort in the hands and feet, substantially worsening patients' overall symptom burden and daily functioning [3]. Effective prevention and management of this complication remain challenging, as the underlying pathophysiological mechanisms are not fully understood and currently available pharmacological treatments provide only limited benefit [6].

Several strategies have been explored for the prevention and management of CIPN. Current clinical guidelines primarily recommend symptomatic pharmacological treatment with antidepressants and anticonvulsants, in particular, Duloxetine; however, their effectiveness is limited and often restricted to a subset of patients [6]. Non-pharmacological approaches, including physiotherapy and physical exercise, have also been investigated, although evidence supporting their preventive efficacy remains inconclusive [7].

Cryotherapy, involving the application of cooling devices such as frozen gloves and socks during chemotherapy infusion, has been investigated as a potential preventive strategy. The proposed mechanism is based on localized vasoconstriction, which may reduce blood flow to distal extremities and

consequently limit the exposure of peripheral nerves to circulating chemotherapeutic agents [8]. Several clinical studies have suggested a potential protective effect of cryotherapy in reducing chemotherapy-induced peripheral neuropathy [8,9]. However, the overall body of evidence remains heterogeneous, with systematic reviews and clinical guidelines reporting inconsistent findings regarding its effectiveness in preventing both the incidence and severity of CIPN [6,10-12]. Differences in study design, patient populations, intervention protocols, and outcome measures contribute to this variability and limit the generalizability of existing data.

Therefore, this prospective controlled study aimed to evaluate the effect of preventive cryotherapy using cooling gloves and socks on neuropathy-related pain and overall symptom burden in patients with breast cancer receiving taxane-containing chemotherapy, using patient-reported outcome measures.

Materials and Methods.

Study design and setting:

This prospective, multicenter controlled study was conducted to evaluate the effect of preventive cryotherapy on neuropathy-related pain in patients with breast cancer receiving taxane-containing chemotherapy. The study was carried out across seven oncology centers in Tbilisi, Georgia.

Patient enrollment and data collection were performed between March 2023 and September 2025. All participants provided written informed consent prior to inclusion. The study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the Bioethical Committee at Ivane Javakhishvili Tbilisi State University (27.04.2022).

Participants:

Eligible participants were female patients aged 18–70 years with histologically confirmed stage I–IV breast cancer who were scheduled to receive taxane-containing chemotherapy. Patients were excluded if they had pre-existing peripheral neuropathy, diabetes mellitus, or Raynaud syndrome, as these conditions could independently affect peripheral nerve function or interfere with cryotherapy procedures.

Treatment regimens:

Patients received taxane-containing chemotherapy according to standard clinical practice. Treatment regimens included paclitaxel administered either weekly (80 mg/m²) or every two to three weeks (175 mg/m²), as well as docetaxel administered every three weeks (75 mg/m²). Taxanes were administered either as monotherapy or in combination with other chemotherapeutic or targeted agents, depending on individual treatment protocols.

Group allocation:

Participants were allocated into two groups based on their decision to undergo cryotherapy during chemotherapy infusion. The cryotherapy group (Group A) consisted of patients who received cooling gloves and socks during taxane administration, while the control group (Group B) included patients who received standard chemotherapy without cryotherapy.

Given the non-randomized nature of group allocation, potential baseline differences and confounding factors were addressed in the statistical analysis through adjusted regression models.

Cryotherapy intervention:

In the cryotherapy group, cooling gloves and socks were applied 15 minutes prior to the start of taxane infusion, worn throughout the infusion, and maintained for 15 minutes after completion of chemotherapy administration.

The cooling devices were pre-cooled to approximately -18 °C (device temperature) before application. To maintain a sustained cooling effect, gloves and socks were replaced periodically when their temperature approached approximately 0°C. This replacement strategy was used to preserve continuous cooling of the distal extremities during treatment.

The rationale for this intervention is based on the hypothesis that local cooling induces vasoconstriction, thereby reducing blood flow to peripheral tissues and potentially limiting the delivery of neurotoxic chemotherapeutic agents to peripheral nerves [8,9].

However, the actual temperature at the skin level and the degree of achieved vasoconstriction were not directly measured in this study.

Outcome measures.

Primary outcome:

The primary outcome was the severity of patient-reported pain at the final assessment, measured using the Edmonton Symptom Assessment System (ESAS). Pain intensity was rated on a numeric scale from 0 (no pain) to 10 (worst possible pain). The ESAS pain score was selected as the primary outcome to capture the global, multidimensional burden of pain in a real-world clinical setting, as it encapsulates overall patient discomfort that may arise not only from neurotoxicity but also from concurrent systemic therapy-related musculoskeletal symptoms.

Secondary outcomes:

Secondary outcomes included:

1. **Change in pain from baseline,** calculated as the difference between final and baseline ESAS pain scores.
2. **Clinically meaningful pain,** defined as an ESAS pain score ≥4 at the final assessment.
3. **Overall symptom burden,** assessed using the ESAS Symptom Distress Score (SDS-9), calculated as the sum of nine symptom items.
4. **Neuropathy-related extremity pain,** assessed using items derived from the EORTC QLQ-CIPN20 questionnaire, with a composite score calculated as the mean of pain scores in the upper and lower extremities.
5. **Functional impairment,** assessed based on patient-reported limitations in daily activities.

The EORTC QLQ-CIPN20 is a validated instrument designed to assess chemotherapy-induced peripheral neuropathy and its impact on patients' daily functioning [13].

All patient-reported outcomes were collected at baseline prior to initiation of chemotherapy and at the completion of treatment.

Statistical analysis:

Statistical analyses were performed using SPSS software (IBM Corp., Armonk, NY).

Continuous variables were summarized as mean ± standard deviation (SD) or median values where appropriate, while

categorical variables were presented as frequencies and percentages.

Baseline comparability between groups was assessed using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables.

To evaluate the effect of cryotherapy on final pain scores, an adjusted linear regression model (analysis of covariance, ANCOVA) was used. The model included treatment group as the main predictor and was adjusted for baseline pain score, age, disease stage, number of chemotherapy cycles, and taxane regimen.

Given the skewed distribution of pain scores with a high proportion of zero values, HC3 robust standard errors were additionally applied to account for potential heteroscedasticity and non-normality of residuals. ESAS pain scores were analyzed as continuous symptom severity measures, and nonparametric analyses were additionally performed where appropriate. Change-from-baseline pain scores were compared between groups using the Mann–Whitney U test.

Clinically meaningful pain (ESAS ≥4) was analyzed using logistic regression, adjusting for baseline pain score and taxane regimen. Results were reported as odds ratios (OR) with 95% confidence intervals.

The effects of cryotherapy on overall symptom burden (SDS-9), neuropathy-related extremity pain, and functional impairment were evaluated using adjusted linear regression models incorporating baseline values where appropriate and taxane regimen as covariates.

All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Results.

Study population:

A total of 243 patients were screened for participation in the study, of whom 190 patients were included in the final analysis. Fifty-three patients were excluded, including 10 patients who did not complete the planned chemotherapy cycles (three discontinued due to systemic chemotherapy toxicity, while no patients discontinued cryotherapy due to cold intolerance., two died before cycle 3, and five withdrew consent) and 43 patients with incomplete or inconsistent questionnaire data that precluded reliable analysis of patient-reported outcomes.

The final study population consisted of 95 patients in the cryotherapy group and 95 patients in the control group.

Baseline characteristics:

Baseline characteristics of the study population are presented in Table 1. The cryotherapy and control groups were comparable with respect to age, disease stage distribution, and baseline ESAS pain scores.

The mean age was 53.5 ± 9.7 years in the cryotherapy group and 54.0 ± 9.5 years in the control group (p = 0.65). Baseline ESAS pain scores were low in both groups (0.57 ± 1.64 vs 0.55 ± 1.15; p = 0.16), indicating that most patients did not report pain prior to initiation of chemotherapy.

The distribution of taxane regimens (including paclitaxel and docetaxel, as well as weekly versus three-weekly schedules) differed between groups at baseline. Because paclitaxel and docetaxel are associated with different neurotoxicity profiles, taxane regimen was additionally incorporated as a covariate in adjusted analyses.

Primary outcome: final ESAS pain:

The primary outcome was the ESAS pain score at the final assessment.

In an adjusted linear regression model controlling for baseline pain, age, disease stage, number of chemotherapy cycles, and taxane regimen, patients in the cryotherapy group demonstrated higher final ESAS pain scores, although the association did not reach statistical significance (B = 0.506). Because ESAS pain scores showed substantial skewness with a high proportion of zero values, HC3 robust standard errors were additionally applied. In the robust model, the association approached but did not reach statistical significance (robust 95% CI −0.023 to 1.036; p = 0.061). Baseline pain remained a strong predictor of final pain outcomes. Each one-point increase in baseline ESAS pain score was associated with an increase of approximately 0.65 points in the final pain score (p < 0.001).

Change from baseline in pain:

Change in pain from baseline (Δ pain) was analyzed as a secondary outcome.

The cryotherapy group showed a greater increase in pain compared with the control group (mean rank 102.05 vs 88.95), although this difference did not reach statistical significance (p = 0.057).

Clinically meaningful pain (ESAS ≥4):

Clinically meaningful pain, defined as an ESAS score ≥4 at the final assessment, was reported in 19 patients (20.0%) in the cryotherapy group and 8 patients (8.4%) in the control group.

This difference was statistically significant in unadjusted analysis (χ^2 test, p = 0.022), indicating a higher proportion of moderate-to-severe pain in the cryotherapy group.

In adjusted logistic regression analysis controlling for baseline pain and taxane regimen, the association between treatment group and clinically meaningful pain remained statistically significant (OR = 0.269; 95% CI 0.095–0.761; p = 0.013). Given the coding of the treatment variable, this result is consistent with a lower likelihood of moderate-to-severe pain in the control group compared with the cryotherapy group. Baseline pain was also a strong predictor of moderate-to-severe pain.

Overall symptom burden (SDS-9):

Overall symptom burden, assessed using the ESAS Symptom Distress Score (SDS-9), increased during chemotherapy in both groups.

In an adjusted analysis controlling for baseline SDS-9 and taxane regimen, no statistically significant difference was observed between the cryotherapy and control groups in final symptom burden (B = 0.357; robust 95% CI −2.114 to 2.828; p = 0.776).

Baseline symptom burden remained a significant predictor of final SDS-9 scores (B = 0.658; p < 0.001).

Neuropathy-related extremity pain:

Neuropathy-related extremity pain was assessed using a composite score derived from the EORTC QLQ-CIPN20 questionnaire.

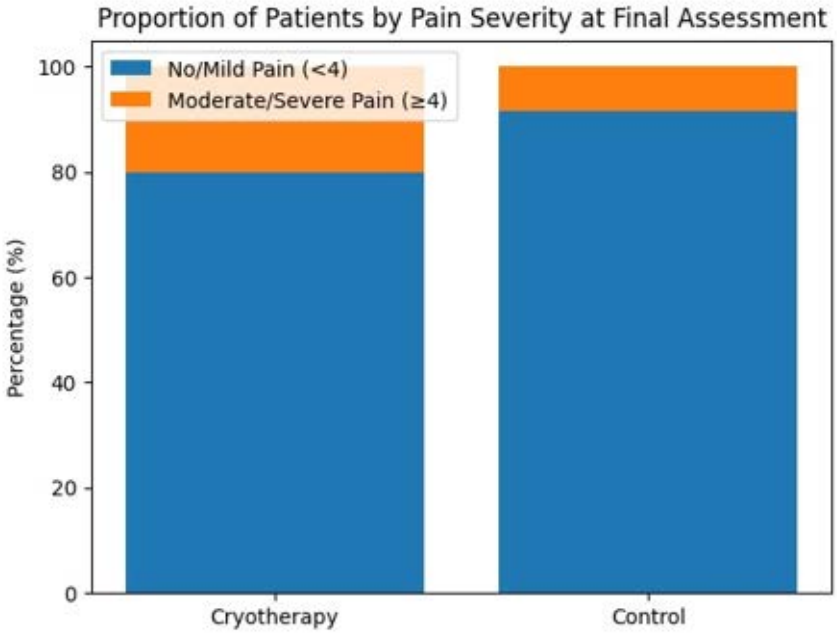

Figure 1. *Proportion of patients with no/mild pain (ESAS <4) and moderate-to-severe pain (ESAS ≥4) at the final assessment by treatment group.*

Table 1. *Baseline characteristics of the study population.*

Characteristic	Cryotherapy (n=95)	Control (n=95)	p-value
Age (years), mean ± SD	53.5 ± 9.7	54.0 ± 9.5	0.65
Baseline ESAS pain, mean ± SD (median)	0.57 ± 1.64 (0)	0.55 ± 1.15 (0)	0.16
Disease stage, n (%)			0.37
– Stage I	10 (10.5%)	10 (10.5%)	
– Stage II	39 (41.1%)	32 (33.7%)	
– Stage III	37 (38.9%)	36 (37.9%)	
– Stage IV	9 (9.5%)	17 (17.9%)	
Taxane regimen			0.006
- Weekly paclitaxel	55 (57.9%)	33 (34.7%)	
- Every 2-3-weeks paclitaxel	18 (18.9%)	28 (29.5%)	
- Docetaxel	22 (23.2%)	34 (35.8%)	

Continuous variables are presented as mean ± standard deviation (SD), with median values where appropriate. Categorical variables are presented as number (percentage). Group comparisons were performed using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables.

Table 2. *Primary and secondary outcomes (adjusted analyses).*

Outcome	Model	Effect estimate	95% CI	p-value
Final ESAS pain	ANCOVA with HC3 robust standard errors (adjusted for baseline pain, age, stage, cycles, and taxane regimen)	B = 0.506	−0.023 to 1.036	0.061
ESAS Symptom Distress Score (SDS-9)	ANCOVA with HC3 robust standard errors (adjusted for baseline SDS-9 and taxane regimen)	B = 0.357	−2.114 to 2.828	0.776
Moderate-to-severe pain (ESAS ≥4)	Logistic regression (adjusted for baseline pain and taxane regimen)	OR = 0.269	0.095–0.761	0.013

Effect estimates for continuous outcomes are presented as regression coefficients (B), representing adjusted mean differences between groups. The direction of the coefficient depends on model coding. For binary outcomes, odds ratios (OR) below 1 indicate a lower likelihood of the outcome in the control group relative to the cryotherapy group.

Table 3. *Neuropathy-related and functional outcomes.*

Outcome	Model	Effect estimate	95% CI	p-value
Extremity neuropathic pain	ANCOVA with HC3 robust standard errors (adjusted for taxane regimen)	B = -0.707	−1.109 to −0.304	0.001
Functional limitation score	ANCOVA with HC3 robust standard errors (adjusted for taxane regimen)	B = −0.184	−0.418 to 0.050	0.123

Extremity neuropathic pain was assessed using a composite score derived from the EORTC QLQ-CIPN20 questionnaire. Because baseline extremity pain scores were zero for all patients, the model reflects differences in final pain scores between groups. Negative regression coefficients indicate lower values in the control group relative to the cryotherapy group.

At baseline, extremity pain scores were zero in both groups. During treatment, neuropathic pain symptoms developed in both groups; however, final extremity pain scores were significantly higher in the cryotherapy group compared with the control group (mean 1.06 ± 1.68 vs 0.45 ± 1.07; p = 0.001).

In adjusted analysis controlling for taxane regimen, extremity pain scores were significantly lower in the control group compared with the cryotherapy group (B = -0.707; robust 95% CI −1.109 to −0.304; p = 0.001).

Functional outcomes:

Functional impairment in daily activities was generally low in both groups.

At the final assessment, some patients reported limitations in daily activities; however, there was no statistically significant difference between the cryotherapy and control groups in either unadjusted or adjusted analyses controlling for taxane regimen (B = −0.184; robust 95% CI −0.418 to 0.050; p = 0.123). No cryotherapy-related frostbite or severe skin toxicities were observed.

Discussion.

Principal findings:

In this prospective multicenter controlled study, preventive cryotherapy using cooling gloves and socks did not demonstrate a significant reduction in patient-reported pain associated with taxane-induced peripheral neuropathy.

Importantly, neuropathy-specific outcomes derived from the CIPN20 questionnaire revealed significantly higher extremity pain scores in patients receiving cryotherapy. In addition, a higher proportion of patients in the cryotherapy group experienced clinically meaningful pain (ESAS ≥4). Taken together, these findings do not demonstrate a clinically meaningful protective effect of cryotherapy on neuropathy-related pain in this cohort and suggest a divergence between general pain measures and neuropathy-specific symptom assessment. This discrepancy underscores that ESAS may lack sensitivity for neuropathy-specific symptom detection, reinforcing the importance of disease-specific instruments such as CIPN20 in CIPN research.

Comparison with previous studies:

Cryotherapy has been proposed as a preventive strategy for chemotherapy-induced peripheral neuropathy based on its presumed ability to reduce drug delivery to peripheral nerves through localized vasoconstriction [8,9]. Several clinical studies have reported a reduction in neuropathy symptoms with the use of cooling interventions [8,9].

However, the overall body of evidence remains inconsistent. Systematic reviews and meta-analyses have highlighted substantial heterogeneity across studies, with variable effects depending on study design, patient population, and outcome measures [10-12]. Moreover, current clinical guidelines do not recommend cryotherapy as a standard preventive intervention due to insufficient and inconclusive evidence [6].

The findings of the present study are aligned with this broader body of literature, reinforcing the notion that cryotherapy does not consistently reduce neuropathy-related symptoms and may not provide clinically meaningful benefit in routine practice settings.

Interpretation of divergent outcomes:

A notable finding of this study is the discrepancy between general pain outcomes and neuropathy-specific measures. While the adjusted ESAS pain score showed no statistically significant difference between groups, analyses based on change-from-baseline and CIPN20-derived extremity pain indicated either no benefit or higher symptom burden in the cryotherapy group.

This divergence may be explained by differences in measurement constructs. The ESAS instrument captures overall pain as part of a broader symptom profile, whereas the CIPN20 questionnaire specifically assesses neuropathy-related sensory symptoms and their functional impact [13]. As a result, neuropathy-specific instruments may be more sensitive to detecting clinically relevant changes in peripheral nerve function.

These findings highlight the importance of selecting outcome measures that are closely aligned with the underlying pathophysiology of the condition being studied.

Potential explanations for lack of effect:

Several factors may explain the absence of a protective effect of cryotherapy in this study.

First, the effectiveness of cryotherapy depends on the degree of cooling achieved at the level of peripheral tissues. Although cooling devices were applied at approximately -18°C and replaced when their temperature approached 0°C, the actual temperature at the skin level and the extent of vasoconstriction were not measured. Variability in tissue cooling may therefore have influenced the effectiveness of the intervention.

Second, adherence to the cryotherapy protocol and patient tolerance to cold exposure were not systematically assessed. Differences in compliance, device positioning, and duration of effective cooling may have introduced variability in treatment exposure.

Third, the non-randomized design of the study introduces the possibility of selection bias. Patients who chose to undergo cryotherapy may have differed in unmeasured ways from those in the control group, including differences in symptom perception or reporting behavior.

Possible explanations for increased neuropathy-related pain:

The observation of higher neuropathy-related extremity pain in the cryotherapy group warrants careful interpretation.

One possible explanation is related to increased symptom awareness. Patients undergoing cryotherapy may have been more attentive to sensory changes during treatment, leading to higher reporting of symptoms in patient-reported outcome measures.

Furthermore, confounding by indication cannot be entirely ruled out; patients with a lower baseline pain threshold or higher anticipatory anxiety regarding chemotherapy-induced side effects might have been more motivated to select the cryotherapy arm. This self-selection bias could artificially inflate the post-treatment pain scores in the intervention group, masking any potential protective effect of the cooling devices.

Alternatively, uneven or insufficient cooling may have resulted in inconsistent vasoconstriction, potentially leading to heterogeneous drug exposure at the level of peripheral nerves. It is also conceivable that repeated exposure to cold stimuli may have contributed to transient discomfort or altered symptom perception in certain patients, although this mechanism remains speculative.

Given the observational design of the study, these findings should not be interpreted as evidence of a causal harmful effect but rather as a signal that warrants further investigation in controlled settings.

Strengths and limitations.

This study has several strengths. It was conducted as a prospective multicenter study and included a relatively large cohort of patients treated in real-world clinical settings. The use of validated patient-reported outcome measures allowed for comprehensive assessment of both general symptom burden and neuropathy-specific symptoms.

However, several limitations should be acknowledged. The non-randomized design and allocation based on patient preference limit causal inference and introduce potential selection bias. The reliance on patient-reported outcomes introduces subjectivity and potential reporting bias. In addition, the actual degree of cooling and adherence to the cryotherapy protocol were not objectively measured. Finally, the absence of objective neurological assessments limits the ability to correlate reported symptoms with physiological measures of neuropathy.

In addition, imbalance in taxane regimens between groups may have influenced neuropathy outcomes, as different agents and schedules are associated with varying risks of neurotoxicity. To address this potential confounding factor, taxane regimen was incorporated as a covariate in adjusted regression analyses. The principal findings remained largely consistent after adjustment.

Clinical implications.

The findings of this study suggest that preventive cryotherapy should be used with caution as a strategy for reducing neuropathy-related pain in patients receiving taxane-based chemotherapy. In the absence of consistent evidence of benefit, and given the observed variability in outcomes, cryotherapy could not be demonstrated to be a reliably effective strategy in routine clinical practice.

Future directions.

Further research is needed to clarify the role of cryotherapy in the prevention of chemotherapy-induced peripheral neuropathy. Future studies should incorporate randomized designs, standardized cryotherapy protocols with controlled temperature monitoring, and combined use of objective neurological assessments and patient-reported outcomes.

In addition, stratification of patients based on baseline symptom burden and treatment characteristics may help identify subgroups that could potentially benefit from targeted preventive strategies.

Conclusion.

Preventive cryotherapy using cooling gloves and socks did not demonstrate a significant reduction in neuropathy-related pain in patients receiving taxane-based chemotherapy. Although adjusted analyses of overall pain showed no statistically significant difference between groups, neuropathy-specific outcomes revealed higher extremity pain in patients undergoing cryotherapy.

These findings highlight the complexity of assessing chemotherapy-induced peripheral neuropathy using patient-reported outcomes and underscore the importance of selecting outcome measures that accurately reflect neuropathic symptomatology.

Given the absence of consistent evidence of benefit and the observed variability in outcomes, cryotherapy could not be reliably demonstrated to be an effective strategy for the prevention of neuropathy-related pain in this setting. Further randomized studies with standardized intervention protocols and integrated objective and patient-reported assessments are required to better define its role. These findings highlight the need for careful validation of supportive care interventions before widespread clinical implementation.

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Author Contributions.

Nana Chikladze and Salome Kordzaia contributed to conducting the study, including patient enrollment, patient assessment, and analysis of final outcomes based on questionnaire evaluation.

Lika Svanadze performed the statistical analysis.

Tamar Rukhadze contributed to the final assessment and revision of the manuscript.

Carlos Centeno provided valuable scientific input regarding symptom assessment according to questionnaires, data interpretation, and revision of the manuscript.

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