Physiology and Pharmacology 30 (2026) 148-158
Clinical Research Article

Preventive effect of L-Carnitine on chemotherapy-induced oral mucositis: A randomized controlled clinical trial

Afshin Shiva[1,2], Mahroo Ghasempour[3], Rahim Asghari[4,5], Shima Hatamkhani[1,2*]

1. Experimental and Applied Pharmaceutical Sciences Research Center, Urmia University of Medical Sciences, Urmia, Iran
2. Department of Clinical Pharmacy, School of Pharmacy, Urmia University of Medical Sciences, Urmia, Iran
3. School of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada
4. Hematology, Immune Cell Therapy, and Stem Cells Transplantation Research Center, Clinical Research Institute, Urmia University of Medical Sciences, Urmia, Iran
5. Department of Internal Medicine, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran

ABSTRACT

Introduction: Mucositis is acute oral toxicity induced by radiation or systemic cytotoxic chemotherapy agents in patients with cancer that may lead to discontinuing the treatment or reducing the administered dose. In this study, we aimed to evaluate the preventive effect of oral L-carnitine on chemotherapy-induced mucositis.

Methods: This prospective clinical trial employed a double-blind, randomized, placebo-controlled design. All consecutive cancer patients who met the inclusion criteria were enrolled in the oncology ward of Imam Khomeini Hospital, Urmia, Iran. Patients were randomly allocated to one of two groups: one receiving L-Carnitine 1000 mg three times daily (total dose 3000 mg/day) and the other receiving a placebo. Mucositis severity was evaluated clinically using the WHO scoring system every week throughout the 21-day study period.

Results: L-carnitine supplementation did not significantly reduce the incidence of mucositis compared to placebo (p-value = 0.748). Among the 40 enrolled patients, 20 (50%) developed mucositis: 9/16 (56.25%) in the L-carnitine group and 11/24 (45.83%) in the placebo group. Grade 2 mucositis was the most common presentation, affecting 31.3% (5/16) of the L-carnitine group and 29.2% (7/24) of the placebo group.

Conclusion: Our investigation did not identify a statistically significant impact of L-Carnitine supplementation on the incidence, severity progression, or WHO grade distribution of chemotherapy-induced oral mucositis compared to the placebo group.

Keywords:
L-Carnitine
Mucositis
Chemotherapy
Cancer
Antineoplastic drugs

* Corresponding author: Shima Hatamkhani, hatamkhani.sh@umsu.ac.ir
Received 6 January 2025; Revised from 15 July 2025; Accepted 25 October 2025

Citation: Shiva A, Ghasempour M, Asghari R, Hatamkhani S. Preventive effect of L-Carnitine on chemotherapy-induced oral mucositis: A randomized controlled clinical trial. Physiology and Pharmacology 2026; 30: 148-158. http://dx.doi.org/10.22034/phypha.30.2.148

Introduction

Cancer therapies frequently induce a spectrum of oral toxicities, with oral mucositis (OM) being a prevalent acute and self-resolving manifestation. Characterized by reversible inflammation and ulcerative lesions within the oral cavity's soft tissues (Peterson et al., 2011), OM affects a significant proportion of cancer patients undergoing treatment. Studies report that 20-40% of individuals receiving standard chemotherapy experience OM, with this incidence escalating to 80% for patients undergoing hematopoietic cell transplantation (HCT) or radiation-involving regimens (Lalla et al., 2014; Sonis 2004; Sonis et al., 2004). The prevailing hypothesis attributes most OM cases to an oxidative stress mechanism, resulting in the generation of reactive oxygen species (ROS) (Nguyen et al., 2022). Excessive ROS production during oxidative stress disrupts cellular homeostasis by damaging DNA and altering protein structures. Furthermore, chemotherapy-induced activation of nuclear factor kappa B (NFκB) stimulates the production of pro-inflammatory cytokines (Pham et al., 2015). In essence, OM represents the culmination of a cascade of inflammatory events leading to mucosal ulceration and increased susceptibility to oral infections (Sangavi and Pandiyan 2024).

A growing body of research explores preventative and therapeutic interventions for chemotherapy-induced mucositis, a prevalent clinical challenge. Several agents demonstrate promise for prophylaxis, including palifermin, glutamine, calcium phosphate rinses, and allopurinol mouthwash (Ana et al., 2020). Management of established mucositis often relies on topical analgesics (lidocaine, morphine), doxepin rinses, diluted hydrogen peroxide solutions, and vitamin E, although further data are needed in this area (Ngeow et al., 2008). Notably, the risk of mucositis is significantly higher with DNA cycle-specific chemotherapeutic agents like bleomycin, fluorouracil, and methotrexate compared to cell phase non-specific drugs (Kaźmierczak-Siedlecka et al., 2023). Drugs secreted in saliva, such as methotrexate and etoposide, further elevate the risk of stomatotoxicity (Śledzińska et al., 2023). Additionally, high-dose regimens of Cytarabine, Doxorubicin, Etoposide, and Melphalan, along with bolus administration schedules of fluorouracil and treatment with mammalian target of rapamycin (mTOR) inhibitors are associated with a substantially increased risk of developing oral mucosal lesions (approximately 70%) (Chaveli-López 2014).

Mammals possess a "carnitine pool" comprised primarily of L-carnitine (3-hydroxy-4-N-trimethylammonium butyrate), a small, polar, and endogenous molecule. The liver, brain, and kidneys synthesize L-carnitine from lysine and methionine (Askarpour et al., 2020). This molecule plays a crucial role in cellular metabolism by facilitating the transport of free fatty acids (FFAs) from the cytosol to the mitochondria (Edwards and Mohiuddin 2023). Within the mitochondria, FFAs undergo beta-oxidation, generating acyl-CoA intermediates. These intermediates then enter the tricarboxylic acid (TCA) cycle, a process that consumes significant oxygen and produces ATP via the electron transport chain and oxidative phosphorylation. Notably, the complete reduction of oxygen at the end of the TCA cycle and its conversion to water (H_2O) minimizes the formation of reactive oxygen species (ROS) (Mayes and Botham 2000).

Beyond its role in fatty acid metabolism, L-carnitine also demonstrates antioxidant and cytoprotective properties. Studies suggest it regulates nitric oxide levels during cellular respiration and helps preserve antioxidant enzymes such as glutathione peroxidase, catalase, and superoxide dismutase (Essawy et al., 2022). Encouragingly, animal studies have shown L-carnitine's potential to mitigate mucosal damage, delay the onset of mucositis, and enhance serum antioxidant levels (Köklü et al., 2015). However, to date, no clinical investigations have explored the impact of L-carnitine on preventing oral ulcers associated with chemotherapy. This research aims to address this gap in knowledge by evaluating the efficacy of L-carnitine supplementation in preventing mucositis in patients undergoing chemotherapy.

Materials and Methods

This controlled, double-blinded, randomized parallel clinical trial compared the effectiveness of a daily oral L-Carnitine supplement (3000 mg) with a placebo in preventing chemotherapy-induced mucositis among cancer patients admitted to the oncology ward (Cruciani et al., 2006). The study period spanned from February 2017 to August 2017. Prior to commencement, ethical approval was granted by the relevant ethics committee (code: 1395-01-63-2524), and the trial was registered with the clinical trial registry (IRCT201102265914N1).

Written informed consent was obtained from all adult participants, and for minors, from their parents or legal guardians.

Study Population

Throughout the study period, all patients referred to the Haematology ward at Urmia Medical Science University, Urmia, Iran, underwent screening for eligibility. Patients were included if they met the following criteria: (1) age 14 years or older, (2) signed informed consent, (3) planned to receive at least one chemotherapy medication with a documented risk of mucositis exceeding 10%, and (4) a history of mucositis from prior chemotherapy regimens was not an exclusion factor.

Conversely, patients were excluded from participation if they presented with (1) head and neck or oral cavity cancers, (2) a documented history of adverse reactions to L-carnitine supplementation, (3) prior radiotherapy treatment, (4) concurrent use of vitamin, carnitine, or mineral supplements within the past eight weeks, (5) severe hepatic or renal dysfunction, or (6) experiencing significant side effects such as extreme nausea that would impede their ability to participate in the study protocol.

Randomization and Intervention

To ensure allocation concealment and minimize bias, a double-blinded approach was implemented throughout the study. Karen Yazd Company supplied both L-carnitine and placebo capsules. The capsules were identical in appearance and packaging, making it impossible to distinguish between the two interventions. Neither investigators nor patients were aware of their assigned group (L-carnitine or placebo). An independent pharmacist performed the randomization process. Medications were allocated into groups A and B, and allocation assignments were concealed within opaque envelopes. This ensured that all participants involved in the trial, including pharmacists, nurses, physicians, and patients, remained blinded to group allocation until the study was completed and data analysis commenced.

Outcomes and follow-up

The World Health Organization (WHO) grading system served as the primary tool for assessing the severity of chemotherapy-induced mucositis in this study (Wilkes 1998). This standardized system employs a five-point scale:

Grade 0: Absence of any signs or symptoms of mucositis.

Grade 1: Non-inflamed ulcers, edema, or mild pain without impacting dietary intake.

Grade 2: Painful erythema, edema, or ulcers; however, patients can still maintain a normal diet.

Grade 3: Presence of painful erythema, edema, or ulcers that significantly impair oral intake, necessitating enteral or parenteral nutritional support.

Grade 4: Severe mucositis requiring complete reliance on enteral or parenteral nutrition.

The Naranjo Adverse Drug Reaction Probability Scale was utilized to evaluate the potential association between any reported nausea and L-Carnitine supplementation (Naranjo et al., 1981). This established scale gives scores based on a number of factors. Scores of nine or higher mean that there is definitely an adverse drug reaction, scores of five to eight mean that there is probably one, scores of one to four mean that there is possibly one, and scores of zero or less mean that there is not one.

Study Protocol and Data Collection

Following assessment for eligibility based on the outlined inclusion and exclusion criteria, patients were randomly allocated to either the L-Carnitine or placebo group using a table of random numbers. Data collection employed a multifaceted approach, encompassing patient interviews, clinical observations, and electronic medical records retrieval from the hospital information system. Demographic information (gender, age, weight, medication history, smoking status, and alcohol consumption) and clinical characteristics (type of cancer/tumor, presence, and severity of oral mucositis) were collected through a combination of interviews, observations, patient charts, and the hospital information system. Data collection occurred on the first day of treatment and continued weekly throughout the 21-day study period.

All participants received standardized instructions to abstain from alcohol, cigarettes, and spicy or sour foods, and to maintain meticulous oral hygiene by brushing twice daily with a soft toothbrush. Mouthwash use was discouraged during the study. While the protocol did not involve the use of any adjuvant or pretreatment medications for mucositis due to ethical considerations, patients experiencing a worsening of symptoms or expressing

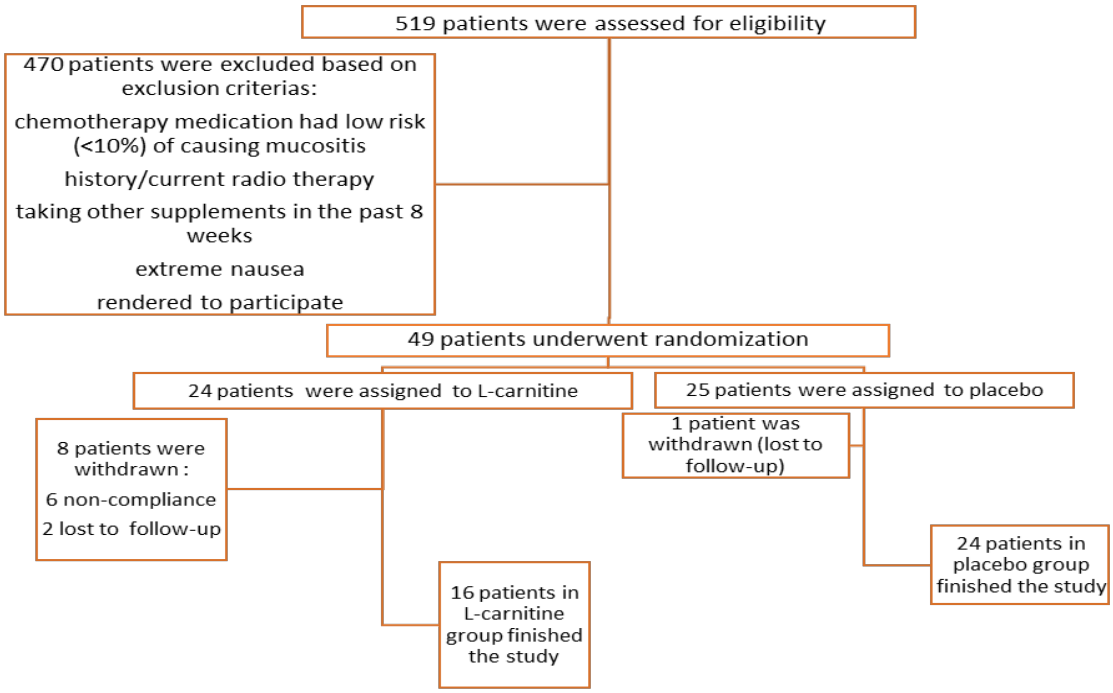

FIGURE 1. Flowchart of the study

dissatisfaction were withdrawn from the study and returned to standard care for mucositis management.

The intervention commenced with the first dose of the chemotherapy regimen. Patients in the L-Carnitine group received a total of 3000 mg daily, divided into three oral doses (1000 mg each) administered in the morning, noon, and evening for 21 days. The placebo group received a matching regimen with identically appearing capsules devoid of the active ingredient.

Statistical analysis

Sample size estimation was based on a review of relevant databases and animal studies demonstrating a potential 20% reduction in mucositis with L-Carnitine supplementation (Köklü et al., 2015). Employing a significance level (α) of 0.05 and a power (β) of 0.2, a sample size of 16 participants per group (L-Carnitine and placebo) was calculated to ensure adequate statistical power for detecting a clinically relevant effect size.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21. Descriptive statistics were generated for both continuous and nominal variables. Continuous variables were expressed as mean ± standard deviation, while nominal variables were presented as frequencies and percentages. Group comparisons for continuous variables were conducted using the independent-samples t-test, assuming normality was confirmed using the Kolmogorov-Smirnov test. For non-normally distributed continuous data, such as age or weight, the Mann-Whitney U test was employed. Categorical variables, including sex, smoking status, and medication use (antibiotics, antifungals, antivirals, and antidepressants), as well as the incidence of mucositis, were analyzed using the chi-square test. A p-value of less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 519 patients were screened for eligibility. Following assessment, 49 patients were enrolled and

randomized into either the L-carnitine (n=24) or placebo (n=25) group (Figure 1). Details regarding randomization procedures should be provided (e.g., sequence generation, allocation concealment). Nine patients were excluded from the study. Six patients experienced adverse effects associated with L-carnitine, while three patients withdrew due to personal reasons. The final analysis included 16 patients in the L-carnitine group and 24 patients in the placebo group. It is important to note that

TABLE 1: Baseline characteristics of patients among L-carnitine and placebo group

		L-carnitine (N=16)	Placebo (N=24)	p-Value
Female: Male		5:11	13: 11	0.154 *
Age (years) §		48 ±12.6	51 ±17.9	0.272
Weight (kg) §		71.8 ±8.5	70 ±12.2	0.138
Smoking, N (%)		4 (25%)	2 (8.2%)	0.195*
Concomitant Antibiotic Use, N (%)		2 (12.5%)	1(4.2%)	0.553*
Concomitant Antidepressant use, N (%)		0	1(4.2%)	1.000*
Concomitant Antiviral use, N (%)		0	1(4.2%)	1.000*
ConcomitantAntifungal use, N (%)		1 (6.2%)	1(4.2%)	1.000*
Oral hygiene with toothbrush		16 (100%)	24 (100%)	-
Tooth decay, N (%)	No tooth	4 (25%)	7 (29%)	0.713
	No decay	3 (18.7%)	2 (8%)	
	1-4 decays	6 (37.5%)	12 (50%)	
	≥ 5 decays	3 (18.7%)	3 (12.5%)	

* Chi-square test. T-test. Mann-Whitney test. § Mean ±SD

all participants were undergoing chemotherapy and had no prior history of radiation therapy.

The baseline characteristics of the study participants were well-matched between the L-carnitine and placebo groups (Table 1). The mean age of the patients was 50 ± 15.9 years old, and a majority (55%) were male. The distribution of cancer types showed gastric cancer as the most prevalent (22.5%), followed by acute lymphocytic leukemia (17.5%), acute myeloid leukemia (15%), breast cancer (10%), and colon cancer (7.5%). Cyclophosphamide (37.5%) and 5-FU (27%) were the most commonly administered chemotherapeutic agents. It is noteworthy that among patients receiving 5-FU, approximately 37.5% belonged to the L-carnitine group (Table 2). Cisplatin plus 5-FU and docetaxel was the most frequent chemotherapy regimen used (10%).

Mucositis, a common side effect of chemotherapy, was observed in 50% of the study population during the followup period. Notably, the incidence of mucositis was numerically higher in the L-carnitine group compared to the placebo group (56.25% vs. 45.83%). However, statistical analysis revealed no significant difference in mucositis rates between the groups (p-value = 0.748) as illustrated in Figure 2.

According to Figure 3 , most patients (27.5%) experienced mucositis during the first week of the treatment, 25% were in L-Carnitine, and 31.3% were in placebo groups, but the difference was insignificant. In the second week, the prevalence of mucositis was the same between L-Carnitine and placebo groups (12.5%). In the third week of treatment, the prevalence of mucositis among placebo recipients was lower (8.3%) than among L-Carnitine recipients (12.5%), (P-value= 0.540) (Fig. 3).

As shown in FIGURE 3, mucositis developed in a substantial proportion of patients throughout the first three weeks of treatment. In the first week, the prevalence of mucositis was highest, affecting 27.5% of all participants. While the incidence appeared slightly higher in the placebo group (31.3%) compared to the L-Carnitine group (25.0%), this difference was not statistically significant (p-value = 0.540). The following two weeks exhibited a downward trend in mucositis, with equal prevalence observed between the groups in week two (12.5% for both) and a lower prevalence in the placebo group (8.3%) compared to the L-Carnitine group (12.5%) in week three. However, similar to week one, the difference in week three did not reach statistical significance (p-value = 0.540).

Nine out of 24 patients (37.5%) receiving L-Carnitine experienced nausea. An assessment using the Naranjo scale revealed that eight of these patients scored between 5-8, indicating a probable association between nausea and L-Carnitine use. Six patients discontinued the study due to nausea, suggesting a possible intolerance. Interestingly, nausea subsided in the two remaining patients despite continued L-Carnitine administration. Notably, no other adverse effects attributable to the drug were ob-

TABLE 2: Administered Chemotherapy medications among L-Carnitine or placebo groups, N (%).

Category	**Specific drug**	L-Carnitine (N=16)	Placebo (N=24)
Chemotherapy agents associated with mucositis[16]			
Alkylating agents	Carboplatin	1 (6.25%)	0 (0%)
	Cisplatin	5 (31.25%)	5 (20.83%)
	Cyclophosphamaide	3 (18.75%)	12 (50%)
	Ifosfamide	1 (6.25%)	0 (0%)
Anthracyclines	Daunorubicin	2 (12.5%)	4 (16.66%)
	Doxorubicin	0 (0%)	8 (33.33%)
	Epirubicin	3 (18.75%)	1 (4.16%)
	Mitoxantrone	1 (6.25%)	1 (4.16%)
Antimetabolites	6-Mercaptopurine	1 (6.25%)	1 (4.16%)
	Capecitabine	3 (18.75%)	1 (4.16%)
	Cytarabine	2 (12.5%)	4 (16.66%)
	Fludarabine	1 (6.25%)	2 (8.33%)
	5- Fluorouracil	6 (37.5%)	5 (20.83%)
	Methotrexate	0 (0%)	1 (4.16%)
Antitumor antibiotics	Bleomycin	1 (6.25%)	2 (8.33%)
Taxanes	Docetaxel	3 (18.75%)	3 (12.5%)
Topoisomerase inhibitors	Etoposide	3 (18.75%)	1 (4.16%)
	Irinotecan	2 (12.5%)	1 (4.16%)
Molecularly targeted agents	Cetuximab	0 (0%)	1 (4.16%)
Other administered drugs	Vincristine	2 (12.5%)	5 (20.83%)
	L-Asparginase	2 (12.5%)	1 (4.16%)
	Oxaliplatin	4 (25%)	4 (16.7%)
	Rituximab	2 (12.5%)	4 (16.66%)
	Pegagen	3 (18.75%)	3 (12.5%)

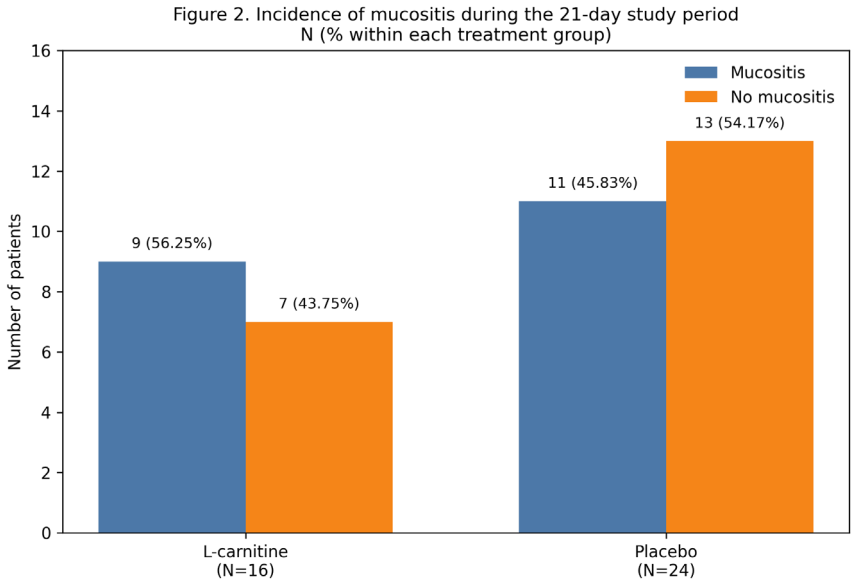

FIGURE 2. The incidence of mucositis among L-Carnitine and placebo groups during the whole study (21 days), N (%)

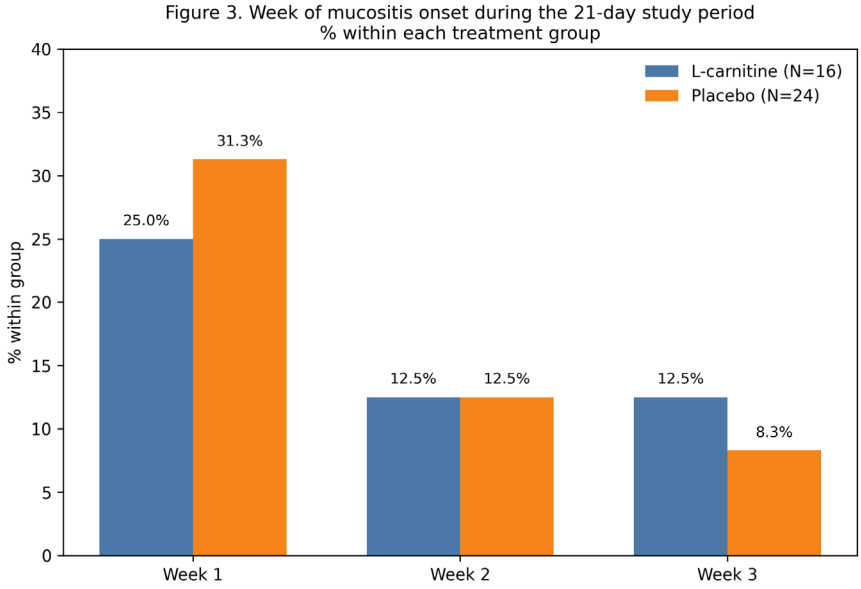

FIGURE 3. The onset time of mucositis in patients during the study period, (%)

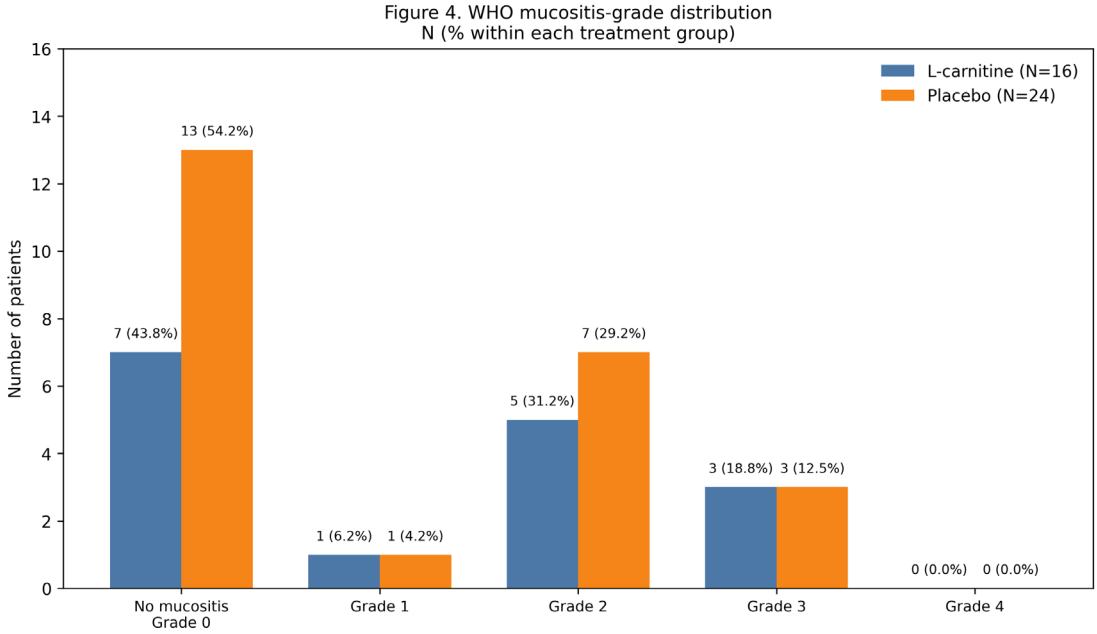

FIGURE 4. Mucositis grading in L-Carnitine and placebo group according to the World Health Organization grading system, N (%).

served in this study.

Discussion

This randomized controlled trial (RCT) represents the first investigation to evaluate the efficacy of oral L-Carnitine in preventing chemotherapy-induced mucositis in humans. While prior research has explored various applications of L-Carnitine, only two pre-clinical studies using animal models have examined its potential role in mucositis management (Cruciani et al., 2006; Köklü et al., 2015; Naranjo et al., 1981; Üçüncü et al., 2006; Wilkes 1998). One study involving 35 male mice with radiation-induced mucositis demonstrated that daily administration of 200 mg/kg L-Carnitine delayed the onset

of mucositis, lessened the severity of mucosal damage, and increased blood antioxidant levels (Köklü et al., 2015). These findings suggest a potential mechanism by which L-Carnitine may exert its protective effects. Another randomized trial compared the effects of daily L-Carnitine (100 mg/kg and 200 mg/kg) with vitamin E (100 mg/kg) and a control group in 24 albino rats. All groups exhibited improvements in serum levels of malondialdehyde (MDA), catalase, and superoxide dismutase, along with enhanced wound healing. Notably, the L-Carnitine groups displayed a faster rate of wound healing compared to the vitamin E group (Üçüncü et al., 2006). These findings warrant further investigation in human trials.

Mucositis and oral ulcers, arising from local tissue damage, are characterized by elevated oxidative stress and increased production of free radicals. These radicals interact with fatty acids in damaged cell membranes, triggering a lipid peroxidation reaction that hinders healing. Multiple studies in animals and humans have demonstrated the wound-healing benefits of antioxidants, which act by preventing and limiting oxidative damage (Fitzmaurice et al., 2011).

L-Carnitine, a naturally occurring antioxidant molecule present in all mammals, has emerged as a potential candidate for wound healing due to its antioxidant properties (Fitzmaurice et al., 2011; Hosseini et al., 2016). Synthesized in the kidneys from methionine and lysine, with additional dietary intake contributing about 75%, L-Carnitine's primary function is facilitating fatty acid transport into the mitochondria for energy production via beta-oxidation. Beyond this essential role, L-Carnitine also plays a crucial part in mitochondrial and peroxisomal metabolism. Notably, L-Carnitine's ability to scavenge free radicals suggests its potential to protect cells from oxidative damage (Flanagan et al., 2010).

Pre-clinical studies suggest that L-Carnitine supplementation may exert its protective effects against mucositis through its antioxidant properties. In elderly mice, L-Carnitine administration increased the activity of glutathione and other antioxidant enzymes, suggesting a potential mechanism for mitigating oxidative stress (Babicova et al., 2013). Furthermore, L-Carnitine's ability to reduce lipid peroxidation safeguards cellular components like DNA, proteins, and lipids from oxidative damage (Babicova et al., 2013). Notably, research has also demonstrated protective effects of L-Carnitine against radiation therapy-induced damage in tissues like the oral mucosa of mice and guinea pigs (Babicova et al., 2013). Given that free radical production and lipid peroxidation are established mechanisms underlying chemotherapy-induced mucositis, L-Carnitine's antioxidant properties make it a rational candidate for mucositis prevention.

Over the 21-day study period, mucositis developed in 50% of the participants. While the incidence was numerically higher in the L-carnitine group (56.25% [9/16]) than in the placebo group (45.83% [11/24]), the difference was not statistically significant (p-value = 0.748). It is noteworthy that the observed mucositis rates (50%) are consistent with findings from a previous review article, which reported mucositis rates of 40% and 75% in patients undergoing standard and high-dose chemotherapy, respectively (Naidu et al., 2004).

The severity of mucositis, as assessed using WHO criteria, did not exhibit a statistically significant difference between the L-Carnitine and placebo groups (p-value = 0.589). Consistent with previous findings (da Cruz Campos et al., 2014; Naidu et al., 2004), grade 2 mucositis was the most prevalent, affecting 30% of participants. Notably, the distribution within each group mirrored this trend, with 31.3% and 29.2% experiencing grade 2 mucositis in the L-Carnitine and placebo groups, respectively.

Similar to the absence of grade 4 mucositis in our study, a 2016 randomized controlled trial by Elyasi et al. investigating silymarin for radiotherapy-induced mucositis reported no patients experiencing grade 4, while the placebo group exhibited grade 3 or 4 mucositis in some patients (Hosseini et al., 2016). This suggests a potential protective effect against severe mucositis in both interventions (L-Carnitine and silymarin) compared to placebo.

Consistent with established literature (Naidu et al., 2004; Wong 2014), our study observed the peak incidence of chemotherapy-induced mucositis during the first week of treatment. In this initial week, 27.5% of participants developed signs and symptoms of mucositis, with a slightly higher prevalence in the placebo group (31.1%) compared to the L-Carnitine group (25.0%). However, this difference was not statistically significant. This initial peak aligns with the findings of Epstein et al. and Naidu et al. who reported that mucositis typically manifests soon after commencing che-

motherapy, reaching its peak around day seven (Naidu et al., 2004; Wong 2014). Following this initial week, the prevalence of mucositis decreased in both groups, with equal rates observed in week two (12.5% for both) and a slightly lower prevalence in the placebo group (8.3%) compared to the L-Carnitine group (12.5%) in week three. The gradual decline in mucositis prevalence after the first week is consistent with the reported resolution timeframe of 10-14 days following chemotherapy (Naidu et al., 2004; Wong 2014).

L-Carnitine has a generally well-tolerated profile in human and animal studies, with both acute and chronic use demonstrating minimal safety concerns (Cruciani et al., 2012; Farahzadi et al., 2016; Hatamkhani et al., 2014; Köklü et al., 2015; Marx et al., 2017; Matsui et al., 2018; Thal et al., 1996; Üçüncü et al., 2006). Gastrointestinal symptoms, particularly nausea, have been reported in rare cases, but these often resolve with continued use (Köklü et al., 2015; Üçüncü et al., 2006). These findings suggest that L-Carnitine, if proven effective in preventing mucositis, has the potential to be a safe therapeutic option. However, our study findings present a nuance to consider. While the overall number of excluded patients was small (n=9), six of these individuals discontinued due to adverse effects attributed to L-Carnitine, as assessed by the Naranjo scale with scores between 5-8 (probable association). Three other patients withdrew for unrelated personal reasons. Further investigation with a larger sample size is warranted to definitively assess L-Carnitine's safety profile in this specific context of preventing chemotherapy-induced mucositis.

Limitations of study

Several limitations may have contributed to the inconclusive findings regarding the primary endpoint of preventing mucositis. The relatively small sample size limited the study's statistical power to detect potential differences between the L-Carnitine and placebo groups. Additionally, the study design did not evaluate the time to mucositis healing, which would provide valuable insights into L-Carnitine's potential impact on the duration of this adverse effect. Furthermore, the probable dose-dependent effect of L-Carnitine warrants further investigation. While previous studies suggest higher doses (above 3g daily) may be more effective (Chaveli-López 2014), the potential for increased adverse effects necessitates a careful risk-benefit analysis. Exploring a loading dose before chemotherapy initiation, as suggested by other research, could also be a promising avenue for future studies (Chaveli-López 2014). Patient compliance also emerged as a potential challenge. The large size of the pills and the required three-times-a-day regimen might have contributed to non-adherence. This is particularly relevant for outpatients, who were more difficult to monitor compared to hospitalized patients (typically admitted for only one week). Ideally, future studies could incorporate strategies to improve adherence, such as directly observing medication intake or utilizing smaller, easier-to-swallow tablets.

Conclusions

This randomized controlled trial did not demonstrate a statistically significant effect of L-Carnitine on preventing chemotherapy-induced mucositis, its progression, or WHO grade severity compared to the placebo group. While these findings do not support the use of L-Carnitine for this specific purpose in clinical practice at present, they contribute valuable data to the limited body of human research on L-Carnitine's impact on mucositis. Further investigation is warranted to address the limitations of the current study and establish a more robust knowledge base for future research. Specifically, exploring the influence of L-Carnitine on mucositis within the context of specific chemotherapy regimens or tumor types may yield more definitive results. Additionally, larger sample sizes and a focus on patient adherence could enhance the generalizability of future trials.

Acknowledgements

The authors would like to express their gratitude to the clinical research development unit of Imam Khomeini Hospital, Urmia University of Medical Sciences, for English editing.

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval

The study was conducted conscientiously, taking into account ethical considerations, and securing approval from the ethics committee at Urmia Medical Science University (code: 1395-01-63-2524), and the trial was registered with the clinical trial registry

(IRCT201102265914N1) while also obtaining written consent from all participants. Furthermore, the research adhered to the ethical guidelines for human experimentation outlined in the Helsinki Declaration.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

M Gh: writing original draft, methodology, investigation, and conceptualization; R A: review and editing and validation; A Sh: software, investigation, and data curation; Sh H: methodology. MF: review and editing, project administration, methodology, investigation, and conceptualization.

Data availability

All relevant data can be found within the manuscript.

Competing interests

The authors declare that they have no competing interests**.**

Funding

This study is funded by Urmia University of Medical Sciences for purchasing drugs and the placebo. It was not applied for the design of the study and collection, analysis, and interpretation of data nor in writing the manuscript.

References

Ana G S, Normando A G C, de Toledo I P, Dos Reis P E D, Guerra E N S. Topical treatment of oral mucositis in cancer patients: a systematic review of randomized clinical trials. Asian Pacific Journal of Cancer Prevention 2020; 21: 1851. https://doi.org/10.31557/APJCP.2020.21.7.1851

Askarpour M, Djafarian K, Ghaedi E, Sadeghi O, Sheikhi A, Shab-Bidar S. Effect of L-Carnitine supplementation on liver enzymes: a systematic review and meta-analysis of randomized controlled trials. Archives of Medical Research 2020; 51: 82-94. https://doi.org/10.1016/j.arcmed.2019.12.005

Babicova A, Havlínová Z, Hroch M, Rezacova M, Pejchal J, Vávrová J, et al. In vivo study of radioprotective effect of NO-synthase inhibitors and acetyl-L-carnitine. Physiological Research 2013; 62: 701. https://doi.org/10.33549/physiolres.932541

Chaveli-López B. Oral toxicity produced by chemotherapy: A systematic review. Journal of Clinical and Experimental Dentistry 2014; 6: 81-90. https://doi.org/10.4317/jced.51337

Cruciani R A, Dvorkin E, Homel P, Malamud S, Culliney B, Lapin J, et al. Safety, tolerability and symptom outcomes associated with L-carnitine supplementation in patients with cancer, fatigue, and carnitine deficiency: a phase I/II study. Journal of Pain and Symptom Management 2006; 32: 551-559. https://doi.org/10.1016/j.jpainsymman.2006.09.001

Cruciani R A, Zhang J J, Manola J, Cella D, Ansari B, Fisch M J. L-carnitine supplementation for the management of fatigue in patients with cancer: An Eastern Cooperative Oncology Group phase III, randomized, double-blind, placebo-controlled trial. Journal of Clinical Oncology 2012; 30: 3864-3869. https://doi.org/10.1200/JCO.2011.40.2180

da Cruz Campos M I, Neiva Campos C, Monteiro Aarestrup F, Vieira Aarestrup B J. Oral mucositis in cancer treatment: natural history, prevention and treatment. Molecular and Clinical Oncology 2014; 2: 337-340. https://doi.org/10.3892/mco.2014.253

Edwards M, Mohiuddin S. Biochemistry, Lipolysis.[Updated 2022 Jul 18]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 2023.

Essawy A E, El-Sayed S A, Tousson E, Abd El-gawad H S, Alhasani R H, Abd Elkader H T A E, et al. Anti-kindling effect of Ginkgo biloba leaf extract and L-carnitine in the pentylenetetrazol model of epilepsy. Environmental Science and Pollution Research 2022; 29(32):48573-48587. https://doi.org/10.1007/s11356-022-19251-6

Farahzadi R, Mesbah-namin S A, Zarghami N, Fathi E. L-carnitine effectively induces hTERT gene expression of human adipose tissue-derived mesenchymal stem cells obtained from the aged subjects. International Journal of Stem Cells 2016; 9: 107-114. https://doi.org/10.15283/ijsc.2016.9.1.107

Fitzmaurice S D, Sivamani R K, Isseroff R R. Antioxidant therapies for wound healing: a clinical guide to currently commercially available products. Skin Pharmacology and Physiology 2011; 24: 113-126. https://doi.org/10.1159/000322643

Flanagan J L, Simmons P A, Vehige J, Willcox M D, Garrett Q. Role of carnitine in disease. Nutrition and metabolism 2010; 7: 30. https://doi.org/10.1186/1743-7075-7-30

Hatamkhani S, Khalili H, Karimzadeh I, Dashti-Khavidaki S, Abdollahi A, Jafari S. Carnitine for prevention of antituber-

culosis drug-induced hepatotoxicity: A randomized, clinical trial. Journal of Gastroenterology and Hepatology 2014; 29: 997-1004. https://doi.org/10.1111/jgh.12474

Hosseini S, Elyasi S, Niazi Moghadam M R, Aledavood S A, Karimi G. Effect of oral silymarin administration on prevention of radiotherapy induced mucositis: A randomized, double-blinded, placebo-controlled clinical trial. Phytotherapy Research 2016; 27: 1879-1885. https://doi.org/10.1002/ptr.5704

Kaźmierczak-Siedlecka K, Bulman N, Ulasiński P, Sobocki B K, Połom K, Marano L, et al. Pharmacomicrobiomics of cell-cycle specific anti-cancer drugs-is it a new perspective for personalized treatment of cancer patients? Gut Microbes 2023; 15: 2281017. https://doi.org/10.1080/19490976.2023.2281017

Köklü A H K, Akkol E K, Kutluay Köklü A H, Küpeli Akkol E, Uğar Çankal D A, Köklü A H K, et al. Biochemical and biomechanical assessment of effects of l-carnitine on oral mucosal wounds. Clinical Oral Investigations 2015; 19: 1101-1106. https://doi.org/10.1007/s00784-014-1329-8

Lalla R V, Bowen J, Barasch A, Elting L, Epstein J, Keefe D M, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014; 120: 1453-1461. https://doi.org/10.1002/cncr.28592

Marx W, Teleni L, Opie R S, Kelly J, Marshall S, Itsiopoulos C, et al. Efficacy and effectiveness of carnitine supplementation for cancer-related fatigue: a systematic literature review and meta-analysis. Nutrients 2017; 9: 1224. https://doi.org/10.3390/nu9111224

Matsui H, Einama T, Shichi S, Kanazawa R, Shibuya K, Suzuki T, et al. L-Carnitine supplementation reduces the general fatigue of cancer patients during chemotherapy. Molecular and Clinical Oncology 2018; 8: 413-416. https://doi.org/10.3892/mco.2018.1557

Mayes P A, Botham K M. Lipids of physiologic significance. A LANGE Medical Book 2000; 24: 146-157.

Naidu M U R, Ramana G V, Rani P U, Suman A, Roy P. Chemotherapy-induced and/or radiation therapy-induced oral mucositis-complicating the treatment of cancer. Neoplasia 2004; 6: 423-431. https://doi.org/10.1593/neo.04169

Naranjo C A, Busto U, Sellers E M, Sandor P, Ruiz I, Roberts E A, et al. A method for estimating the probability of adverse drug reactions. Clinical Pharmacology & Therapeutics 1981; 30: 239-245. https://doi.org/10.1038/clpt.1981.154

Ngeow W C, Chai W L, Zain R B. Management of radiation therapy-induced mucositis in head and neck cancer patients. Part I: Clinical significance, pathophysiology and prevention. Oncology Reviews 2008; 2: 102-113. https://doi.org/10.1007/s12156-008-0064-2

Nguyen H, Sangha S, Pan M, Shin D H, Park H, Mohammed A I, et al. Oxidative stress and chemoradiation-induced oral mucositis: a scoping review of in vitro, in vivo and clinical studies. International Journal of Molecular Sciences 2022; 23: 4863. https://doi.org/10.3390/ijms23094863

Peterson D E, Bensadoun R-J, Roila F. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. Annals of Oncology 2011; 22: 78-84. https://doi.org/10.1093/annonc/mdr391

Pham V H, Nguyen Q, Luu V T. Resistance (ISAAR 2015). 2015; 45: S59-S143. https://doi.org/10.1016/S0924-8579(15)30006-6

Sangavi R, Pandiyan I. Unveiling the multifaceted management of oral mucositis in cancer patients: a narrative review. Cureus 2024; 16: 55213

Śledzińska A, Śledzińska P, Bebyn M, Komisarek O. Chemotherapy-induced oral complications and prophylaxis strategies. Cancer Investigation 2023; 41: 432-455. https://doi.org/10.1080/07357907.2023.2188558

Sonis S T. The pathobiology of mucositis. Nature Reviews Cancer 2004; 20: 277-284. https://doi.org/10.1038/nrc1318

Sonis S T, Elting L S, Keefe D, Peterson D E, Schubert M, Hauer-Jensen M, et al. Perspectives on cancer therapy-induced mucosal injury. Cancer 2004; 100: 1995-2025. https://doi.org/10.1002/cncr.20162

Thal L J, Carta A, Clarke W R, Ferris S H, Friedland R P, Petersen R C, et al. A 1-year multicenter placebo-controlled study of acetyl-L-carnitine in patients with Alzheimer's disease. Neurology 1996; 47: 705-711. https://doi.org/10.1212/WNL.47.3.705

Üçüncü H, Ertekin M V, Yörük Ö, Sezen O, Özkan A, Erdoğan F, et al. Vitamin E and L-carnitine, separately or in combination, in the prevention of radiation-induced oral mucositis and myelosuppression: a controlled study in a rat model. Journal of Radiation Research 2006; 47: 91-102. https://doi.org/10.1269/jrr.47.91

Wilkes J D. Prevention and treatment of oral mucositis following cancer chemotherapy. Seminars in Oncology 1998; 25: 538-551.

Wong H M. Oral complications and management strategies for patients undergoing cancer therapy. The Scientific World Journal 2014; 2014: 581795. https://doi.org/10.1155/2014/581795