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Original Article

The Effectiveness of N-acetylcysteine in Preventing Oral Mucositis Induced by Chemotherapy among Children with Cancer: A Double-Blind Randomized Controlled Trial

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Abstract

Background: Oral mucositis (OM) is a common chemotherapy complication in children, linked to oxidative stress. The aim of the study was to evaluate the efficacy of oral N-acetylcysteine (NAC) compared to placebo in children with malignancy at risk of mucositis induced by chemotherapy.

Materials and Methods: The double-blind randomized controlled trial was performed on 80 children hospitalized in the oncology departments of Shahid Baghaei and Abuzar hospitals in Ahvaz, Iran. The patients were randomly assigned to NAC and placebo groups using a four-block randomization method. The NAC group received oral NAC (20–25 mg/kg on day 1, then 10–15 mg/kg daily for 14 days), while the control group received placebo. The outcomes included OM severity, fever duration, hospital stay, serum malondialdehyde (MDA), and adverse effects.

Results: The rate of no mucositis (grade 0) was higher in the NAC group (72.5% vs. 47.5%, P = 0.030), while severe mucositis (grade 3) occurred only in the control group (10% vs. 0%, P = 0.030). The duration of fever in the NAC and the control groups was 1.63 ± 2.04 and 3.68 ± 4.77 days, respectively (P = 0.016). The hospital stays in the NAC and control groups were significantly different (4.55 ± 1.01 vs. 5.8 ± 1.22, P = 0.001). The level of MDA on the seventh day was significantly different between the two groups (4.73 ± 0.36 µmol/L in the NAC group vs. 8.89 ± 0.26 µmol/L in the control group, P < 0.001). The level of MDA on the fifteenth day in the NAC and control groups was 2.76 ± 0.31 and 6.06 ± 0.23 µmol/L, respectively (P < 0.001).

Conclusion: Given its role in reducing the severity of chemotherapy-induced mucositis, NAC may serve as an effective adjunct in pediatric oncology care alongside standard oral and dental hygiene measures.

Keywords: Cancer, Chemotherapy, Children, Oral mucositis (OM), N-acetylcysteine (NAC)

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Introduction

Cancer is the most common disease-related cause of death among children in developed countries (1, 2). The treatment of pediatric cancer largely relies on chemotherapy as a primary therapeutic modality. Especially in the past two decades, it has remarkably contributed to improving survival outcomes worldwide (3). Oral mucositis (OM), a severe oral ulcer, is a common toxic effect of radiotherapy or chemotherapy and a limiting factor in using the maximum radiation dose for effective cancer treatment (4, 5). Factors such as the type of treatment and the patient's sensitivity affect the occurrence of oral mucositis (6). The pathogenesis of oral mucositis involves direct damage to submucosal epithelial cells and an inflammatory response to high-dose chemotherapy (7).

Activation of nuclear factor kappa B (NF-κB), together with increased levels of pro-inflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor alpha (TNF-α), plays a role in the development and progression of oral mucositis (8).

Chemotherapy increases oxidative stress through increasing the formation of reactive oxygen species, contributing to mucosal cell damage (9). As a result, antioxidant compounds have been suggested as a potential strategy to lessen the incidence or severity of this adverse effect. Antioxidants such as vitamin E, β-carotene, selenium, and zinc sulfate have been studied for their potential to prevent treatment-induced oral mucositis; however, the reported results are not consistent (10). Free radicals are highly reactive and toxic compounds that are produced by oxidative stress reactions. Increased formation of free radicals or decreased antioxidants levels causes cellular oxidative damage to fatty acids in the cell membrane structure, known as lipid peroxidation (11). Malondialdehyde (MDA) is a common byproduct in the peroxidation of the lipid portion of cell membrane phospholipids during oxidative stress reactions (12).

N-acetylcysteine (NAC) is a thiol-containing antioxidant derived from the amino acid cysteine, widely used as a mucolytic agent and an antidote for acetaminophen-induced liver toxicity. NAC promotes glutathione synthesis and contributes to the neutralization of free radicals (13). Some animal studies have shown that NAC may increase inflammatory responses by inhibiting the activation of NF-κB (14, 15).

There are limited clinical studies on the efficacy of NAC administration in preventing oral mucositis induced by radiotherapy and chemotherapy, which they have shown promising results (16). The aim of this study was to investigate the preventive effect of oral NAC compared to placebo in children with malignancy at risk of mucositis induced by chemotherapy.

Material and Methods

Study design and participants

The present study was conducted as a randomized controlled clinical trial. A total of 80 patients, aged between 2 and 18 years, who were admitted to the oncology and hematology wards of Shahid Baghaei and Abuzar hospitals in Ahvaz, Iran, during 2023-2024, participated in the study.

The inclusion criteria were age of 2 to 18 years, reception of antimetabolite chemotherapy drugs with a high risk of developing oral mucositis (such as Doxorubicin, Methotrexate, fluorouracil or 5-FU, Etoposide, Cytarabine, and Melphalan), a Lansky Performance Scale Index of more than 70%, and no cardiovascular diseases. The exclusion criteria were severe hypersensitivity to NAC such as skin reactions, bronchospasm, bronchitis, active gastrointestinal diseases, and cardiovascular diseases.

Oral mucositis severity was evaluated using the World Health Organization (WHO) oral toxicity grading scale (0–4), ranging from no symptoms (Grade 0) to severe ulceration with inability to tolerate oral intake (Grade 4) (17). The patients were evaluated clinically by trained oncology staff during hospitalization.

Sample formula

Based on a similar article (16), considering $\alpha = 0.05$ and power of 80%, the sample size was estimated to be 40 patients in each group. The eligible patients were randomly divided into

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intervention and control groups based on a four-block randomization method. The treatment group received oral NAC (Toliddaru Company, Iran) at a dose of 20 to 25 mg/kg on the first day, followed by a maintenance dose of 10 to 15 mg/kg BID for another 14 days based on a previous study (18). The control group received placebo, the same dose as the intervention group.

Blood samples were collected from the patients prior to the initiation of the study, and on the seventh and fifteenth days. The level of malondialdehyde (MDA) was also examined after centrifugation and plasma separation by UV spectrophotometry. The severity of oral mucositis, duration of treatment, length of hospitalization, fever, mortality rate, and speed of complete recovery were assessed for each patient. The corresponding CONSORT (Consolidated Standards of Reporting Trials) flow diagram is presented in Figure 1.

Randomization method

After informed consent was received from the parents or legal guardians, the eligible participants were randomly allocated to either the intervention or control group in a 1:1 ratio through block randomization with a block size of four. This approach was implemented to maintain balanced group sizes throughout the study. The randomization process was completed prior to the participant enrollment, resulting in 40 patients assigned to each group.

Ethical considerations

The study received approval from the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (ethical code: IR.AJUMS.REC.1401.326), and it was registered in the Iranian Registry of Clinical Trials (IRCT20210622051666N1). Prior to enrollment, written informed consent was obtained from the parents or legal guardians of all the participants.

Statistical analysis

The statistical analysis was performed with the SPSS software version 26 (IBM, USA). The continuous variables were summarized as mean ± SD, while the categorical variables were presented in frequencies (percentages). The data normality was assessed with both the Kolmogorov-Smirnov and Shapiro-Wilk tests.

The analyses were based on Chi-square tests and Fisher's exact tests. The malondialdehyde (MDA) levels were analyzed at different time points using descriptive statistics and between-group comparisons. The level of statistical significance was decided to be < 0.05.

Results

Eighty children participated in the present study. They were divided into two groups of 40 receiving N-acetylcysteine (NAC) (intervention group) and a placebo (control group). Their mean age in the control group was 10.23 ± 5.02 years, compared to 10.23 ± 4.74 years in the intervention group; this difference was not statistically significant (P = 0.99). Gender did not differ significantly between the two groups (0.99). Similarly, there were no statistically significant differences between the groups in terms of mean body mass index (17.42 ± 1.85 kg/m² in the NAC group versus 17.53 ± 1.96 kg/m² in the control group; P = 0.798). The mean body weight was also comparable between the intervention and control groups (30.79 ± 13.1 kg vs. 31.08 ± 13.71 kg; P = 0.923). Acute lymphoblastic leukemia (ALL) was the most common diagnosis in both groups, occurring in 45% of the intervention group and 50% of the control group (P = 0.942). No considerable differences were observed in the disease stage between the two groups (P = 0.952). Overall, the two groups were well matched at baseline with respect to demographic and clinical characteristics (Table I).

The incidence of oral mucositis grade 0 differed significantly between the NAC and control groups (72.5% vs. 47.5%, P = 0.030). Oral mucositis grade 1 was observed in 22.5% of the patients in the NAC group, compared with 2% of the patients in the control group. Furthermore, the occurrence of grade 3 oral mucositis was significantly lower in the intervention group than in the control group (0% vs. 10%, P = 0.030). There was no notable difference in fever episodes between the NAC and control groups (P = 0.071). The duration of fever in the NAC and control groups was 1.63 ± 2.04 and

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3.68 ± 4.77 days, respectively (P = 0.016). The hospital stays in the NAC and control groups was statistically different (4.55 ± 1.01 vs. 5.8 ± 1.22, P = 0.001). More details are shown in Table II.

The distribution of oral mucositis severity and other clinical outcomes is shown in Table III. NAC was associated with a considerable shift toward lower mucositis severity compared to the control group. The incidence of clinically significant oral mucositis (Grade ≥ 2) was notably lower in the NAC group, with a relative risk (RR) of 0.18 (95% CI: 0.04-0.77). The levels of MDA before the start of the study in the NAC and control groups were 8.39 ± 0.40 and 8.57 ± 0.27 µmol/L, respectively, but there was no statistically significant difference (P = 0.72). The levels of MDA on the seventh days were significantly different between the two groups (4.73 ± 0.36 µmol/L in the NAC group vs. 8.89 ± 0.26 µmol/L in the control group, P < 0.001). The levels of MDA on the fifteenth days in the NAC and control groups were 2.76 ± 0.31 and 6.06 ± 0.23 µmol/L, respectively (P < 0.001) (Table IV).

There was no considerable difference in side effects between the NAC and control groups (P = 0.367). No significant difference was also observed between the reasons for patient withdrawal in the NAC and control groups (P = 0.811) (Table V).

Table I: Demographic and clinical parameters in the NAC and control groups

Variable	NAC group (n = 40)	Control group (n = 40)	P-value
Age (in years)	10.23 ± 4.74	10.23 ± 5.02	0.99
Sex, Male	20 (50)	20 (50)	0.99
Weight (kg)	30.79 ± 13.1	31.08 ± 13.71	0.923
Height (cm)	129.04 ± 22.18	128.84 ± 23.46	0.970
BMI	17.42 ± 1.85	17.53 ± 1.96	0.798
Disease type, n (%)			
ALL	18 (45)	20 (50)	0.942
AML	9 (22.5)	9 (22.5)	
HL	8 (20)	6 (15)	
Non-HL	5 (12.5)	5 (12.5)	
Stage of disease, n (%)			
II	16(40%)	15(37.5%)	0.952
III	17(42.5%)	17(42.5%)	
IV	7(17.5%)	8(20%)	

BMI: Body mass index, ALL: Acute Lymphoblastic Leukemia, AML: Acute myeloid leukemia, HL: Hodgkin lymphoma, Non-HL: Non- Hodgkin lymphoma, n: number

Table II: Severity of oral mucositis, fever episodes, duration of fever (days), and length of hospitalization between the two groups

Variable		NAC group (n = 40)	Control group (n = 40)	P-value
Oral mucositis severity	0	29(72.5)	19(47.5)	0.030
	1	9(22.5)	10(25)	
	2	2(5)	7(17.5)	
	3	0(0)	4(10)	
Fever episodes	0	22(55)	23(57.5)	0.071
	1	12(30)	6(15)	
	2	6(15)	6(15)	
	3	0(0)	5(12.5%)	
Fever duration (days)		1.63 ± 2.04	3.68 ± 4.77	0.016
Hospital stay (days)		4.55 ± 1.01	5.8 ± 1.22	0.001

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Table III: Distribution of oral mucositis severity and clinical outcomes with effect size analysis for the two groups

Oral mucositis severity	NAC group (n=40)	Control group (n=40)	Effect size (95% CI)	P-value
Oral mucositis Grade 0, n (%)	29 (72.5)	19 (47.5)	-	0.030
Oral mucositis Grade 1, n (%)	9 (22.5)	10 (25)	-	-
Oral mucositis Grade 2, n (%)	2 (5.0)	7 (17.5)	-	-
Oral mucositis Grade 3, n (%)	0	4 (10)	-	-
Oral mucositis Grade ≥ 2, n (%)	2 (5.0)	11 (27.5)	RR = 0.18 (0.04-0.77)	0.030

Table IV. Malondialdehyde (MDA) enzyme activity in the NAC and control groups

MDA	NAC group (n = 40)	Control group (n = 40)	P-value
Day 0 (µmol/L)	8.39 ± 0.40	8.57 ± 0.27	0.072
Day 7 (µmol/L)	4.73 ± 0.36	8.89 ± 0.26	< 0.001
Day 15 (µmol/L)	2.76 ± 0.31	6.06 ± 0.23	< 0.001
P-value	< 0.001	< 0.001	

Table V: Drug side effects and dropout reason in the NAC and control groups

Variable	NAC group (n = 40)	Control group (n=40)	P-value
Adverse reaction			
Diarrhea	1(2.5)	2(5)	0.367
Fatigue	3(7.5)	3(7.5)	
Flushing	2(5)	0(0)	
Gastrointestinal pain	1(2.5)	0(0)	
Headache	2(5)	3(7.5)	
Nausea	4(10)	2(5)	
Severe allergic reaction	1(2.5)	0(0)	
Stomach pain	0(0)	4(10)	
Vomiting	2(5)	2(5)	
Dropout reason			
COVID-19 infection	1(2.5)	2(5)	0.811
Gastrointestinal pain	1(2.5)	2(5)	
Parental request	2(5)	3(7.5)	
Severe allergic reaction	1(2.5)	0(0)	
Unable to contact	2(5)	3(7.5)	

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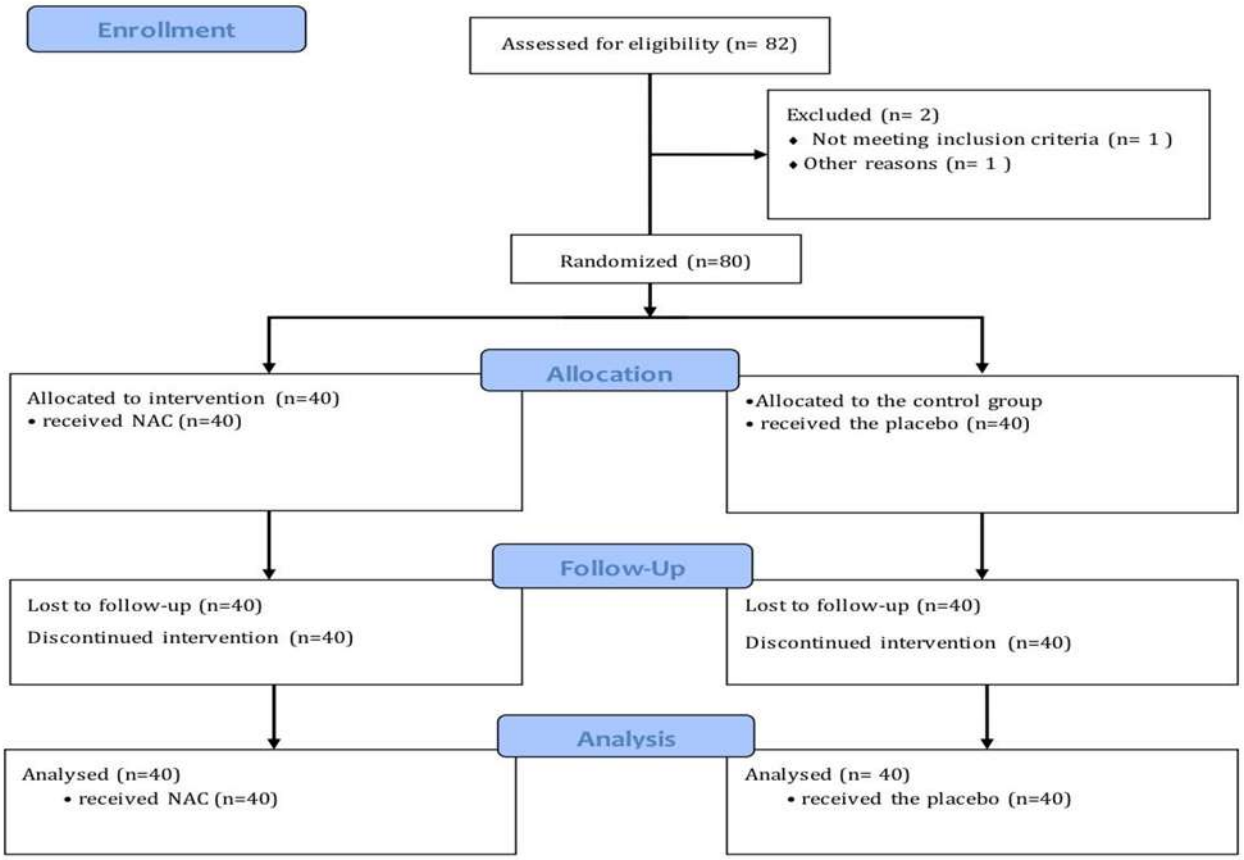

Figure 1. The CONSORT flow diagram

Discussion

Oral mucositis (OM) remains as one of the most clinically relevant and dose-limiting toxicities in pediatric oncology, significantly affecting treatment adherence, quality of life, and healthcare utilization (3, 19). In pediatric oncology, oral mucositis is a common treatment-related toxicity, occurring in approximately 40-60% of the cases. Its occurrence increases with the use of aggressive chemotherapeutic agents, such as methotrexate and 5-fluorouracil (20). In this research, NAC was related to a reduction in the severity of chemotherapy-induced oral mucositis, along with improvements in several related clinical outcomes, including duration of fever, length of hospital stays, and oxidative stress marker levels in pediatric cancer patients.

In line with previous research, the findings of this study correspond to those reported by Moslehi et al. (18), who found that NAC can decrease both the occurrence and duration of severe oral mucositis in hematopoietic stem cell transplant recipients. Similarly, experimental studies have demonstrated that NAC inhibits ROS production and reduces chemotherapy- and radiotherapy-induced mucosal injury, supporting its cytoprotective effects (18).

Also, beyond local mucosal protection, the observed reductions in fever duration and hospitalization length may reflect an overall decrease in systemic inflammatory burden and improved treatment tolerance, which are particularly important in pediatric oncology

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settings. Consistent with our findings, Essam et al. (21) reported that the patients receiving NAC nano-spray experienced a significant decrease in WHO mucositis scores compared to the control group. These beneficial effects persisted throughout the treatment period.

In addition, Sio et al. (22) demonstrated that NAC-based interventions may improve oral mucosal symptoms and xerostomia during and after radiotherapy, highlighting its clinical tolerability and potential benefit in supportive care settings. Furthermore, Kim et al. (23) showed that NAC can attenuate radiation-induced oxidative stress and inhibit mucosal cellular damage through the suppression of ROS production and downstream signaling pathways. Experimental evidence by Fonseca et al. (24) also supports the anti-inflammatory and antioxidant effects of cysteine-related compounds in chemotherapy-induced mucosal injury models. Unlike the study by Fonseca's team, which was performed on a hamster model, the present study was performed on a human pediatric population, thereby providing direct clinical evidence of the effects of NAC in chemotherapy-induced oral mucositis.

In another study, Trimarchi et al. (25) examined the effects of NAC, an antioxidant compound, on malondialdehyde (MDA) levels in patients undergoing hemodialysis (HD). They reported a significant reduction of MDA in the NAC group. Their findings were consistent with our results.

Our findings are also in similar to those of Lalla et al. (26), who reported that topical NAC could significantly reduce the severity of oral mucositis during radiotherapy.

Due to certain limitations, the results of this study should be viewed with caution. Since it was a single-center study, the applicability of the findings to broader patient populations and different clinical contexts may be reduced. Additionally, the rather small sample size may have limited the statistical power of the study and the feasibility of conducting more detailed subgroup analyses. Third, the heterogeneity of the chemotherapy regimens administered to the patients, including methotrexate, 5-fluorouracil, melphalan, doxorubicin, and other agents with different mucotoxic profiles, may have introduced residual confounding. Since the type and intensity of chemotherapy can have significant impacts on the severity of oral mucositis, this variability may have affected the interpretation of NAC efficacy. In this regard, and no stratified or multivariable adjustment was performed. Finally, the relatively short follow-up duration may have limited the assessment of long-term outcomes and delayed adverse events.

Conclusion

The use of NAC contributed to a lower severity of oral mucositis in patients undergoing chemotherapy. It also improved some related clinical outcomes, including duration of fever, length of hospital stays, and oxidative stress marker levels in pediatric cancer patients. Despite these promising findings, caution is warranted in their interpretation because of the study's single-center design, limited sample size, and variability in chemotherapy regimens. Future multicenter studies involving larger populations, longer follow-up periods, and regimen-specific stratified or adjusted analyses are needed to confirm the observed effects and enhance the generalizability of the results.

Availability of Data

Available upon reasonable request from the authors.

Acknowledgements

None. No AI program was used during the development of this research paper.

Conflict of Interest

There is no conflict of interests regarding this research.

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Ethical Considerations

The study received approval from the Ethics

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Committee of Ahvaz Jundishapur University of Medical Sciences (ethical code: IR.AJUMS.REC.1401.326), and it was registered in the Iranian Registry of Clinical Trials (IRCT20210622051666N1). Prior to enrollment, written informed consent was obtained from the parents or legal guardians of all the participants.

Authors' Contributions

S.D, and F.H did the conceptualization and design of the study. M.AS and F.H, S.D, K.J, R.G and N.NGF contributed to the data collection. M.AS and F.H, S.D, Z.D, L.K, K.J and N.NGF prepared the first draft of the manuscript. Z.D and K.J, L.K, and R.G critically revised and closely checked the proposal, the analysis and interpretation of the data and the design of the article. All the authors read and approved the final manuscript.

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