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The effect of oral curcumin on vincristine-induced neuropathy in pediatric acute lymphoblastic leukemia: A double-blind randomized controlled clinical trial

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Abstract

Background Peripheral neuropathy is a major adverse effect of Vincristine (VCR) in pediatric acute lymphoblastic leukemia (ALL) patients. Curcumin can prevent the development of many neurological diseases.

Method This clinical trial study was conducted on 141 pediatric ALL patients, all over 5 years old. The subjects were randomly divided into a curcumin-treatment group and a placebo group. In the curcumin-treatment group, patients received 3 mg/kg oral curcumin capsules twice a day for 3 months. In the placebo cohort, participants were administered placebo capsules twice a day for 3 months. Administration of VCR was started in all patients in both groups, with a weekly dose of 1.5 mg/m².

Result Overall, 39.4% of participants in the curcumin treatment group and 70.0% in the placebo group had VIPN. Thus, a significant difference in the incidence of VIPN was observed in the two groups ($P < 0.001$). A significantly higher frequency of motor nerve abnormalities in all types of nerves was observed in the placebo group than in the curcumin treatment group ($P < 0.05$).

Conclusions The results of our study showed that curcumin is effective in preventing the development of VIPN and leads to the improvement of VIPN in these patients. Our findings indicate that the prevalence of VIPN was substantially lower in the curcumin-treated group compared to the placebo group, as confirmed by both NCS and EMG assessments. Furthermore, curcumin demonstrated a protective effect against motor and sensory nerve damage, with a significant reduction in motor nerve abnormalities.

Trial registration This study was registered at <https://irct.behdasht.gov.ir/trial/73161>. Trial registration number: IRCT20201107049296N3. Date of registration: 2022-09-11.

Keywords Curcumin, Acute lymphoblastic leukemia, Pediatrics, Vincristine, Neuropathy

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Introduction

Approximately a quarter of the cancers that have been identified can be attributed to pediatric acute lymphoblastic leukemia (ALL) [1–3]. As a result, ALL stands as the most prevalent form of cancer in children [4]. The age range at which the incidence of ALL reaches its highest point is typically between the ages of two and five [5]. In Iran, hematological malignancies are among the sixth most common types of malignancies in both men and women [6–8].

Vincristine (VCR) is a vinca alkaloid that is used to treat several malignancies, such as acute lymphoblastic leukemia, neuroblastoma, juvenile stromal tumor, Wilms' tumor, rhabdomyosarcoma, Hodgkin's lymphoma, and non-Hodgkin's lymphoma in children [9]. The VCR blocks cell division by inhibiting the mitotic spindle [10]. VCR has been a widely used chemotherapy agent in pediatric oncology for decades [11]. It has been found in previous studies that VCR administration as part of a chemotherapy regimen is known to cause peripheral neuropathy [12, 13]. Unfortunately, chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect of anticancer therapy caused by vinca alkaloids and other chemotherapy medications, affecting approximately 30–40% of patients [14]. Pain, reduced sensitivity, areflexia, paresthesia, and muscle weakness are symptoms of peripheral sensory-motor neuropathy caused by VCR [15]. Studies have shown that VIP can be related to gender, age, high-risk ALL patients, etc [16, 17].

Non-steroidal anti-inflammatory drugs and opioids, which are conventional analgesics, are clinically ineffective in reducing CIPN. Therefore, finding a suitable method to prevent or treat VCR-induced peripheral neuropathy (VIPN) is valuable.

Nowadays, curcumin (diferroylmethane) present in turmeric has been noticed due to its anti-cancer, anti-inflammatory, antioxidant, and neuroprotective properties and activities both in animal models and in humans [18–20].

In several animal pain models, including diabetic neuropathic pain, curcumin has also been reported to have antinociceptive effects. Curcumin can prevent many neurological diseases for various reasons, including versatility, cheap cost, long history of use, and oral safety [21]. It has been found that curcumin can potentially reduce the damage caused by spinal cord injury by reducing the expression of glial fibrillary acidic protein [22]. Curcumin can promote neuronal survival in SCI by reducing glial fibrillary acidic protein expression, protecting spinal cord tissues against oxidative stress, lowering tissue malondialdehyde levels, and increasing tissue glutathione peroxidase, superoxide dismutase, and catalase activity and anti-inflammatory effects [22, 23]. In a meta-analysis study, the authors concluded that curcumin improves

neurological recovery and antioxidant effects in SCI in mouse models. The mechanism of action of curcumin in SCI may be related to its antioxidant effect, including inhibition of free radicals, or neuroprotective action [24]. In another study aimed at investigating the effect of curcumin on diabetic peripheral neuropathic pain, the authors concluded that curcumin can be considered as a new therapeutic potential for the treatment of diabetic neuropathic pain, and the activation of the opioid system may be involved in the analgesic effect of curcumin [25]. In another study, the authors concluded that curcumin can prevent the development of chronic neuropathic pain in rats with peripheral nerve damage [26].

In human studies, a study has shown that curcumin supplementation can improve and reduce the severity of diabetic sensorimotor polyneuropathy in patients with type 2 diabetes [27]. This double-blind, randomized, controlled clinical trial was conducted to investigate the effect of oral curcumin in preventing the development of VIPN in pediatric ALL patients.

Materials and methods

Study participants

This double-blind, randomized trial was carried out between July 2022 and October 2023. A total of 155 new cases of pediatric ALL patients were randomized in this study at Ali-Asgar Hospital, Tehran, Iran. A checklist was used to collect demographic and basic clinical data before the study began. Newly diagnosed pediatric oncology patients aged 5 to 15 years were included in the study. Patients whose treatment protocol included at least four VCR administrations within six weeks were eligible for the study. The determination of the sample size was conducted by considering a study power of 80%, along with a type one error (α) of 5% and a statistical significance level (α) of 95% ($P=0.05$). For this purpose, the SPSS 25.0 software (Inc., Chicago, IL, USA) was utilized. A biostatistician performed the randomization process, employing a 1:1 allocation rate. The randomization method followed a simple approach using a computerized random number table located within the clinic. Consequently, the patients were allocated randomly into two groups, namely the curcumin-treatment group and the placebo group. All classification was conducted according to prognostic factors and divided into two categories: standard and high risk [28]. The flowchart of the study is shown in Fig. 1.

Inclusion and exclusion criteria

Inclusion criteria included the following: male and female patients with ALL aged 5 to 15 years; children who were recently diagnosed with ALL and had not yet started treatment with VCR; and the signing of an informed consent form by parents.

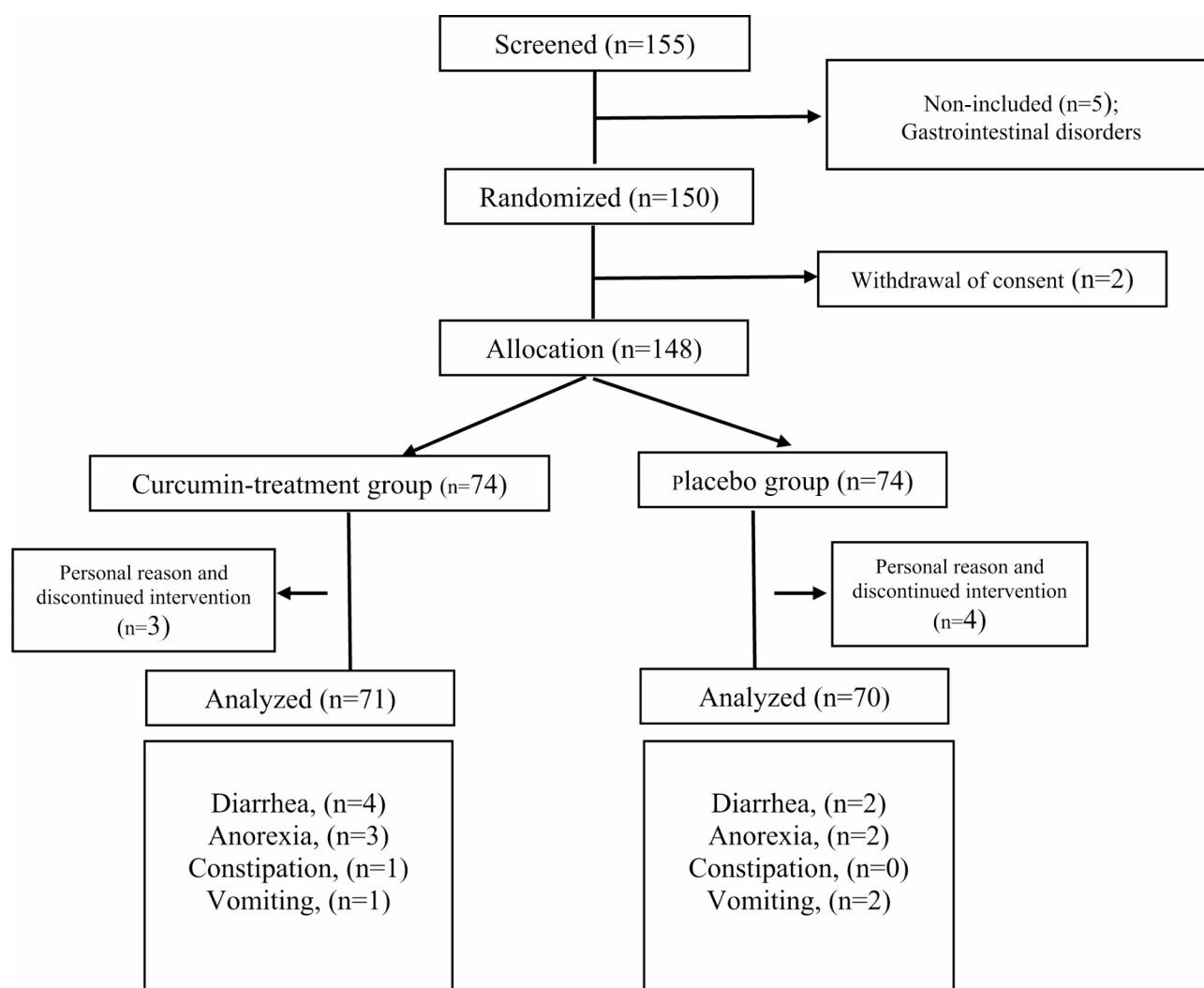


Fig. 1 Flow chart of study procedure. No significant difference was observed in terms of gastrointestinal complications between the two groups ($P > 0.05$)

Study exclusion criteria included the presence of neuropathy and myopathy before treatment with VCR, patients treated with other drugs leading to neuropathy such as etoposide and platinum-based agents, taxanes, and thalidomide and its analogs, taking anti-inflammatory and antioxidant drugs during the study, children who underwent cranial irradiation, primary involvement of the central nervous system, patient non-cooperation in taking curcumin, preexisting intellectual disability and congenital anomalies, and developmental problems.

Study interventionintervention

Administration of VCR was started in all patients in both groups, with a weekly dose of 1.5 mg/m^2 . In the curcumin-treatment group, patients received 3 mg/kg oral curcumin capsules twice a day for 3 months (prepared by Dineh Pharmaceutical Company, Tehran, Iran). In the placebo cohort, participants were administered placebo capsules (comprised of starch) twice a day for 3 months

(prepared by Dineh Pharmaceutical Company, located in Tehran, Iran).

Curcumin and placebo were labeled by nurses with black and white markers, respectively, so researchers and patients were blinded to treatment allocation until the end of the study. Then, based on the randomization program, the nurse distributed colored capsules to the patients by assigning an identification code to each patient. Parents were asked to be careful when taking medicine and not to stop taking medicine for any reason without consulting a doctor. Parents were also asked to record the number of supplements taken to determine treatment adherence. Ultimately, the results were collected and subjected to analysis by the assigned identification codes. The parents were duly advised to exercise caution in the administration of the medications and were expressly instructed not to discontinue their usage without prior consultation with a medical professional. The parents were also requested to maintain a record of

the number of supplements taken, thereby enabling the determination of the adherence level to the prescribed treatment.

During the treatment period, the patients were subjected to clinical and physical examinations, and any type of side effect caused by the use of the drug was recorded.

Electrophysiological studies

Before starting treatment with VCR, the presence or absence of neuropathy in patients was evaluated by electrophysiological nerve conduction studies (NCSs). The electrodiagnostic evaluation included a Nerve Conduction Study (NCS) and needle electromyography (EMG) (Nemus, Biomedica, model number 00655, Galileo NT software version 3.71/00, Italy). During NCS, sensory and motor responses of bilateral upper (i.e., median, ulnar, and radial nerves) and lower (i.e., peroneal, tibial, and sural nerves) extremities were recorded using the techniques provided by Dumitru and Amato [29]. The reference values for each nerve were according to Preston and Shapiro [30]. After the completion of the 3-month treatment period with curcumin and placebo, the patients of the two groups underwent electrophysiological testing again, and the presence or absence of neuropathy was evaluated in the two groups.

Differences between motor and sensory findings will be reported in the NCS results. For the NCS motor, the peroneal and tibial nerves in the lower limb and the median and ulnar nerves in the upper limb were examined for each section. For sensory NCS, superficial peroneal and sural nerves were examined in the lower limb and median and ulnar nerves in the upper limb for each section. Room temperature and skin temperature were maintained at around 32 °C during the procedure. Children who were at least 4 years old were deemed to have achieved the NCS reference ranges typically seen in adults [31]. Therefore, for this group, values that deviated from the normal mean values of our laboratory by more than 2 standard deviations were considered abnormal [32]. Electrophysiological evidence of neuropathy was defined as the presence of abnormal NCS parameters (including distal motor latencies, motor and sensory action potential amplitudes, and/or motor and sensory nerve conduction velocities) in two or more nerves. Following the NCS, we performed an EMG on the upper and lower limbs.

The Total Neuropathy Score Pediatric VCR (TNS-PV) evaluation includes tendon reflex, vibration, temperature, subjective symptoms, muscle tone, and the presence of autonomic and laryngeal neuropathy. The seven items obtained ratings ranging from 0 to 4 on a Likert-type scale. The cumulative scores of TNS-PV are evaluated within the interval of 0 to 28, with higher scores reflecting greater severity of peripheral neuropathy.

TNS-PV and NCS were performed at the Ali-Asghar Hospital, Tehran, Iran. The diagnosis of VIPN was established solely if both the TNS-PV score ≥ 4 and electrophysiological criteria were simultaneously observed, based on the consensus on the definition of symmetrical polyneuropathy [33]. Considering that different results of the relationship between VIPN and gender have been reported in previous studies, we evaluate the relationship between VIPN and gender in this study [34, 35]. The occurrence of VIPN was considered the primary endpoint.

Statistical analysis

Statistical analyses were performed using SPSS 25.0 software (Inc., Chicago, IL, USA). The results were presented as the mean $\pm$ standard deviation (SD) for numerical variables. A one-way analysis of variance was used to compare the mean of the variables. The statistical significance of the differences in the curcumin and placebo groups was calculated using Pearson's χ^2 test. Statistical significance was defined as a *p*-value less than 0.05.

Results

Demographics

A total of 141 pediatric ALL patients were analyzed in this study. Seventy-five patients (53.2%) were male, and 66 patients (46.8%) were female. The mean $\pm$ SD age of the patients was 8.4 ± 2.3 years. According to the tabulation of the number of capsules consumed, it was determined that a proportion exceeding 94% of the capsules were utilized by the patients, thus indicating that the patient's compliance with the prescribed treatment regimen was deemed satisfactory. None of the patients disclosed any particular adverse reactions as a result of their ingestion of curcumin, and all patients exhibited a generally favorable tolerance towards the encapsulated form of the substance. A few patients experienced mild gastrointestinal symptoms, which subsequently resolved without intervention within a short period. Gastrointestinal (GI) complications were also evaluated in patients of both groups based on diarrhea, anorexia, constipation, and vomiting. No significant difference was observed in terms of gastrointestinal complications between the two groups (*P* > 0.05).

There was no statistically significant difference between the study groups in the mean age, height, weight, body mass index, or gender (Table 1).

Nerve conduction study data

The mean and standard deviation of TNS-PV after intervention in two groups are shown in Table 2. In total, According to TNS-PV, about 52.3% of patients had VIPN, and according to NCS, about 75.7% of patients had VIPN. According to TNS-PV, 42.6% of patients in the curcumin

Table 1 Demographic characteristics

Characteristics	Curcumin group (N= 71)	Placebo group (N= 70)	P _{value}
Mean age ± SD, yrs	8.4 ± 2.2	8.5 ± 2.5	0.587
Min-Max	5–14	5–15	
Gender, n (%)			
Male	41 (57.7)	34 (48.6)	0.275
Female	30 (42.3)	36 (51.4)	
Mean weight ± SD, Kg	36.2 ± 18.2	34.4 ± 14.7	0.497
Mean height ± SD, Cm	138.1 ± 19.9	137.9 ± 20.1	0.656
Mean body mass index ± SD, Kg/m ²	14.3 ± 8.9	14.1 ± 10.0	0.881
Cumulative dose of Vincristine (mg / m ²), median (min-max)	39 (13.2–54.4)	36 (14.0–53.5)	1.000
ALL classification, n (%)			
ALL standard risk	44 (62.0)	35 (50.0)	0.152
ALL high risk	27 (38.0)	35 (50.0)	

SD; Standard of deviation, n; number, ALL; acute lymphoblastic leukemia. ^aPearson's χ^2 test was used, ^bStudent t-test was used. The student's t test is used to compare the means between two groups (continuous variables). Pearson's χ^2 test for dichotomous variables. $p < 0.05$ was considered significant

Table 2 Involvement pattern of nerves in VIPN in patients with ALL

Variable	Curcumin group (N= 71)	Placebo group (N= 70)	p-value
Motor Nerve; n			0.012 ^{a, c}
Median	7/71	16/70	
Ulnar	5/71	10/70	
Peroneal	12/71	18/70	
Tibial	6/71	10/70	
Total	30/284	54/280	
Sensory Nerve; n			0.444 ^{a, c}
Median	4/71	3/70	
Ulnar	2/71	2/70	
Superficial peroneal	5/71	2/70	
Sural	3/71	3/70	
Total	14/284	10/280	
TNS-PV, Mean ± SD			
After intervention	3.0 ± 1.4	7.8 ± 3.6	< 0.001 ^b
VIPN, n (%)	28 (39.4)	49 (70.0)	< 0.001 ^a
EMG results; Myopathy, n (%)			0.002 ^a
Lower limb	6 (8.5)	20 (28.6)	
Upper limb	6 (8.5)	17 (25.4)	

VIPN; Vincristine-induced peripheral neuropathy, n; number, ALL; acute lymphoblastic leukemia, TNS-PV; Total Neuropathy Score Pediatric Vincristine. ^aPearson's χ^2 test was used, ^bStudent t-test was used. ^cp value for the total number of motor or sensory nerves with abnormal results. $p < 0.05$ was considered significant

treatment group and 66.4% of patients in the placebo group had VIPN, and according to NCS, 62.1% of patients in the curcumin treatment group and 82.5% of patients in the placebo group had VIPN. Overall, 39.4% of participants in the curcumin treatment group and 70.0% in the placebo group had VIPN. Thus, a significant difference in the incidence of VIPN was observed in the two groups ($P < 0.001$). There was no significant difference in the prevalence of VIPN between males and females ($P > 0.05$).

In this study, the incidence of VIPN was significantly higher in the high-risk ALL group compared to the standard-risk group (55/79 vs. 25/62, $P = 0.026$).

NCS was performed on all patients. We considered abnormal NCS results as the potential presence

of neuropathy. Abnormal findings were found in one or more motor or sensory nerves. The rate of damaged nerves in the curcumin-treatment group among motor and sensory nerves was 10.5% and 4.9%, respectively, which shows a statistically significant difference ($P = 0.02$). This rate in the placebo group was 19.2% and 3.5%, respectively, for motor and sensory nerves, which also showed a significant difference ($P < 0.001$). In the curcumin group, most motor and sensory nerve abnormalities were observed in the peroneal and superficial peroneal nerves, respectively. Also, in the placebo group, the most involvement of the motor nerves was seen in the peroneal nerves and in the sensory nerves in the median and sural nerves (Table 2).

A significantly higher frequency of motor nerve abnormalities in all types of nerves was observed in the placebo group than in the curcumin treatment group ($P=0.012$).

Twenty-one (29.5%) patients in the curcumin treatment group had sensorimotor abnormalities, and in the placebo group, 26 (37.1%) patients had sensorimotor abnormalities in NCS examinations ($P=0.440$).

Needle electromyography data

There were findings of abnormal needle EMG in 17.0% of patients in the curcumin treatment group and 54.0% of patients in the placebo group. Thus, a significant difference in the incidence of VIPN was observed in the two groups ($P=0.002$). In the curcumin group, neuropathy or abnormal needle EMG was diagnosed in 26/71, or 36.6%, of the patients. Neuropathy and abnormal needle EMG were present in (10/71, 14.0%) patients. In the placebo group, neuropathy or abnormal needle EMG was diagnosed in 38/70 (54.3%) of the patients. Neuropathy and abnormal needle EMG were present in 19 out of 70 (27.2%) patients.

Discussion

ALL is one of the most common cancers in children, and multi-agent chemotherapy regimens are used to treat it. Severe forms of CIPN usually improve after completion of the chemotherapy protocol, but about 8% remain, mainly due to VCR [36, 37]. The difference in the prevalence of VIPN in different studies is caused by different risk factors, including treatment factors such as dose, duration, concurrent medication, disease factors such as hematological malignancy, and patient factors such as age, genetic alterations in pharmacokinetic pathways, genetic alterations in pharmacodynamic pathways, and genetic susceptibility to hereditary neuropathy [36].

VCR serves as a highly significant therapeutic agent employed in the treatment of childhood malignancies. One of the side effects of VCR is neuropathy and abnormal needle EMG, so to continue treatment with VCR, patients must be protected from side effects [38]. If VIPN is not treated, it has destructive effects on the patient and reduces their quality of life [39].

So far, several methods have been reported to reduce the effects of VIPN, including the simultaneous administration of chemicals with VCR as well as pharmaceutical methods such as the administration of duloxetine, methadone, gabapentin, and group B vitamins. However, according to the guidelines of the American Society of Clinical Oncology, so far no effective factor has been identified to improve this complication, and this issue encourages us to study more about different factors in reducing VIPN [40].

In this study, the protective effect of curcumin was evaluated in pediatric ALL patients. The results of our

study showed that curcumin is effective in preventing the development of neuropathy caused by VCR and leads to the improvement of VIPN in these patients. In accordance with our results, some studies, as well as animal studies, have shown beneficial preventive effects of curcumin from the development of neuropathy.

In a study in a mouse model of VIPN, the authors recorded that curcumin significantly attenuated VIPN, which may be due to its multiple actions, including antinociceptive, calcium-inhibitory, and antioxidant effects [41]. In another study in patients with Type 2 diabetes mellitus, the authors reported that curcumin supplementation for 2 months improved and reduced the severity of diabetic sensorimotor polyneuropathy in patients with Type 2 diabetes mellitus [27]. Another study conducted in a mouse model provided evidence that curcumin administration over four weeks could effectively reduce neuropathic pain through inhibition of tumor necrosis factor- α and nitric oxide [42]. In another animal study, curcumin administration reduced neuropathic pain in diabetic rats through inhibition of NADPH oxidase [43].

In this study, the prevalence of VIPN was 62.1% based on NCS alone after VCR administration in the curcumin treatment group and 82.5% of patients in the placebo group, which is consistent with several previous studies in which the range of VIPN incidence during chemotherapy is 23.5–96.0% [44–46]. However, the diagnosis of VIPN based on both criteria was 39.4% in the curcumin treatment group and 70.0% in the placebo group. In a study that involved 54 4–18-year-old ALL survivors, VIPN based on both criteria was found in 15.8% of patients [16]. Tunjungsari et al. showed that 76.9% of patients had VIPN based on TNS-PV [17]. Another study diagnosed VIPN in 78% of patients using TNS-PV [44]. In this study, VIPN was diagnosed based on TNS-PV in 52.3% of patients. Also, in this study, it was observed that motor neuropathy predominates over sensory neuropathy in the electrophysiology of neuropathy in pediatric ALL patients in both groups. Similar results have been reported in previous studies in pediatric ALL patients [39].

Different results of the association between VIPN and gender have been reported. In agreement with previous studies [44, 47], in this study, there was no difference in the prevalence of VIPN between males and females. Other studies have shown that VIPN is related to gender, although results have been inconsistent [34, 35, 48].

In this study, the incidence of VIPN was significantly higher in the high-risk ALL group compared to the standard-risk group (55/79 vs. 25/62, $P=0.026$). These data are consistent with previously published data [16, 17]. The cause of this event can be due to the increase in the cumulative dose of VCR in the group of high-risk patients. Also, out of 27 high-risk patients in the

curcumin group, 22 patients showed VIPN, while 33 out of 35 patients in the placebo group had VIPN ($P=0.074$).

Oxidative stress has been implicated in nerve damage in animal and human studies [49, 50]. Although the underlying mechanisms of neuropathy in ALL patients are not fully understood, current evidence suggests that oxidative stress caused by chemotherapy agents is one of its main factors. An increase in the production of reactive oxygen species has been observed in previous studies in neurons exposed to some chemotherapy agents, such as cisplatin [51, 52]. Curcumin exhibits a broad range of pharmacological activities, including anti-inflammatory, antioxidant, anticancer, antimicrobial, reduction of blood fat, inhibition of lipoxygenase, liver protection, inhibition of cyclooxygenase, removal of free radicals, inhibition of proteases, inhibition of fat oxidation, reduction of platelet aggregation, reduction of cholesterol, and reduction of proliferation [53–56]. Through each of these mentioned mechanisms, curcumin, which has anti-inflammatory and antioxidant effects, can be useful in the treatment of neuropathy and abnormal needle EMG.

Our study had some limitations. The use of glucocorticoids is common in treatment protocols for ALL. The administration of these agents may result in adverse reactions that can simulate manifestations of VIPN, which cannot be attributed to VCR. However, we performed a similar distribution of common drug types in the two randomized groups to minimize bias. Furthermore, VIPN is a multifactorial phenomenon that is also influenced by VCR pharmacokinetics and single-nucleotide polymorphisms. Therefore, collecting data related to VCR pharmacokinetics and single nucleotide polymorphisms and analyzing these data can provide valuable information. It is also suggested to use a nano curcumin supplement instead of curcumin to increase bioavailability, but this needs further study. Another limitation of the study was the lack of genetic information and genetic markers that could be the reason for differences in neuropathy.

Conclusion

The results of our study showed that curcumin is effective in preventing the development of VIPN and leads to the improvement of VIPN in these patients. Our findings indicate that the prevalence of VIPN was substantially lower in the curcumin-treated group compared to the placebo group, as confirmed by both NCS and EMG assessments. Furthermore, curcumin demonstrated a protective effect against motor and sensory nerve damage, with a significant reduction in motor nerve abnormalities. Given its strong antioxidant and anti-inflammatory properties, curcumin may serve as a promising adjunct therapy for mitigating chemotherapy-induced neuropathy. However, further studies, including pharmacogenetic analyses and investigations into

nano-formulated curcumin, are warranted to optimize its therapeutic potential in ALL patients.

Abbreviations

VCR	Vincristine
ALL	Acute lymphoblastic leukemia
VIPN	VCR-induced peripheral neuropathy
TNS-PV	Total Neuropathy Score Pediatric VCR
CIPN	Chemotherapy-induced peripheral neuropathy
NCSs	Nerve conduction studies
EMG	Electromyography
SD	Standard deviation

Acknowledgements

We would like to thank all the individuals who contributed to this research at Ali-asgar Hospital, Tehran, Iran.

Author contributions

AE, AYE: Methodology, Project administration, Data curation, Software, Validation, Writing—original draft. MA, KM: Investigation, Methodology, Writing—original draft. FF: Writing—review and editing. RRA: Writing—review and editing. AG, KG: Conceptualization, Methodology, Funding acquisition, Formal Analysis, Supervision, Visualization, Writing—original draft, Writing—review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The present study was supported by Iran University of Medical Sciences, which has provided funding for this research (Grant No: 23534).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The local ethics committee of the Iran University of Medical Sciences approved the research protocol by the ethical code IRIUMS.FMD.REC.1401.313. The trial was registered at the Registry of Clinical Trials as IRCT20201107049296N3, First Trial Registration: 11/09/2022, Access: <https://irct.behdasht.gov.ir/trial/73161> and according to the CONSORT reporting guidelines. By the Helsinki Convention, and after obtaining informed consent from the patients (informed consent was obtained from parents for patients under the age of consent and from the patients themselves for those over the age of consent), the patients were included in the study. A safety committee that operates autonomously receives annual updates regarding the progress of the study, the occurrence of severe adverse events, and their characteristics. This committee concluded that there were no reasonable grounds to terminate the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 8 October 2024 / Accepted: 17 February 2025

Published online: 25 February 2025

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