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Comparing the Cardiotoxic Effects of Continuous Infusion and Bolus Injection of Doxorubicin in Children with Acute Lymphoblastic Leukemia (ALL): A Randomized Clinical Trial

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Abstract

Background: Cardiotoxicity is a common complication associated with chemotherapy drugs. However, limited evidence exists regarding the cardiotoxic effects of continuous infusion versus bolus injection of doxorubicin. Since no comprehensive study has been conducted on this issue in our country—particularly in Yazd city—this study aimed to compare the cardiotoxicity of bolus injection and continuous infusion of doxorubicin in children with malignancy.

Materials and Methods: This single-blind randomized clinical trial was conducted on 61 children with acute lymphoblastic leukemia (ALL) who were treated with doxorubicin in the Oncology Department of Shahid Sadoughi Hospital. Patients were randomly assigned into two groups: one group received doxorubicin via bolus injection (n=30), and the other via continuous infusion (n=31). Cardiac function was assessed using echocardiography before treatment and again 6 months after the start of chemotherapy. Data were analyzed using the Chi-square test, and independent T test. A p-value < 0.05 considered statistically significant.

Results: The mean age of participants was 9.2 ± 3.5 years. Of the 61 patients, 31 (50.8%) were boys and 30 (49.2%) were girls. Before treatment, all patients had a normal ejection fraction (EF). After 6 months of treatment, 30 patients (96.8%) in the continuous infusion group maintained a normal EF. In contrast, only 24 patients (80%) in the bolus injection group had a normal EF after treatment. The difference between the two groups in terms of EF was statistically significant (p = 0.04).

Conclusion: The frequency of cardiotoxicity was significantly higher in the bolus injection group compared to the continuous infusion group. Therefore, continuous infusion may be the preferred method of administering doxorubicin to reduce its cardiotoxic effects in pediatric patients.

Keywords: Acute lymphoblastic leukemia**,** Bolus, Injection, Cardiotoxicity, Doxorubicin

Introduction

Acute lymphoblastic leukemia (ALL) is the most common form of leukemia in children (1–4), with the highest incidence occurring between the ages of 2 and 5 years. Approximately 6,000 new cases of ALL are diagnosed annually in the United States (1). The development of this disease is thought to result from a combination of exogenous and endogenous factors, along with genetic susceptibility (1). Due to advancements in treatment, the global survival rate of childhood ALL has improved to approximately 90% (1-5). Doxorubicin, formerly known by the generic name Adriamycin (6, 7), is an effective treatment for patients with ALL. Although doxorubicin contributes to long-term survival, its use is associated with cardiotoxic effects, which can be chronic and progressive (7).

The exact mechanism of doxorubicin-induced cardiotoxicity remains unclear. However, studies suggest that the primary

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metabolite, doxorubicinol, plays a significant role. Doxorubicinol is more potent than doxorubicin in impairing both systolic and diastolic cardiac function. It is also more effective at inhibiting the sarcoplasmic reticulum calcium pump, the sarcolemmal Na^+/K^+-ATPase pump, and the F_0F_1 proton pump in mitochondria. Furthermore, doxorubicinol tends to accumulate in cardiac tissue, contributing to chronic cumulative cardiotoxicity. Notably, it is less effective than doxorubicin at inhibiting tumor cell growth (6).

Recent studies have explored whether bolus injection or continuous infusion of doxorubicin is more likely to cause cardiotoxicity.

Ejection fraction (EF) is a key indicator of cardiac function, representing the percentage of blood pumped out of the ventricles with each heartbeat. It provides valuable insight into a range of myocardial conditions, including ischemia, congenital heart disease, conduction abnormalities, infectious and granulomatous diseases (8).

Lipshultz et al. (7) reported that a 48-hour continuous infusion of doxorubicin in children offered no cardioprotective benefit compared to bolus infusion. Similarly, Gupta et al. (9) evaluated cardiotoxicity in patients 7 years after doxorubicin via bolus or continuous infusion. They found that 20% of patients in the bolus group and 11% in the infusion group exhibited reduced cardiac function, though the difference was not statistically significant. Given that cardiotoxicity is a known complication of chemotherapy (6), and because the impact of continuous versus bolus infusion of doxorubicin on heart health is still not well understood—with contradictory findings reported in the literature (10–15)—and considering that no comprehensive study has been conducted on this topic in children with malignancy in our country, particularly in Yazd city, this study was designed to compare the cardiotoxic effects of bolus injection versus continuous infusion of doxorubicin in pediatric patients with malignancy.

Materials and Methods

Sample selection

This single-blind randomized clinical trial was conducted on 61 children diagnosed with acute lymphoblastic leukemia (ALL) who received doxorubicin treatment in the Oncology Department of Shahid Sadoughi Hospital. All patients were managed in accordance with the established treatment protocol. Then patients were randomly assigned to two groups: one group received doxorubicin via bolus infusion (n = 30), and the other via continuous infusion (n = 31), at a dosage of 40–60 mg/m². Cardiac function was assessed using echocardiography before treatment and again 6 months after the initiation of chemotherapy. It should be noted that in this study, the researcher was unaware of the prescribed drug (single-blind design).

Figure 1 shows the consort flowchart.

The inclusion criteria were:

- Normal baseline echocardiography
- Written informed consent from parents or guardians
- Age under 18 years
- Newly diagnosed cases of ALL undergoing treatment with doxorubicin as part of their chemotherapy regimen

Exclusion criteria included:

- Prior history of chemotherapy or radiation therapy
- Diagnosis of congenital heart disease
- Existing heart failure
- Renal failure

EF of these patients was classified as follows (8).

EF> 55% Normal. Indeed, participants in the Framingham Heart Study with an ejection fraction (EF) of 50–55% had a higher risk of heart failure and death

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compared to those with an EF greater than 55%. Olivieri reported that the LVEF normal range was 55-74% (16).

Ethical Consideration

The Ethics Committee of Shahid Sadoughi University of Medical Sciences approved the current study (IR.SSU.MEDICINE.REC.1402.126).
Moreover, this study was registered in The Iranian Registry of Clinical trial (IRCT20180209038673N7).

Statical analysis

Data were entered and analyzed using SPSS software, version 19. The distribution of patients between the two groups was assessed using the Chi-square test. The comparison of the mean age between the two groups was assessed using Independent T test. A p-value of < 0.05 was considered statistically significant.

Results

In the present study, the mean age of patients was 9.2 ± 3.5 years. Of the total participants, 31 were boys and 30 were girls. A comparison of the demographic characteristics of the patients is presented in Table I. As shown in Table I, no significant differences were observed between the two groups in terms of gender and age (P > 0.05).
The distribution of patients in the two groups before chemotherapy regarding echocardiography status is presented in Table II.
The comparison of patients in the two groups in terms of EF value is shown in Table III. As shown in Table III, a significant difference was seen between the two groups in terms of the frequency of patients in the two groups (P<0.05).

Table I: The comparison of demographic characteristics of patients

Variables	Group 1	Group 2	P-value
Gender			
Boy	17	14	0.52
Girl	14	16	
Age (years)	9.2±3.3	9.3±3.51	0.9

Table II: The frequency of patients in the two groups before chemotherapy

Frequency of patients before chemotherapy	Normal Echocardiography
61 (100)	*61 (100)*

Table III: The comparison of patients in the two groups in terms of EF value (after therapy)

EF value	Bolus infusion N (%)	Continuous infusion N (%)	Total	P-value
Normal	*24 (80)*	*30 (96.8)*	*54 (88.53)*	
Abnormal	*6 (20)*	*1 (3.2)*	*7 (11.47)*	*0.04*
Total	*30 (100)*	*31 (100)*	*61 (100)*	

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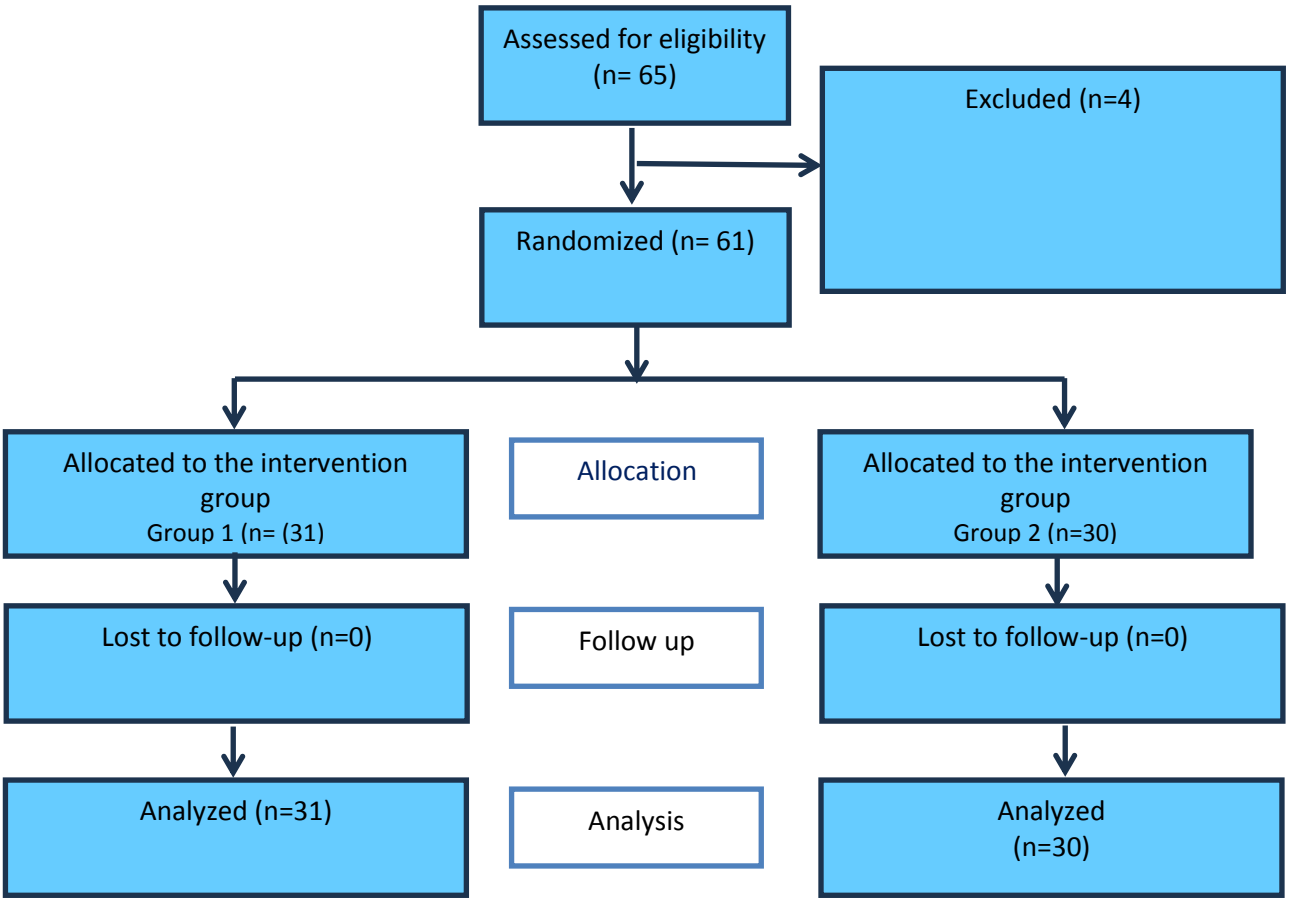

Figure 1. The consort flowchart

Discussion

Anthracyclines have been used to treat childhood malignancies for over three decades. Treatment protocols have varied depending on tumor type, dosage, and total cumulative dose; however, the primary concern remains anthracycline-induced cardiotoxicity (10, 11).

There are limited and conflicting findings comparing bolus and infusion administration of doxorubicin in terms of cardiac outcomes in pediatric cancer patients (11). In our study, we compared continuous infusion versus bolus injection of doxorubicin in children with ALL and found that the cardiotoxic effects were lower in the continuous infusion group. Steven E. Lipshultz et al. (12) evaluated the effects of continuous and bolus infusion of doxorubicin in children with ALL. Both groups had normal baseline left ventricular (LV) characteristics, and the median follow-up was 8 years. Their findings indicated no long-term cardioprotective benefit of continuous infusion over bolus infusion. It appears that the difference between our results and those of Lipshultz et al. may be due to the duration of follow-up.

In another randomized study by Lipshultz et al. (7), children with ALL were divided into two groups. One group received doxorubicin (360 mg/m² in 30 mg/m² doses) via bolus infusion over 1 hour every 3 weeks, and the other received it via continuous infusion over 48 hours. Echocardiograms were conducted before treatment and at the longest follow-up

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period. The study concluded that there was no cardioprotective advantage of continuous infusion over bolus injection, with both methods leading to progressive subclinical cardiotoxicity. These findings suggest that alternative cardioprotective strategies may be necessary.

Ephraim S. Casper investigated the impact of bolus versus continuous infusion in patients with soft tissue sarcoma and discovered that cardiotoxicity was observed in 61% of patients receiving bolus infusion (median dose 420 mg/m²), whereas it occurred in 42% of those receiving continuous infusion (median dose 540 mg/m²) (13). These results support our findings, indicating a higher cardiotoxicity rate with bolus administration.

Crammer et al. assessed the cardiotoxic effects of bolus versus continuous infusion of doxorubicin in patients with sarcoma and breast cancer. Their results showed similar cardiac event rates in both groups, regardless of the mode of administration (14). This discrepancy may be attributed to differences in cancer type, treatment duration, or cumulative dose.

G. N. Hortobagyi et al. investigated the cardiac toxicity of doxorubicin in patients with metastatic breast cancer and found that continuous intravenous infusion (over 48 or 96 hours) was better tolerated and safer than bolus injection (15). Doxorubicin induces cardiotoxicity not only through well-known mechanisms like oxidative stress, mitochondrial and DNA damage, and iron accumulation, but also through emerging pathways including autophagy and CYP1 enzyme activation (17). Similarly, Quintana et al. studied patients with sarcomas who received continuous infusion of doxorubicin (90 mg/m²) and ifosfamide (10 g/m²) for up to six cycles. Among 48 patients, none exhibited clinical signs of heart failure, though 4 out of 38 patients with serial LVEF assessments developed subclinical cardiotoxicity. These findings suggest that continuous infusion may help limit doxorubicin-related cardiotoxicity (18). Dorup et al. compared the effects of a cumulative doxorubicin dose of 180 mg/m² administered either by bolus or infusion, with follow-up periods of 5.3 ± 2.0 and 5.4 ± 1.0 years, respectively. They found subclinical abnormalities in left ventricular function in both groups, indicating that both methods may result in mild cardiac impairment (11).

Hany et al. also examined chemotherapy-induced cardiotoxicity and concluded that switching from bolus to infusion could reduce toxicity. Furthermore, they noted that cardioprotective agents, such as dexrazoxane, may reduce chemotherapy-induced cardiotoxicity in high-risk populations (19).

Droup reported that cardiotoxicity is primarily dependent on the cumulative dose of doxorubicin. To mitigate these side effects, several strategies have been proposed, including the use of novel anthracycline formulations, dose reduction, cardioprotective agents, prolonged infusions (6 to 96 hours), and modified scheduling (11).

Conclusion

Based on our findings, cardiotoxicity was significantly more frequent in the bolus injection group than in the continuous infusion group. Therefore, continuous infusion may be the preferred method for administering doxorubicin to reduce its cardiotoxic effects in pediatric patients with ALL.

Ethical Considerations

The Ethics Committee of Shahid Sadoughi University of Medical Sciences approved the current study (IR.SSU.MEDICINE.REC.1402.126).

Moreover, this study was registered in The Iranian Registry of Clinical trial (IRCT20180209038673N7).

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During the preparation of this work the author(s) did not use AI.

Authors' Contributions
A.H and SM. S Conceived, designed the analysis and edited the manuscript. E. Sh and F. Gh, R.K collected the data. R. K, E. Sh, and F. Gh wrote the paper.

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Conflict of Interest
None

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