Original Article *Iran J Ped Hematol Oncol. 2021, Vol 11, No 2, 91-95*

The role of supine and prone positions on central nervous system involvement in patients with acute lymphoblastic leukemia

Azam Hashemi MD [1,*]

1. Hematology and Oncology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
*Corresponding author: Dr Azam Hashemi, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Email: drazamhashemi@yahoo.com. ORCID ID: 0000-0002-1725-2007

Received: 19 September 2020 **Accepted:** 17 January 2021

Abstract

Background: Acute lymphoblastic leukemia (ALL) affects both children and adults, with a peak incidence between the ages of 2 and 5 years. ALL cells sometimes penetrate the central nervous system (CNS) and patients with CNS diseases at initial presentation have been reported to experience a significantly greater risk of treatment failure compared with CNS negative patients. This study hypothesized that the prone position may reduce the CNS involvement compared with the supine position, therefore the aim of this study was to evaluate the role of supine and prone positions on CNS involvement in ALL patients.

Materials and Methods: This randomized clinical trial was conducted on 38 patients with ALL admitted in Shahid saddughi Hospital from 2006 to 2016. In this study, 14 patients received prophylaxis intrathecal chemotherapy with post-injection supine position (control group) and 22 patients received prophylaxis intrathecal chemotherapy with post-injection prone position (intervention group) White blood cell (WBC) count (CNS involvement) was evaluated in two groups.

Results: Among 22 patients in the intervention group, 16 (72.7%) were males, and 6 (27.3%) were females and of the 14 patients in the control group, 8 (57.1%) were males and 6 (42.9%) were females. The difference in the mean WBCs in the cerebrospinal fluid between the two groups was as follows: the mean WBCs in the control group was 8.7143 and the mean WBCs in the intervention group was 4.9524. The difference between the two groups was statistically significant (P-value =0.039). However, no significant difference was seen between the two groups in terms of sex, age, and duration of disease ($p>0.05$).

Conclusion: The incidence of CNS involvement was significantly decreased when patients were placed in the post-puncture prone position for 3 hours.

Keywords: Acute lymphoblastic leukemia, Prone position, Supine Position

Introduction

Acute lymphoblastic leukemia (ALL) is an acute form of leukemia, in which there is an overproduction of cancerous, immature white blood cells, known as lymphoblasts. The overproduced lymphoblasts cause damage and death by inhibiting the production of normal cells in the bone marrow and by infiltrating other organs (1). It affects both children and adults in bimodal age distribution, with peak incidence between the ages of two and five years and another peak in old age (2).

The development of treatment methods has led to a cure rate of more than 80% in children (3, 4). There are several risk factors which lead to treatment failure, one of them is central nervous system (CNS) involvement (5, 6). Since ALL cells sometimes penetrate the CNS, and patients with CNS disease at initial presentation have been reported to experience significantly greater risk of treatment failure compared with CNS negative patients, it is a major clinical concern and prophylactic CNS directed conventional intrathecal chemotherapy is required for relapse-free survival (6-8). CNS relapse occurs in about 3-8 % of patients (9). There have been ongoing efforts to reduce treatment failure and relapse and improve survival outcomes in patients with ALL (10). The present study made patients lie prone after intrathecal injection. The authors hypothesized that the post-injection prone position would reduce the CNS involvement compared with the post-injection supine position.

[DOI: 10.18502/ijpho.v11i2.5841]

Materials and Methods

Study design: This study was a randomized clinical trial that selected patients with ALL admitted to shahid sadoughi Hospital of Yazd University from 2006 to 2016. The Ethical approval was obtained from the clinical research and ethics committees of the Yazd universityof medical sciences (IR.SSU.MEDICINE.REC.1394.473).

Patients: From 2006 to 2014, 14 patients who received prophylaxis intrathecal chemotherapy with the post-injection supine position were selected retrospectively as the control group and from 2014 to 2016, 22 patients who received the prophylaxis intrathecal chemotherapy with the post-injection prone position were selected as the intervention group. In this study, five patients were placed in the post-injection supine position for a while and then placed in the post-injection prone position. Inclusion criteria included: less than ten years of age and indications for the prevention of CNS involvement caused by the disease. The following patients were excluded: those with contraindications for lumbar puncture (LP) and intrathecal chemotherapy, those with pre-existing CNS involvement, those with post-injection leakage, and those who failed to complete the required rest-time in post-injection position without authorization. The sex distribution of the control group was six female and eight male patients and for the intervention group was five females and 14 males. All included patients signed the informed consent forms.

Treatment plan: The control group was selected randomly among patients admitted to the pediatric oncology ward of the shahid saddughi Hospital from 2005 to 2014, and the intervention group was selected randomly among the patients from 2014 to 2016 admitted to the same place.

Patients underwent dexamethasone (6 mg/m^2).

The patients went under general anesthesia before LP with intrathecal injections of Ketamine, Propofol, and Midazolam in toddler age patient and only Ketamine in infants. In patients with the positive history of seizure, general anesthesia was performed with thiopental. LP and intrathecal injection were performed at the same time in the $L_3 – L_4$ interspace. First, two milliliters l of the cerebrospinal fluid (CSF) were collected and then Methotrexate was injected intrathecally. Methotrexate dosage was as follows: 12.5 milligrams (five milliliters) were injected in patients more than three years of age and ten milligrams (five milliliters) injected for under the three years patients. The patients were conscious after 30 to 60 minutes and then to complete post-injection rest-time (Three hours in sum) in supine or prone position according to their group. Pulse rate assessed every 15 minutes in the anesthetic and rest of the rest time.

Outcomes: The CSF analysis was performed for determining CNS involvement and evaluating the difference between the two groups. The CNS relapse is defined as follows: positive cytomorphography and White blood cells (WBC) > five /µicroliter and/ or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome (9).

Statistical analysis

In the current study, SPSS version 22.0 was used for the statistical analysis. T and chi-square tests were used to compare ratios. P-Value < 0.05 was considered statistically significant.

Results

In this study, 33 patients were admitted to Shahid sadoughi Hospital of Yazd University and 2 patients were excluded. Of the 33 subjects, 24 (66.7%) were males, and 12 (33.3%) were females. Of the 22 patients in the intervention group, 16 (72.7%) were males, and 6 (27.3%) were females. From the 14 patients in the control group, 8 (57.1%) were males and 6 (42.9%) were females. The difference in mean WBCs in CSF between the two groups was as follows: the mean WBCs in the control

[DOI: 10.18502/ijpho.v11i2.5841]

group was 8.7143 (5.70329 SD) and the mean WBCs in the intervention group was 4.9524 (4.59865 SD). The difference between the two groups was statistically significant (P-value = 0.039). The demographic and clinical characteristics of the two groups were assessed and there was no significant difference between the two groups (table-1).

Table I: Comparison of demographic and clinical characteristics between patients were place in prone position (case group) and patients were placed in supine position (control group) following intrathecal chemotherapy.

characteristic	Control group (Mean)	Case group (Mean)	P-value
WBC count	8.7143	4.9524	.039
Age (year)	5.21	5.05	.858
Gender			.334
Male	8(57.1%)	16(72.7%)	
Female	6(42.9%)	6(27.3%)	
Treatment duration(day)	459.57	396.32	.540

Pearson Chi-Square)

Discussion

Intrathecal chemotherapy is a type of regional therapy through which the limitations imposed by the brain-blood barrier circumvented. Thus, the CSF drug concentration was maximized while systemic drug toxicity was eliminated or reduced. Since prophylaxis therapy has been associated with CSF drug concentration (11), Intrathecal chemotherapy is the method of choice for prophylaxis. However, despite the high drug concentration achieved at the site of drug injection (lumbar sac), distribution of drug throughout the CSF is limited following intralumbar administration. One of the most important agents that affect the CSF drug administration is the post-puncture body position. The authors evaluated the effect of post-puncture prone position on CSF drug concentration and accordingly CNS involvement by placing the patients in the prone position for 3 hours rather than the supine position for the same time. Previous studies assessed the effect of the post-puncture body position on complications of LP and concluded that post-puncture flat position was associated with less post-puncture headache (12). Although, another study demonstrated that there was no difference in the incidence or duration of the post-puncture headache between the post-puncture flat position and immediately mobilization after puncture (13). Previous studies also evaluated the CSF drug concentration in the supine position (14) or immediately upward position after intrathecal injection. Non-human evaluations of the CSF drug concentration after the intralumbar drug injection demonstrated that post-puncture body position influenced the drug distribution throughout the CSF (15, 16). Another study demonstrated that the mean peak ventricular methotrexate concentration was 15-folds higher in animals placed in the prone position for 1 hour after the intralumbar methotrexate dose (17), but no study assesses this effect in human. Furthermore, there is no study comparing the effect of the post-puncture prone position in drug concentration rather than the post-puncture supine position. The probable mechanism is that the CSF bulk flow to the ventricles in the post-puncture flat position is greater compared with the upward position. For justification of the difference between the post-puncture prone and supine positions, the researchers should consider CSF distribution in both positions.

[DOI: 10.18502/ijpho.v11i2.5841]

A study evaluated the effect of patients' position on the distribution of the subarachnoid CSF. They found that the subarachnoid CSF decreased in the gravitational direction, due to a downward shift of grey and white matter tissues. Therefore, CSF decreased in the anterior section of the intracranial cavity in the prone position (18). This pattern of distribution in the prone position probably increased the drug concentration in the posterior section of the intracranial cavity during the horizontal position and then in the anterior section after finishing the procedure. The limitations of the study included the following items: First, the low sample size. Second, the authors could not control all factors that affect the prognosis. For instance, because of financial reasons, the assessment of progenitor types of ALL or karyotype determination was not possible. An increased risk of CNS involvement has been observed in patients affected by the mature B-cell subtype of ALL (B-ALL) (19) and the All with Philadelphia (Ph) chromosome-positive karyotype (20). Another risk factor predicting CNS relapse was the WBCs count at diagnosis. The authors didn't assess this factor. Another limitation of this study was the lack of evaluatiion of systemic chemotherapy and systemic relapse and its relevance with CNS relapse.

Conclusion

In conclusion, the incidence of CNS involvement was significantly decreased when patients were placed in the post-puncture prone position for 3 hours. The patient's age and sex made no significant difference in outcomes. These findings supported that the optimal post-injection position for decreasing the incidence of CNS involvement was the prone position.

Conflict of Interest

The authors declare that they have no conflicts of interest.

References

1. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood cancer J 2017;7(6):e577-e588.
2. Kim S-Y, Park JH, Yoon SY, Cho Y-H, Lee MH. A pilot study of daunorubicin-augmented hyper-CVAD induction chemotherapy for adults with acute lymphoblastic leukemia. Cancer Chemother Pharmacol2018;81(2):393-398.
3. Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet 2008;371(9617):1030-1043.
4. Jabbour E, Kantarjian H. Treatment of Adult Acute Lymphocytic Leukemia (ALL) in 2017. Clinical Lymphoma, Myeloma and Leukemia 2017;17:S57-S60.
5. Faderl S, O'brien S, Pui CH, Stock W, Wetzler M, Hoelzer D, et al. Adult acute lymphoblastic leukemia: concepts and strategies. Cancer: Interdisciplinary International J American Canc Soci. 2010;116(5):1165-1176.
6. Münch V, Trentin L, Herzig J, Demir S, Seyfried F, Kraus JM, et al. Central nervous system involvement in acute lymphoblastic leukemia is mediated by vascular endothelial growth factor. Blood 2017; 03:769315-769318.
7. Wilson R, Osborne C, Halsey C. The Use of Ommaya Reservoirs to Deliver Central Nervous System-Directed Chemotherapy in Childhood Acute Lymphoblastic Leukaemia. Pediatr Drugs 2018:1-9.
8. Dara A, Mook B, Doorduijn J, Van den Bent M, Dinmohamed A, Bromberg J. Efficacy of intrathecal chemotherapy in patients with central nervous system involvement of hematological malignancies: a retrospective analysis. J neuro-oncology 2018:1-7.
9. Lanzkowsky P, Lipton JM, Fish JD. Lanzkowsky's manual of pediatric hematology and oncology: Academic Press; 2016.
10. Jabbour E, O'Brien S, Konopleva M, Kantarjian H. New insights into the pathophysiology and therapy of adult acute

[DOI: 10.18502/ijpho.v11i2.5841]

lymphoblastic leukemia. Cancer 2015;121(15):2517-2528.
11. Bleyer A. Clinical pharmacology of intrathecal methotrexate. II. An improved dosage regimen derived from age-related pharmacokinetics. Cancer Treat Rep 1977;61(8):1419-1425.
12. Vallejo MC, Mandell GL, Sabo DP, Ramanathan S. Postdural puncture headache: a randomized comparison of five spinal needles in obstetric patients. Anesth Analg 2000;91(4):916-920.
13. Vilming ST, Schrader H, Monstad I. Post-lumbar-puncture headache: The significance of body posture: A controlled study of 300 patients. Cephalalgia 1988;8(2):75-78.
14. Li J, Li X, Tong X, Liu J, Huang B, Chen M, et al. Investigation of the optimal duration of bed rest in the supine position to reduce complications after lumbar puncture combined with intrathecal chemotherapy: a multicenter prospective randomized controlled trial. Support Care Cancer 2018:1-8.
15. McCully C, Balis F, Bacher J, Phillips J, Poplack D. A rhesus monkey model for continuous infusion of drugs into cerebrospinal fluid. Lab Anim Sci 1990; 40(5):520-52.
16. Poplack DG, Bleyer WA, Wood JH, Kostolich M, Savitch JL, Ommaya AK. A primate model for study of methotrexate pharmacokinetics in the central nervous system. Cancer Res 1977;37(7 Part 1):1982-1985.
17. Blaney SM, Poplack DG, Godwin K, McCully CL, Murphy R, Balis FM. Effect of body position on ventricular CSF methotrexate concentration following intralumbar administration. J clinoncol 1995;13(1):177-179.
18. Bijsterbosch JD, Lee K-H, Hunter MD, Wilkinson ID, Farrow T, Barker AT, et al. The effect of head orientation on subarachnoid cerebrospinal fluid distribution and its implications for neurophysiological modulation and recording techniques. Physiol Meas 2013;34(3):N9-N12.
19. Cortes J, O'Brien SM, Pierce S, Keating MJ, Freireich EJ, Kantarjian HM. The value of high-dose systemic chemotherapy and intrathecal therapy for central nervous system prophylaxis in different risk groups of adult acute lymphoblastic leukemia. Blood 1995;86(6):2091-2096.
20. Bleyer WA, Poplack DG, editors. Prophylaxis and treatment of leukemia in the central nervous system and other sanctuaries. Seminars in oncology 1985: 1-9.

[DOI: 10.18502/ijpho.v11i2.5841]