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ORIGINAL ARTICLE

Influence of Hypoalbuminemia on Methotrexate Clearance in Children Receiving High Dose Methotrexate Therapy

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ABSTRACT

Aim: Methotrexate, a structural counterpart of folic acid, is well recognized as a very efficacious pharmaceutical agent utilized in the treatment of several pediatric oncological conditions. A high-dose methotrexate is employed as a therapeutic intervention for a diverse range of malignant conditions including leukemia, lymphomas, and osteosarcoma. Hypoalbuminemia also decreases the methotrexate clearance leading to increased toxicity.

Objective: To determine the frequency of side effects among patients receiving high dose methotrexate therapy based on baseline albumin levels.

Study Design: A quasi-experimental trial was conducted at the Pakistan Institute of Medical Sciences, Islamabad, from January 1, 2023, to July 31, 2023. A total of thirty-four children receiving HDMTX were enrolled in the study. Albumin level, grade of liver toxicity, renal function tests, gastrointestinal and neurological toxicity, and mucositis were noted. Length of stay and methotrexate level at 24 hours were also noted. All the information was recorded in proforma.

Results: In this study, we included 34 children with a mean age of 6.29 ± 2.97 years. Out of 34 children, there were 24 (70.6%) male children, while 10 (29.4%) were female children. The most common diagnosis was leukemia [14 (41.2%)], followed by non-Hodgkin lymphoma [9 (26.5%)], leukemia relapse [6 (17.6%)], and osteoarthritis [5 (14.7%)]. The albumin level was low in 11 (32.4%) children while normal in 23 (67.6%) children. Toxicities were compared in children with low and normal albumin levels. Hepatotoxicities and gastrointestinal toxicities were insignificant between both groups ($p > 0.05$). But myelosuppresion and mucositis significantly showed higher grades in low albumin groups. Nephrotoxicity and neurological toxicities were only noted in children with low albumin groups, while no patients in normal albumin groups had neurological or nephrotoxicity. The mean length of stay of low albumin level children was longer than that of normal albumin level children (7.45 ± 3.24 vs. 4.17 ± 3.39 days, $p<0.05$), and the mean methotrexate level after 24 hours was also significantly higher ($p<0.05$) in the low albumin group (69.22 ± 97.40) than the normal albumin level (0.40 ± 1.14).

Practical Implication: This would not only lessen toxicity but also enhance children's health and quality of life. Before starting high-dose methotrexate (HDMTX) cycles, serum albumin levels should be evaluated. This is especially important in low-resource areas where malnutrition is common and serum methotrexate (MTX) monitoring may not be available.

Conclusion: In this study, we conclude that hypoalbuminemia therapy has an effect on the reduction of hospital stays and methotrexate toxicity in high-risk children. In the future, we can recommend adding hypoalbuminemia therapy to reduce the toxicities of HDMTX.

Keywords: High dose methotrexate therapy, albumin levels, renal function test, gastrointestinal toxicity, neurological toxicity, mucositis.

INTRODUCTION

Current chemotherapy has been shown to be highly effective in treating children and early adolescents diagnosed with leukemia. Conversely, achieving clinical remission in young adults and older patients proves to be a challenging task, with a higher prevalence of early recurrence. 1 Methotrexate, a structural counterpart of folic acid, is well recognized as a very successful pharmaceutical agent utilized in the treatment of several pediatric oncological conditions. 2 The administration of high-dose methotrexate at a dosage exceeding 500 mg/m2 has been found to be more efficacious in several individuals while still maintaining a satisfactory safety profile. However, it is important to note that a subset of patients may have substantial toxicity as a result of this treatment. 3 High-dose methotrexate is used to treat a variety of malignant diseases like leukemia, lymphomas, and osteosarcoma. HDMTX can cause bone marrow suppression, mucositis, CNS toxicity, and hepatic dysfunction. It has been reported that the combined incidence of toxicities was 45/151 cycles (29.8%) of HDMTX. 6

HDMTX is given with pre-infusion hydration and leucovorin rescue to enhance efficacy and reduce toxicity. 7 Methotrexate is a weak acid and has variable protein binding. About 50 percent of the drug binds to serum albumin. 8, 9 The binding of methotrexate to albumin enhances the effectiveness of methotrexate. 10, 11 Hypoalbuminemia also decreases methotrexate clearance, leading to increased toxicity. 1 The primary objective of this study is to evaluate the influence of serum albumin on the pharmacokinetics of methotrexate. This study aims to examine the toxicity of methotrexate in patients with normal blood albumin levels versus those with hypoalbuminemia. This has significant importance, particularly in nations with low resources where malnutrition prevails and access to methotrexate levels may be lacking. To determine the frequency of side effects among patients receiving high dose methotrexate therapy based on baseline albumin levels.

MATERIAL AND METHODS

Study Design: quasi-experimental trial
Study Place: Pakistan Institute of Medical Sciences, Islamabad
Study Period: 1st January 2023 to 31st July 2023
Sample Size: Sample size (n) was estimated by using 95% confidence level, (15.5%) margin of error and percentage of toxicities i.e. 29.8% with HDMTX.[7]
Sampling Technique: Non-probability, consecutive sampling.
SELECTION OF PATIENTS:
Inclusion Criteria: Patients less than 12 years of age receiving high dose methotrexate therapy, with normal liver and kidney function indices before HDMTX treatment.
Exclusion Criteria: Children already having renal / hepatic / hematological / gastrointestinal insufficiencies before methotrexate therapy.
Data Collection: Total thirty four children receiving high dose methotrexate therapy were enrolled in the study. Informed consent was taken from parents or guardians. Demographics (name, age, gender, weight, socioeconomic status, residence), diagnosis, duration of receiving high dose methotrexate therapy, laboratory parameters (albumin level, grade of liver toxicity, renal function test) were noted. Then length of stay and methotrexate level at 24

hours were also noted. All the information was recorded in proforma.

Analysis: Data was analysed using SPSS version 23. P-value ≤0.05 was taken as significant.

RESULTS

In this study, we included 34 children with a mean age of 6.29 ± 2.97 years. Out of 34 children, there were 24 (70.6%) male children, while 10 (29.4%) were female children. The most common diagnosis was leukemia [14 (41.2%)], followed by non-Hodgkin lymphoma [9 (26.5%)], leukemia relapse [6 (17.6%)], and osteoarthritis [5 (14.7%)]. The albumin level was low in 11 (32.4%) children while normal in 23 (67.6%) children. Table 1

Out of 34 children, 16 had hepatotoxicities, out of which 4 (25.0%) had grade 1 toxicity, 6 (37.5%) had grade 2 toxicity, and 6 (37.5%) had grade 3 toxicity; no one had grade 4 toxicity. Out of 34 children, 16 had myelosuppression, out of which 4 (25.0%) had grade 1 toxicity, 9 (56.3%) had grade 2 toxicity, and 3 (18.8%) had grade 3 toxicity; no one had grade 4 toxicity. Mucositis was noted in 21 children, out of which 3 (14.3%) had grade 1 toxicity, 9 (42.9%) had grade 2 toxicity, 8 (38.1%) had grade 3 toxicity, and 1 (4.8%) had grade 4 toxicity. Nephrotoxicities were noted in 4 cases, out of which 3 (75.0%) had grade 1 toxicity and 1 (25.0%) had grade 2 toxicity. Gastrointestinal toxicity was noted in 10 cases, out of which 3 (30.0%) had grade 1 toxicity, 6 (60.0%) had grade 2 toxicity, 1 (10.0%) had grade 3 toxicity, and no one had grade 4 toxicity. Neurological toxicity was noted in 3 cases, out of which none (0%) had grade 1 toxicity, 2 (66.7%) had grade 2 toxicity, 1 (33.3%) had grade 3 toxicity, and no one had grade 4 toxicity. Table 2

After hypoalbuminemia treatment, the mean length of stay of children was 5.24 ± 3.64 days, and the methotrexate level after 24 hours was 22.66 ± 62.80 mg/dl. Table 3

Table 1: Basic Information of Children

	Mean ± SD, F (%)
n	34
Age (Y)	6.29 ± 2.97
Gender	
Male	24 (70.6%)
Female	10 (29.4%)
Diagnosis	
Leukemia	14 (41.2%)
Non-Hodgkin Lymphoma	9 (26.5%)
Leukemia relapse	6 (17.6%)
Osteoarthritis	5 (14.7%)
Albumin level	
Low	11 (32.4%)
Normal	23 (67.6%)

Table 2: Side Effects of Methotrexate in Children (n = 34)

		Frequency (%)
Hepatotoxicity grade	1	4 (25.0%)
	2	6 (37.5%)
	3	6 (37.5%)
Myelosuppression grade	1	4 (25.0%)
	2	9 (56.3%)
	3	3 (18.8%)
Mucositis	1	3 (14.3%)
	2	9 (42.9%)
	3	8 (38.1%)
	4	1 (4.8%)
Nephrotoxicity	1	3 (75.0%)
	2	1 (25.0%)
Gastrointestinal toxicity	1	3 (30.0%)
	2	6 (60.0%)
	3	1 (10.0%)
Neurological toxicity	2	2 (66.7%)
	3	1 (33.3%)

Toxicities were compared in children with low and normal albumin levels. Hepatotoxicities and gastrointestinal toxicities were insignificant between both groups (p > 0.05). But myelosuppresion and mucositis significantly showed higher grades in low albumin groups, i.e., 7 (70.0%) had grade 3 toxicity, while in the normal albumin group, only 1 (9.1%) had grade 3 toxicity and 1 (9.1%) had grade 4 toxicity. But nephrotoxicity and neurological toxicities were only noted in children with low albumin groups, while no patients in normal albumin groups had neurological or nephrotoxicity. The mean length of stay of low albumin level children was longer than that of normal albumin level children (7.45 ± 3.24 vs. 4.17 ± 3.39 days, p<0.05), and the mean methotrexate level after 24 hours was also significantly higher (p<0.05) in the low albumin group (69.22 ± 97.40) than the normal albumin level (0.40 ± 1.14). Table 4

Table 3: Outcome of Hypoalbuminemia Treatment in Children (n = 34)

	Mean ± SD
n	34
Length of stay	5.24 ± 3.64
Methotrexate level after 24 hours	22.66 ± 62.80

Table 4: Comparison of Toxicities in Low Versus Normal Albumin Level at Baseline

		Albumin level		P-value
		Low	Normal	
n		11	23	
Hepato-toxicity	1	3 (33.3%)	1 (14.3%)	0.347
	2	4 (44.4%)	2 (28.6%)	
	3	2 (22.2%)	4 (57.1%)	
Myelosuppresion	1	0 (0.0%)	4 (66.7%)	0.009
	2	7 (70.0%)	2 (33.3%)	
	3	3 (30.0%)	0 (0.0%)	
Nephrotoxicity	1	3 (75.0%)	0 (0.0%)	NA
	2	1 (25.0%)	0 (0.0%)	
Gastrointestinal toxicity	1	3 (37.5%)	0 (0.0%)	0.435
	2	4 (50.0%)	2 (100%)	
	3	1 (12.5%)	0 (0.0%)	
Neurological	2	2 (66.7%)	0 (0.0%)	NA
	3	1 (33.3%)	0 (0.0%)	
Mucositis	1	0 (0.0%)	3 (27.3%)	0.024
	2	3 (30.0%)	6 (54.5%)	
	3	7 (70.0%)	1 (9.1%)	
	4	0 (0.0%)	1 (9.1%)	
Length of stay	Days	7.45 ± 3.24	4.17 ± 3.39	0.012
Methotrexate level at 24th hour		69.22 ± 97.40	0.40 ± 1.14	0.041

DISCUSSION

The administration of high-dose methotrexate (HDMTX) on many occasions is an essential element of current therapeutic protocols for pediatric acute leukemia. Serum albumin is widely recognized as a transport protein for methotrexate (MTX) inside the bloodstream. The presence of hypoalbuminemia is a common occurrence in pediatric patients diagnosed with leukemia. [12] Albumin has alkalotic properties and has the ability to bind to weak acids present in the serum. Serum albumin serves as a drug carrier for methotrexate (MTX) in the bloodstream due to its ability to bind to around 50% of the MTX molecules. This binding occurs as a result of MTX's weak acidic properties. [12] Regrettably, prior to the initiation of chemotherapy, hypoalbuminemia was observed in a significant proportion, around 50%, of pediatric patients diagnosed with cancer. The presence of hypoalbuminemia may indicate a compromised nutritional state in individuals diagnosed with hematologic or lymphatic malignancies and solid metastatic tumors. These patients often experience cachexia, malnutrition, and overall worse health compared to individuals with localized, non-metastatic tumors. The use of L-asparagine during the induction phase of chemotherapy in pediatric patients diagnosed with leukemia has been found to potentially result in hypoalbuminemia. [13, 14]

In our study, we observed that after hypoalbuminemia treatment, the mean length of stay of children was 5.24 ± 3.64 days, and the methotrexate level after 24 hours was 22.66 ± 62.80

mg/dl. Toxicities were compared in children with low and normal albumin levels. Hepatotoxicities and gastrointestinal toxicities were insignificant between both groups ($p > 0.05$). But myelosuppresion and mucositis were significant in low albumin groups, i.e., 7 (70.0%) had grade 3 toxicity, while in the normal albumin group, only 1 (9.1%) had grade 3 toxicity and 1 (9.1%) had grade 4 toxicity. But nephrotoxicity and neurological toxicities were only noted in children with low albumin groups, while no patients in normal albumin groups had neurological or nephrotoxicity.

According to the findings, there was no discernible correlation found between pre-infusion hypoalbuminemia and the occurrence of G3–4 neutropenia, hepatotoxicity, or nephrotoxicity. [12] In their study, Wiczer et al. (year) examined several factors that might potentially contribute to the development of methotrexate-induced renal toxicity in adult patients undergoing high-dose methotrexate (HDMTX) therapy for the treatment of leukemia or lymphoma. The researchers identified a significant association between low levels of serum albumin and the occurrence of renal toxicity. [15] In the research done by Reiss et al., a total of 167 cases were examined. The findings of the study revealed a significant association between hypoalbuminemia and a larger proportion of patients having edema, ascites, or pleural effusions (34% vs. 12%, $p = 0.006$). Additionally, it was observed that the concurrent use of nephrotoxic medications was more prevalent among patients with hypoalbuminemia (41% vs. 20%, $p = 0.021$). There was a significant association between hypoalbuminemia and a longer duration for methotrexate (MTX) clearance, with a median time of 96 hours compared to 72 hours ($p = 0.004$). Furthermore, it was observed that those diagnosed with hypoalbuminemia exhibited a greater prevalence of hyperbilirubinemia and experienced considerably prolonged hospital stays (with a median duration of 14 days compared to 5 days for those without hypoalbuminemia), with statistical significance indicated by a p-value of less than 0.001. In summary, it can be concluded that hypoalbuminemia exhibited a correlation with the prolonged time required for methotrexate (MTX) clearance and the extended duration of hospital stay. The administration of high-dose methotrexate (MTX) is considered safe in patients who have low levels of albumin, provided that suitable leucovorin rescue and enough supportive care are provided. [16]

In research done by Kataoka et al. (year), a cohort of 74 patients was examined, revealing the identification of serum albumin as a significant risk factor. The analysis conducted involved both univariate and multivariate approaches, which provided insights into the relationship between low ALB levels (<3.7 g/dL) and types of cancer with delayed MTX elimination. The univariate analysis demonstrated significant associations, with odds ratios of 6.00 ($P = 0.004$) and 4.33 ($P = 0.039$) for low ALB level and type of cancer, respectively. The multivariate analysis, after adjusting for confounding factors, revealed adjusted odds ratios of 6.45 ($P = 0.006$) and 8.11 ($P = 0.018$) for low ALB level and type of cancer, respectively. There was no statistically significant difference in adverse effects seen between the two groups, with the exception of cases with renal impairment. [17]

Khera et al. concluded that hypoalbuminemia and solitary serum MTX levels predict HDMTX-induced nephrotoxicity in centers where serial MTX level monitoring is not feasible. [18] Mohassel et al. conducted another trial on 510 cases and found that there were 204 adult patients and 106 pediatric patients. Among pediatricians, 23% had hypoalbuminemia. Leukemia was the most prevalent condition among the pediatric patient population, accounting for the majority of cases at 55%. In the field of pediatrics, there was no statistically significant disparity observed between the two cohorts (low albumin group versus normal albumin group) in terms of the average duration required for methotrexate (MTX) to be eliminated from the body. The average duration of hospitalization was found to be 7.6 days in the low albumin group, whereas it was 4.4 days in the normal albumin group ($p<0.00001$). There were no statistically significant variations seen in the average methotrexate (MTX) levels at the time points of 24, 48, or 72 hours. Children with hypoalbuminemia had a higher prevalence of hepatitis compared to those without hypoalbuminemia (58.3% vs. 47.9%; $p = 0.017$). [19]

Mucositis after administration of HDMTX is common, with 72% of patients experiencing at least grade 1 mucositis and a third of HDMTX administrations leading to mucositis. In addition, previous analyses have evaluated the impact of changes in supportive care on HDMTX-induced mucositis and other adverse events. [20] In our study, mucositis was noted in 21 children, out of which 3 (14.3%) had grade 1 toxicity, 9 (42.9%) had grade 2 toxicity, 8 (38.1%) had grade 3 toxicity, and 1 (4.8%) had grade 4 toxicity.

Mirza et al. conducted research in India and reported a little connection between the cumulative albumin levels during all four cycles and the cumulative occurrence of hazardous events. The median number of hazardous episodes seen was 19, with a range of 16 to 23. The Spearman correlation coefficient (ρ) yielded a value of 0.055, with a corresponding p-value of 0.460. There was no observed correlation between albumin levels and methotrexate (MTX) toxicity in the analysis conducted on a cycle-wise basis. There was no statistically significant disparity observed in the toxicities experienced by individuals with hypoalbuminemia compared to those with normal levels of albumin in each cycle. The only variable that exhibited a statistically significant ($P < 0.05$) negative association with albumin levels was vomiting. Patients with hypoalbuminemia had a substantially greater degree of nausea in comparison to those with normoalbuminemia, as shown by a statistically significant p-value of less than 0.01.1.

CONCLUSION

Hypoalbuminemia therapy has an impact on the reduction of hospital stays and methotrexate toxicity in high-risk children. In the future, we can recommend adding hypoalbuminemia therapy to reduce the toxicities of HDMTX. This would not only reduce toxicities but also improve the condition and quality of life of children. It is advisable to assess serum albumin levels before initiating high-dose methotrexate (HDMTX) cycles, particularly in locations with low resources where malnutrition is prevalent and serum methotrexate (MTX) monitoring may not be accessible. The optimization of serum albumin levels prior to high-dose methotrexate (HDMTX) administration may potentially reduce the occurrence of HDMTX toxicities.

REFERENCES

1. Mirza MA, Aruna D, Konatam ML. Effect of serum albumin level on high-dose methotrexate induced toxicities in acute lymphoblastic leukemia patients. IInt. J. Health Sci.. 2023;17(2):3-9.
2. Koźmiński P, Halik PK, Chesori R, Gniazdowska E. Overview of Dual-Acting Drug Methotrexate in Different Neurological Diseases, Autoimmune Pathologies and Cancers. Int. J. Mol. Sci. 2020;21(10).
3. Wang G, Peng X. A Review of Clinical Applications and Side Effects of Methotrexate in Ophthalmology. Journal of ophthalmology. 2020;2020:1537689.
4. Halik PK, Koźmiński P, Gniazdowska E. Perspectives of Methotrexate-Based Radioagents for Application in Nuclear Medicine. Mol. Pharmaceutics. 2020;18(1):33-43.
5. Wei CW, Yu YL, Chen YH, Hung YT, Yiang GT. Anticancer effects of methotrexate in combination with α-tocopherol and α-tocopherol succinate on triple-negative breast cancer. Oncol Rep. 2019;41(3):2060-6.
6. Mandal P, Samaddar S, Chandra J, Parakh N, Goel M. Adverse effects with intravenous methotrexate in children with acute lymphoblastic leukemia/lymphoma: a retrospective study. Indian J Hematol Blood Transfus. 2020;36(3):498-504.
7. Koźmiński P, Halik P, Chesori R, Gniazdowska E. Overview of Dual-Acting Drug Methotrexate in Different Neurological Diseases, Autoimmune Pathologies and Cancers. Int. J. Mol. Sci. 2020;21:3483.
8. Awuchi CG, Okpala COR. Natural nutraceuticals, especially functional foods, their ma-jor bioactive components, formulation, and health benefits for disease prevention-An overview. Journal of Food Bioactives. 2022;19.
9. Topless R, Green R, Morgan SL, Robinson P, Merriman T, Gaffo AL. Folic acid and methotrexate use and their association with COVID-19

diagnosis and mortality: a case–control analysis from the UK Biobank. BMJ Open. 2022;12(8):e062945.
10. Zarou MM, Vazquez A, Vignir Helgason G. Folate metabolism: a re-emerging therapeutic target in haematological cancers. Leukemia. 2021;35(6):1539-51.
11. Barakat S, Assem H, Salama M, Mikhael N, El Chazli Y. Is hypoalbuminemia a risk factor for high-dose methotrexate toxicity in children with acute lymphoblastic leukemia? J Egypt Natl Canc Inst. 2022;34(1):17.
12. McLean TW, Stewart RM, Curley TP, Dewsnup MY, Thomas SG, Russell TB, et al. Hypoalbuminemia in children with cancer treated with chemotherapy. Pediatr Blood Cancer. 2020;67(2):e28065.
13. Schmiegelow K, Rank CU, Stock W, Dworkin E, van der Sluis I. SOHO state of the art updates and next questions: management of asparaginase toxicity in adolescents and young adults with acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk. 2021;21(11):725-33.
14. Wiczer T, Dotson E, Tuten A, Phillips G, Maddocks K. Evaluation of incidence and risk factors for high-dose methotrexate-induced nephrotoxicity. J. Oncol. Pharm. Pract. 2016;22(3):430-6.
15. Reiss S, Buie L, Adel N, Goldman D, Devlin S, Douer D. Hypoalbuminemia is significantly associated with increased clearance time of high dose methotrexate in patients being treated for lymphoma or leukemia. Annals of Hematology. 2016;95.
16. Kataoka T, Sakurashita H, Kajikawa K, Saeki Y, Taogoshi T, Matsuo H. Low Serum Albumin Level Is a Risk Factor for Delayed Methotrexate Elimination in High-Dose Methotrexate Treatment. Ann Pharmacother. 2021;55(10):1195-202.
17. Khera S, Sharma G, Negi V, Shaw SC. Hypoalbuminemia and not undernutrition predicts high-dose methotrexate-induced nephrotoxicity in children with acute lymphoblastic leukemia in resource-constrained centers. Pediatr Blood Cancer. 2022;69(9):e29738.
18. Mohassel L, Griffin S, Binder N, Barnett SD, Cuevo R. Evaluation of Methotrexate Clearance in Adult and Pediatric Patients with Hypoalbuminemia. Blood. 2019;134:2906.
19. Taylor ZL, Miller TP, DeGroote N, Pommert L, Awoniyi O, Board S, et al. Influence of albumin and methotrexate clearance on high-dose methotrexate-induced mucositis. J. Clin. Oncol. 2022;40 (16_suppl): e15081-e.

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