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**ORIGINAL ARTICLE**

# Efficacy of Furosemide in Methotrexate Clearance in Patients Treated with High Dose Methotrexate: A Cohort Study

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## ABSTRACT

**Background:** Methotrexate was first used in 1947 as a chemotherapeutic drug in the treatment of acute lymphoblastic leukemia (ALL). Methotrexate has been extensively explored as an anticancer drug since that time. High dose methotrexate is a term used for doses above 1000mg/m2.

**Objective:** To determine efficacy of Furosemide in methotrexate clearance in patients treated with high dose methotrexate

**Methodology:** The current study was prospective cohort study carried out at the Oncology department of tertiary care hospitals of Peshawar for a period of one year from January 2020 to January 2021. A total of 80 patients were enrolled in the study. All patients received daily hydration of at least 5 liters along with urine alkalization with sodium bicarbonate and on calcium rescue as per protocol. All patients were given Furosemide 40 mg three times a day. Methotrexate levels were monitored every 24 hours to follow its clearance. All the Data analysis was done by using IBM SPSS version 24.

**Results:** The mean (SD) hospital stay in the current study was 4 (±1) days. Frequency of delayed methotrexate clearance was observed in 16 (20%) patients. The mean (SD) time of methotrexate clearance was 4 (±1) days. Renal injury was observed in 8 (10%) subjects, electrolyte imbalance in 12 (15%) subjects, transaminitis in 11 (13.75%) subjects while mucositis was observed in 8 (10%) subjects.

**Conclusion:** Our study concludes that furosemide is highly effective in methotrexate clearance in patients treated with high dose methotrexate. The use of furosemide reduces the cost and hospital stay. As furosemide is cheaper and easily available so it can be used easily in the methotrexate clearance.

**Key words:** Furosemide; Methotrexate clearance; High dose methotrexate; Cancer

## INTRODUCTION

Methotrexate was first used in 1947 as a chemotherapeutic drug in the treatment of acute lymphoblastic leukemia (ALL)[1]. Methotrexate has been extensively explored as an anticancer drug since that time. One of the most distinguishing characteristics of methotrexate is that it may be provided securely in a variety of dosage schemes. High dose methotrexate is a term used for doses above 1000mg/m2 [2]. HDMTX has been shown to be clinically effective in the management of non-lymphomas, acute lymphoblastic leukemia and sarcoma [3-5]. Dihydrofolic acid reductase and thymidylate synthase enzymes are blocked by methotrexate, which is a traditional antifolate. The suppression of these enzymes impedes with the repair and synthesis of DNA and cell replication [5].

Higher doses of methotrexate offers various benefits, including the ability to circumvent resistance mechanisms, stimulate the creation of active polyglutamates and increase penetration of central nervous system [6]. But, early research employing HDMTX to increase cellular kill revealed a slew of side effects, many of which were life-threatening or serious. Microprecipitation of methotrexate in tubules of kidneys was prevalent, resulting in kidney damage and delay in methotrexate excretion. Methotrexate has been linked to myelosuppression and gastrointestinal side effects as a result of extended clearance. Studies eventually discovered that measures such as boosting fluid intake and urine outputs, providing sodium bicarbonate for urine alkalization and enhance solubility of methotrexate and using leucovorin rescue might significantly minimize these toxicities [7]. Despite proper measures, nephrotoxicity induces by HDMTX take place in 2 to 10% of patients, resulting in significant morbidity and death [8]. Nephrotoxicity is a potential side effect of high-dose methotrexate treatment, with the majority of cases involving grade 1–2 toxicity. Patients may be predisposed to nephrotoxicity if they are male, have low albumin, or given interfering medications or furosemide during clearance of high-dose methotrexate [4]. A previous study reported that in order to avoid kidney damage, forced diuresis with hydration and furosemide supplementation is effective [9]. On the basis of literature search, no study has been done to determine the effectiveness of furosemide in methotrexate clearance in patients treated with high dose methotrexate. This study was thus conducted to determine whether the addition of furosemide after HDMTX helps in early clearance of MTX and results in shorter hospital stay.

## MATERIALS AND METHODS

The current study was prospective cohort study carried out at the Oncology departments of tertiary care hospitals of Peshawar. Study duration was one year from January 2020 to January 2021. Study approval was taken from the ethical and research committee of the hospital. The criteria for inclusion in our study include all the subjects with oncological disorder treated at lady reading hospital with high dose methotrexate of 3g/m$^2$. All the patients of age range 18 to 90 years with normal transaminases and baseline creatinine of upto 1.6 mg/dL were included in the current study. The exclusion criteria of our study were all the subjects with chronic kidney disease, on dialysis, third space body fluids and with ejection fraction less than 50%. A total of 80 patients were enrolled in the study. Consent form was signed from all the subjects. All patients received daily hydration of at least 5 liters along with urine alkalization with sodium bicarbonate and on calcium rescue as per protocol. All patients were given Furosemide 40 mg three times a day. Methotrexate levels were monitored every 24 hours to follow its clearance. Patients were not be given any drug that interferes with MTX clearance such as NSAIDS, phenytoin, ciprofloxacin, amiodarone and proton pump inhibitors. The primary endpoint of our study was evaluation of effectiveness of Furosemide in terms of MTX clearance and hence lesser hospital stay whereas the secondary endpoint was incidence of selected > grade 2 toxicities (including renal injury, electrolyte imbalance, transaminitis and

mucositis and better quality of life.) All the Data analysis was done by using IBM SPSS version 24. Continuous variables were computed as mean and standard deviation whereas categorical variables were counted as frequency and percentages.

## RESULTS

In the current study, a total of 80 patients were enrolled. There were 50 (62.5%) males and 30 (37.5%) females. (Figure 1) The mean age was 48 years with standard deviation of 5.12. (Table 1) Based on diagnosis, osteosarcoma was observed in 37 (46.25%) patients, primary CNS lymphoma in 23 (28.75%) patients and diffuse large B-cell lymphoma (DLBCL) was observed in 20 (25%) patients. (Figure 2) The mean (SD) hospital stay in the current study was 4 (±1) days. (Table 1) Frequency of delayed methotrexate clearance was observed in 16 (20%) patients while it was not observed in 64 (80%) patients. The mean (SD) time of methotrexate clearance was 4 (±1) days. (Table 1) Renal injury, electrolyte imbalance, transaminitis and mucositis were the adverse complications observed in the current study. Renal injury was observed in 8 (10%) subjects, electrolyte imbalance in 12 (15%) subjects while transaminitis was observed in 11 (13.75%) subjects. Majority of the transaminitis patients (72.73%) were grade 1-2 while grade 3 transaminitis was observed in only 3 (27.27%). Mucositis was observed in 8 (10%) subjects, amongst which grade 1 mucositis was observed in 6 (75%) patient's grade 2 in 1 (12.5%) subjects while grade 3 mucositis was also observed in 1 (12.5%) subjects. (Figure 3)

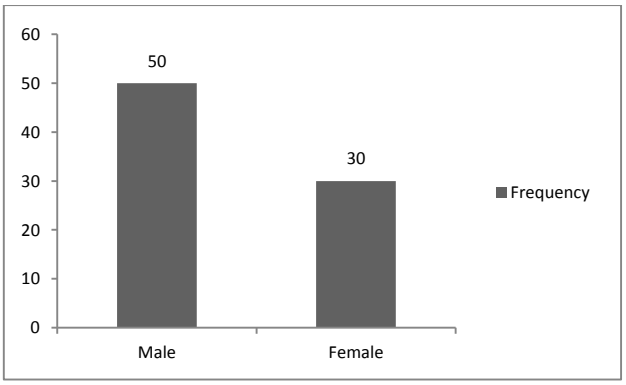


Figure 1: Gender wise distribution of participants

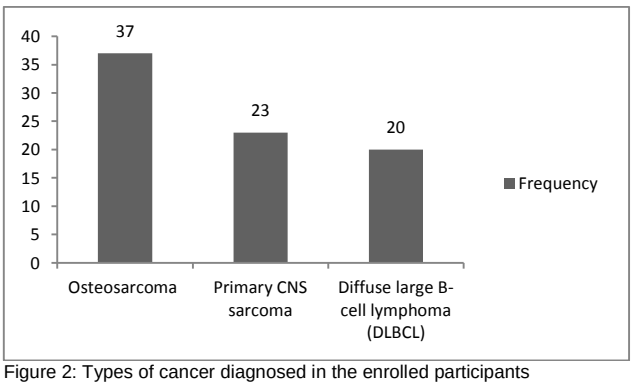


Figure 2: Types of cancer diagnosed in the enrolled participants

Table 1: Outcomes of the patients enrolled in our study

| Parameter | Sub category | Mean (SD)/frequency (%) |
|---|---|---|
| Age (years) | - | 48 (5.12) |
| Mean hospital stay (Days) | - | 4 (±1) |
| Mean methotrexate clearance time (days) | - | 4 (±1) |
| Delayed methotrexate clearance | Yes | 16 (20%) |
| | No | 64 (80%) |

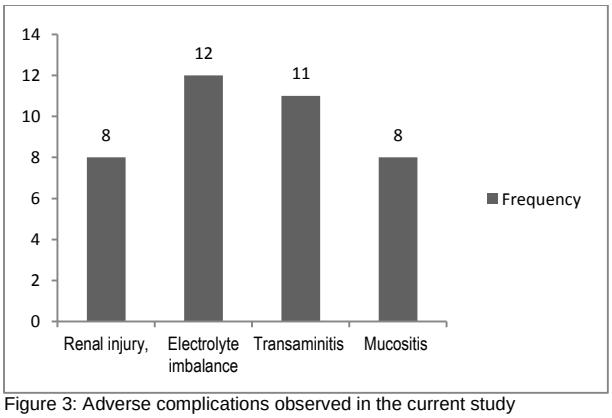


Figure 3: Adverse complications observed in the current study

## DISCUSSION

HD-MTX has been extensively employed in the treatment of a variety of cancers. This medication has been introduced to conventional chemotherapy regimens for several forms of cancer in cancer patients, and the results of various cancer types have drastically improved in comparison to the pre-HD-MTX period [10-14]. Methotrexate is a chemotherapeutic drug that is cell cycle-specific and may be given as an infusion for a few hours or as a 24 hour continuous drip [15, 16]. The negative effects of HD-MTX treatment have long been known, including mucositis of varying degrees, suppression of bone marrow, kidney injury and liver toxicity. Several strategies, such as the utilization of leucovorin in HD-MTX-containing treatments and monitoring of plasma methotrexate level recommendations to optimize the amount and frequency of given leucovorin, have been established to avoid these problems. Another strategy employed in HD-MTX treatments is intensive hydration; however the exact quantity of intravenous hydration necessary to avoid the drug's side effects is unknown. The majority of research investigations have concentrated on the effectiveness of HD-MTX-containing cancer therapy regimens; but, only a few have examined explicitly at the safety of this chemotherapeutic drug and, in particular, the approach to avoid related adverse effects. Our study was conducted with the aim to assess the efficacy of Furosemide in methotrexate clearance in patients treated with high dose methotrexate.

In the current study, there were 50 (62.5%) males and 30 (37.5%) females. A previous study also reported high frequency of cancer in males as compared to female [17]. ) The mean (SD) hospital stay in the current study was 4 (±1) days. These findings shows that use of furosemide in methotrexate clearance reduced the hospital stay. In contrast to our study, another study who used other procedure for methotrexate clearance reported mean hospital stay of 8 [18]. In our study, frequency of delayed methotrexate clearance was observed in 16 (20%) patients while it was not observed in 64 (80%) patients. The mean (SD) time of methotrexate clearance was 4 (±1) days. A previous study carried out by Michael Karremann et al. reported delayed methotrexate clearance in more than 70% patients. These finding shows that furosemide has efficiency against methotrexate clearance.

Renal injury, electrolyte imbalance, transaminitis and mucositis were the adverse complications observed in the current study. Renal injury was observed in 8 (10%) subjects, electrolyte imbalance in 12 (15%) subjects while transaminitis was observed in 11 (13.75%) subjects. Majority of the transaminitis patients (72.73%) were grade 1-2 while grade 3 transaminitis was observed in only 3 (27.27%). Mucositis was observed in 8 (10%) subjects, amongst which grade 1 mucositis was observed in 6 (75%) patient's grade 2 in 1 (12.5%) subjects while grade 3 mucositis was also observed in 1 (12.5%) subjects. Tracy Wiczer et al. revealed in a prior research that a significant percentage of patients were given furosemide dosages during methotrexate clearance. They reported that when furosemide is

given concurrently with methotrexate, the risk of nephrotoxicity rises by 156 percent. But, since their research was retrospective, it is difficult to link nephrotoxicity to the use of furosemide when patients had measurable methotrexate levels in their blood. The majority of the toxicity observed in this research was grade 1 [4]. In accordance with our study, another study carried out by Howell et al. reported that in order to avoid kidney damage, forced diuresis with hydration and furosemide supplementation is effective [9].

## CONCLUSION

Our study concludes that furosemide is highly effective in methotrexate clearance in patients treated with high dose methotrexate. The use of furosemide reduces the hospital stay which in turn reduces the cost associated with hospital stay. As furosemide is cheaper and easily available so it can be used easily in the methotrexate clearance in patients treated with high dose methotrexate. Other studies based on large sample size and including multiple centers should be conducted to get better results.

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