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Comparison of Efficacy of Mesna and Hydration with Only Hydration in the Prevention of Cyclophosphamide Induced Hemorrhagic Cystitis in Rheumatic Diseases

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ABSTRACT

Background: Cyclophosphamide can cause hemorrhagic cystitis depending on dose, duration and routes of administration which can be prevented by hydration, mesna and other measures. This study was aimed to compare the efficacy of mesna and hydration with hydration alone in preventing cyclophosphamide induced hemorrhagic cystitis in order to review the rationale and evidence for prescribing mesna to prevent such bladder toxicity in rheumatology setting.

Materials and methods: This non-blind, controlled, interventional study was conducted among patients who were selected for intravenous pulse cyclophosphamide for rheumatic diseases. After obtaining informed written consent, 69 subjects were enrolled and divided into two groups, group A (Received mesna along with hydration with one liter normal saline) group B (Received only one liter normal saline). Cyclophosphamide dose was 500 – 1000 mg/m^2 BSA and mesna dose was 60% of the total cyclophosphamide dose. Urinalysis was done in the second and tenth day of each CYC pulse and prior to next pulse. Phase contrast microscopy was done when urine R/M/E revealed hematuria.

Results: Mean age of the patients was 31.59±7.6 and 32.95±8.1 years in group A and group B respectively. Male patients were 9.4% and female 90.6% in group A and 100% patients in group B were female. Mean dose of cyclophosphamide in 1st cycle was 748.8±90.8 and 729.1±48.9 and in 2nd cycle 1099.6±172.2 and 1083.6±120.7 mg in group A and Group B respectively. None of the patients in either group developed hemorrhagic cystitis and leucopenia or any adverse effect of mesna.

Conclusions: In rheumatology setting use of adequate hydration alone in the prevention of pulse cyclophosphamide induced hemorrhagic cystitis may be sufficient, mesna is not necessary.

KEY WORDS

Cyclophosphamide; Hemorrhagic Cystitis; Hydration; Mesna.

INTRODUCTION

Cyclophosphamide has been used since the 1960s to treat severe manifestations of autoimmune inflammatory diseases such as systemic lupus erythematosus, systemic vasculitis, and systemic sclerosis.[1] This alkylating agent has well-established efficacy in lupus nephritis and systemic necrotizing vasculitis, like ANCA associated vasculitis, conditions for which it is the standard of care by the 1980s.[2] The doses of cyclophosphamide prescribed in autoimmune diseases are lower than the doses typically prescribed for cancer chemotherapy. However in rheumatic diseases the drug is often used for extended periods of time and, due to a high rate of clinical relapse, treatment often requires repeated courses. Cyclophosphamide causes hemorrhagic cystitis.[3] The prospect of preventing these serious bladder toxicities with mesna has led to the common use of this agent, which is considered safe and is frequently recommended in textbooks and clinical guidelines for routine use.[4] Hemorrhagic cystitis has been defined as 'the presence of sustained haematuria and lower urinary tract symptoms (e.g. Dysuria, frequency, urgency) in the absence of active tumour and other conditions, such as vaginal bleeding, general bleeding diathesis, and bacterial or fungal urinary tract infections.[5] HC can also develop weeks to months after treatment in 20%–25% of patients who receive high dose cyclophosphamide.[6] Hemorrhagic cystitis is generally graded as mild,

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moderate or severe according to the degree of pain and haematuria. Severe hemorrhagic cystitis typically includes the presence of gross haematuria with clots and occurrence of clinical complications, it is usually painless but can be extremely painful and debilitating, requiring prolonged hospitalization.[7] In patients who develop severe bladder haemorrhage mortality rates range from 2% to 4%.[8] Studies on rheumatic patients showed the incidence of hemorrhagic cystitis ranged from 12% to 41%.[9,10] This study was aimed to compare the efficacy of mesna and hydration with hydration alone in preventing cyclophosphamide induced hemorrhagic cystitis.

MATERIALS AND METHODS

This prospective, interventional study was conducted in Rheumatology Outpatient and Inpatient Department of Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka from March 2015 to September 2017, in patients who were selected for Intravenous (IV) pulse cyclophosphamide for rheumatic diseases. In this study, efficacy of mesna and hydration was compared with only hydration in the prevention of IV pulse CYC induced HC in rheumatology setting. Sixty nine subjects were enrolled after having informed written consent. The primary outcome variable was non glomerular RBC. Secondary outcome variables were short term toxicity of CYC and adverse effects of mesna. At baseline urine routine microscopic examination, complete blood count, serum creatinine and serum alanine amino transferase were done and demographic details were recorded in a semi-structured questionnaire. The study subjects were divided into two groups following computer generated random number. The group A subjects received mesna and hydration. The group B subjects received only hydration in the form of normal saline. One liter of intravenous normal saline was given over a two to four hour period before the cyclophosphamide infusion. Both groups of patients received monthly CYC infusions in a dose of 500 mg-1000 mg/ m^2 BSA. CYC was infused over one hour. Mesna dose were 60% of the total cyclophosphamide dose, which were added to intravenous saline. Urinalysis was done in the second and tenth day of each CYC pulse and prior to next pulse. Efficacy of mesna plus hydration and only hydration in preventing CYC induced HC was assessed by comparing baseline urine R/M/E finding with the urine finding on the second and tenth day of each CYC pulse and prior to next pulse. Phase contrast microscopy was done when urine R/M/E revealed hematuria to differentiate between glomerular and non glomerular RBC. CBC was done on tenth day of each CYC pulse and prior to next pulse to see WBC count. HC was defined by the presence of 10% dysmorphic RBC in the absence of RBC cast, new onset proteinuria and renal insufficiency. After the administration of CYC, all patients were instructed to drink at least one liter of fluid every six to eight hours for 24 hours afterwards, and to void as frequently as possible. Demographic and clinical data were collected by structured questionnaire and analysis was done with the help of SPSS version-22. The test statistics used to analyze the data were Fisher's exact test for nominal variables, inter group analysis was done by student "t' test (Unpaired). Mann-Whitney U test was done for analysis of non normally distributed observations. p value ≤0.05 was considered significant. Before starting the study, ethical clearance was taken from Institutional Review Board (IRB) BSMMU.

RESULTS

Mean age of the patients was 31.59±7.6 and 32.95±8.1 years in group A and group B respectively. Male patients were 9.4% and female 90.6% in group A and 100% patients in group B were female. Indications of cyclophosphamide were Systemic Lupus Erythematosus (SLE) with lupus nephritis, Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) systemic sclerosis with Diffuse Parenchymal Lung Disease (DPLD) Granulomatosis with Polyangiitis (GPA) rheumatoid arthritis with DPLD, SLE vasculitis, dermatomyositis with DPLD. Mean dose of cyclophosphamide in 1st cycle was 748.8±90.8 and 729.1±48.9 and in 2nd cycle 1099.6±172.2 and 1083.6±120.7 mg in group A and Group B respectively. None of the patients in either group developed hemorrhagic cystitis and leucopenia or any adverse effect of mesna.

Table I Indication of cyclophosphamide

Indication of cyclophosphamide	Group A (n=32) n (%)	Group B (n=37) n (%)
SLE with Lupus nephritis	19 (59.4)	19 (51.4)
NPSLE	5 (15.6)	6 (16.2)
Systemic sclerosis with DPLD	6 (18.8)	9 (24.3)
GPA	1(3.1)	0(0)
RA with DPLD	1(3.1)	0 (0)
SLE vasculitis	0 (0)	2 (5.4)
Dermatomyositis with DPLD	0 (0)	1 (2.7)

Table II Dose of cyclophosphamide and mesna and occurrence of Hemorrhagic cystitis (n=69)

Dose of cyclophosphamide and mesna	Group A (n=32) Mean± SD	Group B (n=37) Mean± SD	Hemorrhagic cystitis in both groups
1st dose of cyclophosphamide (mg)	748.8± 90.8	729.1± 48.9	0
1st dose of mesna (mg)	449.9± 53.3		
2nd dose of cyclophosphamide (mg)	1099.6± 172.2	1083.6± 120.7	0
2nd dose of mesna (mg)	658.8± 104.1		

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DISCUSSION

Although hemorrhagic cystitis is a potentially severe complication, which can cause significant morbidity and considerable expense due to prolonged hospitalization, there is no published national or international consensus on the optimal preventive strategy.[11] Several studies have evaluated the use of standard prophylactic measures, including hydration, bladder irrigation and the use of mesna, to reduce the risk of hemorrhagic cystitis, but the results have been variable. As per literature search, there is no such study comparing the efficacy of mesna and hydration with that of only hydration in the prevention of cyclophosphamide induced hemorrhagic cystitis in rheumatology setting, however, several studies were done in different parts of the world to assess the individual efficacy and comparative efficacy in the oncology setting. In this study none of the patients in either group developed hemorrhagic cystitis and leucopenia or any adverse effect of mesna.

The incidence of hemorrhagic cystitis varies in different studies in the rheumatology literature. Monach, et alpublished a review on bladder toxicity of CYC therapy in a mixed group of patients with rheumatic diseases in 2010.[12] The review showed a significantly greater incidence rate of hemorrhagic cystitis in patients treated with oral CYC compared with IV treatment regimens, regardless of disease subset. However, this finding could be explained mainly by a more than 3 times higher cumulative CYC dose (> 100 g) in patients receiving oral CYC. Because the cumulative dose is significantly lower and/or hydration is more prominent in intermittent IV CYC than oral CYC regimens, Monach, et al concluded that total dose of CYC is the main factor for bladder toxicity rather than the route of administration.

To assess bladder toxicity of CYC and uroprotective effect of mesna in rheumatic diseases Neslihan Y et al evaluated 1018 patients in a retrospective study[13] They identified 17 patients (1.67%) with hemorrhagic cystitis. The median time for diagnosis to hemorrhagic cystitis was 10 months. They observed similar incidence rate for hemorrhagic cystitis in both patient groups concomitantly treated with or without mesna [9/583 (1.5%) vs 8/425 (1.8%) respectively, p = 0.08]. Cumulative CYC dose (HR for 10-g increments 1.24, p < 0.001) was associated with hemorrhagic cystitis. The findings of the above study are consistent with our result in that we observed no HC in low dose pulse CYC therapy which was much lower than the dose associated with HC used in oncology setting.

However if HC could ever occurred it is likely that both modalities of preventive measure effectively prevent it. Other possible explanation of absent HC in our study is adequate IV hydration and use of corticosteroid. All patients in our study were on prednisolone of variable dose and duration for their main rheumatic diseases. HC is a complex inflammatory response, induced by acrolein with subsequent immunocompetent cells activation and release of many proinflammatory agents, mesna is necessary for the initial uroprotection through its neutralizing effect on urothelial damage initiated by acrolein, while steroid may inhibit the mediators of the inflammatory process that follow.[14]

As stated in the critical review by Siu and Moore and supported by the review by Links and Lewis, adverse effects with mesna prophylaxis are uncommon although when administered orally mesna is associated with gastrointestinal effects including nausea, vomiting and crampy abdominal pain.[15,16] Siu and Moore claimed that the adverse effects associated with mesna were generally less with intravenous doses, especially at the doses routinely administered. Vomiting and diarrhea occurred only after doses of more than 80 mg/kg (Klein HA et al).[17] This is consistent with our finding. Similar to Siu and Moore's observation, no adverse effects of mesna was observed in our study possibly due to low dose and IV use. No patient was dropped due to adverse effects.[16]

A prospective randomised study was carried out by Hows JM et al to compare the effect of mesna with that of forced diuresis in preventing cyclophosphamide induced haemorrhagic cystitis in marrow transplant recipients.[18] Sixty one consecutive BMT recipients were randomized for treatment with forced diuresis or mesna. The incidence of macroscopic haematuria was significantly lower in the mesna treated group (χ^2= 4.03, p <0.05). No specific side effects of mesna were detected. The authors concluded mesna is more effective than forced diuresis in preventing cyclophosphamide induced haemorrhagic cystitis in BMT recipients (p<0.05).

A retrospective analysis was conducted by Murphy C et al to assess the efficacy of hyperhydration versus hyperhydration plus mesna in preventing cyclophosphamide induced hemorrhagic cystitis.[19] 110 patients received hyperhydration alone (Baseline intravenous intake of dextrose at least 3.61/m ^{2}/day) and 107 patients received hyperhydration plus intravenous mesna (120% of daily cyclophosphamide dose) while both groups receiving cyclophosphamide (Total dose 150-200 mg/kg) as part of a dose intensive regimen. Macroscopic hematuria was noted in 17 (16%) and 9 (8%) patients who received hyperhydration with or without mesna, respectively (p=0.08). This analysis failed to demonstrate a benefit in adding mesna to hyperhydration in preventing cyclophosphamide induced hemorrhagic cystitis.

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A randomised controlled trial by Shepherd et al evaluated the efficacy of mesna compared to hyperhydration in reducing haemorrhagic cystitis in 100 patients undergoing autologous or allogeneic bone marrow transplant conditioning with high-dose cyclophosphamide.[20] The investigators concluded that both approaches were equally effective in preventing cyclophosphamide-induced HC in BMT patients. Those results were similar in our study.

Several studies found no difference in HC incidence and severity when patients were treated with mesna compared with hyperhydration.[21] Interestingly, Tsuboi et al. found that prophyłactic administration of mesna (p=0.0105) and bladder irrigation (p=0.0001) were significant risk factors of early-onset HC in a multivariate analysis.[22]

LIMITATION

This study was an open-label one. Desired sample size was not achieved due to time frame. Failed to ensure mono-branded medicine in both study groups.

CONCLUSION

Both mesna with hydration and only hydration seem to be equally effective in the prevention of pulse cyclophosphamide induced hemorrhagic cystitis. In rheumatology setting hydration is enough and adding mesna is unnecessary and adds to the cost.

RECOMMENDATION

Use of only hydration in the prevention of pulse cyclophosphamide induced hemorrhagic cystitis may be sufficient in rheumatology setting, mesna is not necessary.

DISCLOSURE

All the authors declared no competing interest.

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