

Experimental study of Comparison of Uro -protective efficacy of Mesna versus Hyperhydration in Cyclophosphamide-induced haemorrhagic Cystitis in Rats

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Received Date: September 23, 2022; Accepted Date: September 30, 2022; Published Date: October 03, 2022.

Citation: Yasin Idweini, B. Umbert, M. Sole and Pablo Carretero (2022) Experimental study of Comparison of Uro -protective efficacy of Mesna versus Hyperhydration in Cyclophosphamide-induced haemorrhagic Cystitis in Rats. *Journal of Scientific Research and Biomedical Informatics*, 1(1); Doi: 10.31579/2834-8745/004

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Abstract

Background: Haemorrhagic Cystitis (H.C) is a dose limiting side effect of cyclophosphamide (CyP).

Aim: in this study we aimed to investigate the role of Mesna in the protection of CyP-induced H.C and compare its efficacy with hyper hydration.

Setting and design: This animal study was conducted in the experimental Animals Breeding and Medical Research Centre of Hospital Clinic de Barcelona in the University of Barcelona.

Material and Methods: Male Sprague Dawley rats (360-510 gr weight, 5 rats per group were randomly assigned to four groups): Group 1 (Control group) received no drugs, Group 11(received CyP 150mg/kg alone intraperitoneal), Group 111(received CyP150mg/kg, and mesna 150% of the CyP dose immediately and at 4 and 8 hour after administration of CyP, both drugs IV injection by intra jugular vein) ,Group 1V (received CyP150mg/kg, and hyperhydration by catheterization of the animal jugular vein with continual infusion).

Bladder of animals were assessed macroscopically and histologically 48 hours later. Gross assessment for presence of oedema and haemorrhagic and histological evaluation of damage to the bladder were scored and statistical analysis used.

Results: All the animals in group 11 had evidence of HC. Significant histological damage and macroscopic changes were present in this group compared to group1 ($p < 0.001$).

The median scores of bladder damage in group111 and 1V were significantly lower compared to group 11. When the median scores for bladder damage in group 11, 111 and 1V were compared there was no significant difference among these groups.

Conclusion: This study demonstrates the efficacy of mesna or hyperhydration in prevention cyclophosphamide-induced haemorrhagic cystitis

Key words: mesna, cyclophosphamide, haemorrhagic cystitis, hyperhydration

Introduction:

Haemorrhagic cystitis (HC) has been acknowledged as a significant complication following allogeneic hematopoietic cell transplantation since its inception. High dose chemotherapy used in conditioning regimens, namely cyclophosphamide and busulfan or its combination, directly damages the bladder mucosa resulting in early HC [1,2]

Cyclophosphamide (CyP) is an alkylating chemotherapeutic agent that is used in a variety of malignant conditions including lymphoma, ovarian and breast cancer.

Haemorrhagic cystitis is well known and potentially life-threatening adverse effect of this drug [3].

CyP is a pro drug that is transformed into the active metabolites phosphoramidate mustard and acrolein by the P-450 enzymes in the liver. Acrolein has been proven to be a potent urothelial irritant and is currently accepted as a major cause of cyclophosphamide induced HC. It has been proposed that urothelial damage occurs by direct contact with acrolein which causes oedema, ulceration neovascularization, haemorrhage and necrosis [4].

Adequate hydration and the concurrent administration of sodium-2-mercaptoethane (mesna) are the most widely employed methods for prevention of CyP induced HC in clinical practice, however, HC still occurs in 10-40% of mesna-treated patients [5].

Material and Methods:

A total of 20 male Sprague Dawley was allowed free access to food and water and were randomly assigned to one of the four groups of five rats each group. Male Sprague Dawley rats (about 360-510 gr weight) Five rats per group. Group I (Control group): received no drugs. Group II: (received CyP 150mg/kg alone intraperitoneal). Group III: (received CyP 150mg/kg, and mesna 150% of the CyP dose, in three doses : immediately and at 4 and 8 hour after the administration of CyP, both drugs by intravenous injection by intra jugular catheterization). Group IV: (received CyP 150mg/kg and hyperhydration by intra jugular vein infusion).

The animals were sacrificed 48 hours later after the administration of CyP, their bladders, ureters and kidneys were removed by careful dissection and fixed in 10% formalin and all sent for histopathological evaluation.

Bladder of animals were assessed macroscopically and histologically. Gross assessment for presence of oedema and haemorrhage and histological evaluation of damage to the bladder were scored and statistical analysis used.

Results:

All animals were almost identical in weight. Diuresis :No significant difference between group II and III but there is big difference between group II and IV ($p=0.0169$) and between III and IV ($p=0.0318$). Histopathological lesions : good efficacy was demonstrated In both methods mesna ($p=4.512E-03$) and hyperhydration group ($p=0.0301$). Mesna group efficacy was superior to the hyperhydration group ($p=0.0301$).

Mesna group is superior to hyperhydration group regarding to prevention of vesical oedema ($p=0.0379$).

Discussion:

In this study we investigated the role of mesna and hyperhydration in prevention of CyP induced HC and compared the efficacy of both. The use of CyP is associated with mutagenesis and bladder cancer, particularly

in those patients who developed cystitis [6,7]. Haemorrhagic cystitis is a syndrome associated with certain disease status as well as exposure to drugs, viruses, and toxins. It manifests as diffuse bleeding of the endothelial lining of the bladder. Studies indicate that mesna probably has no adverse effect on engraftment. This is consistent with its chemistry and pharmacology as the drug is hydrophilic and activated only in the kidneys, thus, it is inactive in the bloodstream and unable to penetrate cell membranes and interfere with the action of CyP. Based on this mesna and hyperhydration are equally effective in preventing CyP induced haemorrhagic cystitis in bone marrow transplantation patients. [8,9]

Conclusion:

This study demonstrates the efficacy of mesna is better in the prevention of CyP induced haemorrhagic cystitis, also hyperhydration demonstrated good efficacy, but not as same as mesna in preventing HC.

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