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Research Article

MANNITOL FOR THE PREVENTION OF CISPLATIN-INDUCED NEPHROTOXICITY: A PROSPECTIVE COMPARISON OF HYDRATION PLUS MANNITOL VERSUS HYDRATION ALONE IN THE MILITARY HOSPITAL IN TUNISIA.

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ABSTRACT

Background: Cisplatin isa very effective drug for the treatment of several malignancies, and their use has contributed to an increase in the long-term survival of patients with cancer. Unfortunately, the risk of nephrotoxicity is a dose limiting adverse effect that occurs in nearly one-third of patients receiving cisplatin-based chemotherapy.
The study aim was to evaluate the incidence of cisplatin-induced nephrotoxicity in patients treated with and without mannitol. **Material and methods:** A comparative prospective study enrolling patients treated with cisplatin. All patients received 1000 ml of normal saline (0.9%) infused over 1 hour prior to Cisplatin administration, and 2000 mL infused over 3 hours after Cisplatin administration. The Mannitol group received 250 mL of Mannitol 10% concomitant with Cisplatin, infused over 1 hour if the dose of cisplat in is inferior to 70mg/m^2 orover 3 hours if the dose of Cisplatin is superior to 70mg/m^2. The primary outcome was mean change in serum creatinine from baseline .Secondary outcomes included incidence of acute nephrotoxicity. The difference in the incidence of nephrotoxicity was compared using the Fischer's exact test and the change in serum creatinine was compared using the Student's t-test (P<0.05).
Results: 35 patients (17with Mannitol and 18 without) were evaluated.The average increase in serum creatinine (mg/dL) was 0.107 in patients who received Mannitol while 0.114 in those who received hydration alone (p= 0.67). In the group which received mannitol, 7.4% experienced nephrotoxicity while 21.7% in the hydration alone group experienced nephrotoxicity (p=0.47). Patients who received doses >=70mg/m2 of cisplatin had a slightly lower rates of nephrotoxicity with mannitol.
Conclusion: These results demonstrate that the new hydration protocol comprising Mannitol10% specially when the dose is superior to 70mg/m² could prevent the nephrotoxicity induced by cisplatin without affecting the treatment outcome

INTRODUCTION

Background

Cisplatin is a platinum-based chemotherapeutic agent used in the treatment of many malignancies, including testicular, lung, head, neck, bladder, gynecologic, hepatobiliary cancers and sarcomas. The adverse effect profile of cisplatin consists of nausea and vomiting, myelosuppression, ototoxicity, and dose-limitingnephrotoxicity.(1)

Nephrotoxicity occurs in roughly one-third of all patients who receive cisplatin with an increase in serum creatinine (SCr) observed within 6-7 days and remaining elevated up to 3 weeks. Cisplatin is renal eliminated and accumulates in the renal tubules. It is up taken into the proximal tubules, which makes it a potent nephrotoxic (2).

Direct damage of the proximal tubules results in mitochondrial damage and generation of reactive oxygen species contributing to the epithelial dysfunction. The activated inflammatory response is mediating renal injury by enhanced renal expression of tumor necrosis factor-α and other cytokines in the kidney (3). Several histologic changes occur becauseof these molecular effects, including necrosis of the distal tubules

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and dilatation of convoluted tubules, and formation of casts(4).Renal tubular function in patients receiving cisplatin is often affected. This leads to a decrease in glomerular filtration rate, a decrease in proximal reabsorption of sodium and water, as well as an increase in urinary excretion of protein andelectrolytes.

Currently, preventative strategies including forced diuresis with either mannitol, furosemide, or a combination of the two are set up in order to prevent the nephrotoxicity of cisplatin.

Aim

The aim of this study is to evaluate the effect of mannitol combined with hydration on renal function and describe the incidence of cisplatin-induced nephrotoxicity in patients treated for a variety of cancer chemotherapy regimens with and without mannitol. This study tested if the addition of mannitol to cisplatin therapy significantly reduced the increase in SCr from baseline and the incidence of acute nephrotoxicity in patients receiving various regimens containing cisplatin.

MATERIAL AND METHODS

This is a comparative prospective cohort study. All eligible patientstreated with cisplatin during the study period are enrolled in the study. Only patients who are treated with Cisplatin are included. Other inclusion criteria included age ≥18 years and a cisplatin dose ≥ 40 mg/m2. The patients were divided into two groups, those who received mannitol and those who did not receive during their treatment with a cisplatin. All patients received 1000 ml of normal saline (0.9%) infused over 1 hour prior to Cisplatin therapy, and 2000 mL infused over 3 hours after Cisplatin therapy. The Mannitol group received 250 mL of Mannitol 10% concomitant with Cisplatin dose, infused over 1 hour if the dose of cisplatin is inferior to 70mg/m2 or over 3 hour if the dose of Cisplatin is superior to 70mg/m2. The primary outcome is mean change in serum creatinine from baseline. The secondary outcomes included incidence of acute nephrotoxicity.

Regarding the primary outcome, the mean change in SCr (mg/dL) from baseline after the initiation of cisplatin therapy is measured by calculating the difference between the baseline SCr and the highest SCr during the treatment duration up to a month after the last given dose of cisplatin. Regarding the secondary outcomes, it includes the incidence of acute nephrotoxicity and the incidence of grade 1 or higher acute nephrotoxicity as defined by the Common Terminology

RESULTS

From January 2016 to January 2017, fifty patientswere included in our study. Twenty three of themdid not receive mannitol, and twenty seven received mannitol. The characteristics of patients in the 2 study groups were similar at baseline (Table 1).

Table1 Patient baseline characteristics

	Mannitol 27	Without Mannitol 23	P value
Mean age(years)	54.19 ± 10.41	52.87 ± 14.08	0.09
Sex(%male)	74.07	82.6	0.46
BSA (m^2)	1.76 ± 0.21	1.79 ± 0.19	0.53
Malignancy, n (%)			0.59
Head/neck	13	11	
Lung	0	2	
Gynecologic	2	0	
Urinary tract	5	4	
Gastric	4	6	
Other	3	0	
Combined agent, n (%)			
Fluorouracil	7	9	
Vinorelbine	1	2	
Gemcitabine	8	4	
Etoposide	1	2	
Docetaxel	0	1	
Capecitabine	1	1	
Methotrexate	0	1	
Adriamycin	5	3	
Radiotherapy , n(%)	7	8	
Mean Cisplatine dose(mg/m^2)	93,27	95,11	0.12
Median of cycles	2.15	2.61	0.97
Baseline SCr (range)	77.14	72.54	0.33

The primary outcome, mean increase in SCr, was found to be lower in the mannitol group.

The average increase in serum creatinine (mg/dL) was 0.107 in patients who received Mannitol while it was 0.114 in those who received hydration alone (p= 0.67). In the group which received mannitol, 7.4% experienced nephrotoxicity while 21.7% of patients in the hydration alone group experienced nephrotoxicity (p=0.47).

The overall results of the study are summarized in Table2.

Table2 Results

	Mannitol	Without Mannitol	P value
	27	23	
Mean change in SCr	0.107	0.114	0.67
Nephrotoxicity n,(%)	2 (7.4%)	5 (21.7%)	0.47
Nephrotoxicity Grade1 n,(%)	0	1 (4.34%)	
Nephrotoxicity Grade2 n,(%)	2 (7.4%)	3 (13%)	
Nephrotoxicity Grade3 n,(%)	0	1 (4.34%)	

Patients who received doses>=70mg/m² of cisplatin had non-significant lower rates of nephrotoxicity with mannitol (3.7%vs 8.6%: p=0.47) Figure1.

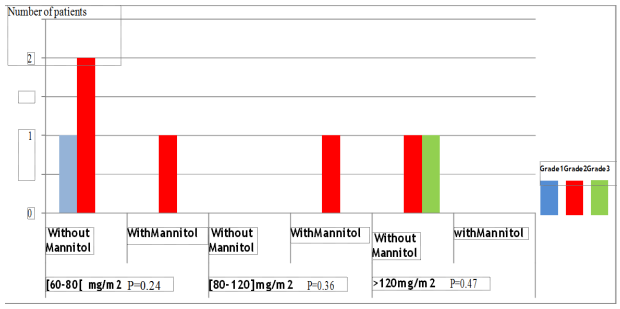

Figure1 Grade of nephrotoxicity by Cisplatin dose quartile: Mannitol vs no mannitol

DISCUSSION

Our results suggest that the use of mannitol and hydration is comparable directly to hydration alone, mannitol shows no benefit. These results are similar to those found by Leu *et al* (6), where the addition of mannitol did not appear to be nephroprotective when compared to normal saline alone. The findings from our evaluation were also in accordance with the study from Santoso *et al*. (7) a trial comparing sodium hydration to sodium hydration in addition to either mannitol or furosemide. Their study found that there was an insignificant difference between sodium hydration and forced diuresis as well. Currently there is no convincing evidence to advocate the use of forced diuresis with mannitol to prevent cisplatin-induced nephrotoxicity. However these results are different to those found by Morgan *et al*.(8) , Williams *et al*.(9), Mc Kibbin *et al*.(10) and Williams, R. P *et al* where a reduction in nephrotoxicity rates in patients treated with mannitol was

observed. The results of the last study suggest that mannitol may be most effective when used with non-gynecologic regimens and with cisplatin doses ≥70 mg/m^2 (11).

Studies comparing hydration versus hydration with forced diuresis have shown conflicting results. Some have suggested that mannitol decreases cisplatin toxicity, while others have shown that the use of mannitol may have no effect in reducing cisplatin toxicity. There are no guidelines that provide standard dosing for hydration or forced diuresis; therefore, the dose of hydration or mannitol and duration of therapy were variable across studies and may explain the conflicting results between studies.

It should be noted that in our study, the dose of mannitol was the same in all patient receiving the mannitol hydration in accordance with the hypothesis that mannitol dosing has no significant influence, suggesting that doses may be standardized across cisplatin regimens (12).

Although we did not randomly assign patients to be treated with or without mannitol. The lack of changes in practice or demographics created a quasi-high-quality experiment that allowed us to evaluate the possible nephroprotective role of mannitol in the context of cisplatin administration and hydration.

Using average change in SCr as the primary outcome allowed us to observe the changes in renal function of two groups that had similar baseline renal function. We chose not to use change in estimated CrCl as our outcome for various reasons, including the fact that it is subject to changes in weight that are very likely in this patient population. Moreover, the equations to estimate CrCl were studied to estimate renal function in patients whose renal function was not changing, thus using it in patients where there is a known decrease in renal function was not appropriate in our view. Last, the various systems used to define nephrotoxicity use percent changes in SCr, which makes it easier to relate our results to these systems.

Although our sample size was relatively small compared to other randomized trials, our study is prospective which is contrary to other trials. Our analysis focus on trends of serum creatinine value. Conclusion

This is the first study in Tunisia to evaluate the effect of mannitol on renal function and describe the incidence of cisplatin-induced nephrotoxicity in patients treated with and without mannitol.

There was no significant difference observed regarding the increase in serum creatinine from baseline and the incidence of acute nephrotoxicity between the 2 groups treated with and without mannitol.

Due to the limited number of our population, further studies are needed to confirm our results with a wider population including patient with and without comorbidities.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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