


# The Nephroprotective Effect of Mannitol in Head and Neck Cancer Patients Receiving Cisplatin Therapy

Erik Hägerström<sup>1</sup> , Lotte Lindberg<sup>2</sup>, Jens Bentzen<sup>3</sup>, Kasper Brødbæk<sup>4</sup>, Bo Zerahn<sup>2</sup> and Bent Kristensen<sup>2</sup>

<sup>1</sup>Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, Copenhagen, Denmark. <sup>2</sup>Department of Clinical Physiology and Nuclear Medicine, Herlev Hospital, Herlev, Denmark. <sup>3</sup>Department of Oncology, Herlev Hospital, Herlev, Denmark. <sup>4</sup>Department of Clinical Biochemistry, Rigshospitalet, Copenhagen, Denmark.

Clinical Medicine Insights: Oncology  
Volume 13: 1–5  
© The Author(s) 2019  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/1179554918821320  


## ABSTRACT

**INTRODUCTION:** Cisplatin is used as treatment for several different malignancies and a well-known complication is irreversible kidney damage. To protect the kidneys, this treatment is often combined with mannitol infusion to promote osmotic diuresis. Earlier studies investigating the nephroprotective effect of mannitol have shown conflicting results.

**OBJECTIVE:** To investigate changes in kidney function in head and neck cancer patients treated with cisplatin with and without additional mannitol infusion.

**METHODS:** A single center, retrospective cohort study of patients with squamous cell carcinoma of the head and neck receiving radiotherapy with cisplatin. Patient data were collected from November 2013 to December 2014.

**RESULTS:** After exclusion, a total of 78 patients were considered evaluable. They were equally distributed between a mannitol and a non-mannitol group and anthropomorphometrically similar. <sup>51</sup>Cr-EDTA clearance declined in the mannitol group from 99.7 (19.9) to 96.4 (20.8) mL/min and in the non-mannitol group from 102.2 (17.8) to 92.3 (23.1) mL/min.

**CONCLUSIONS:** There was a significantly smaller decrease in <sup>51</sup>Cr-EDTA clearance in the mannitol group indicating a nephroprotective effect of mannitol.

**KEYWORDS:** Chemotherapy, head and neck cancer, toxicity management, hypopharyngeal cancer, laryngeal cancer, oropharyngeal cancer, radiotherapy, squamous cell carcinoma of the head and neck

**RECEIVED:** June 6, 2018. **ACCEPTED:** November 26, 2018.

**TYPE:** Original Research

**FUNDING:** The author(s) received no financial support for the research, authorship, and/or publication of this article.

**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.

**CORRESPONDING AUTHOR:** Erik Hägerström, Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. Email: erik.hagerstrom@gmail.com

## Introduction

Cisplatin is a widely used chemotherapeutic agent, both as monotherapy and as a part of a concomitant regimen. This article focuses patients with squamous cell carcinoma of the head and neck (SCCHN) receiving radiotherapy with concomitant cisplatin.

Cisplatin has a well-documented array of toxic side-effects, of which some are potentially irreversible, including nephrotoxicity.<sup>1,2</sup> Accordingly, cisplatin infusion is usually combined with saline to hydrate and mannitol infusion to promote osmotic diuresis to prevent permanent damage to the renal tubules.<sup>2–4</sup>

The rationale of using mannitol as a nephroprotective agent has been examined in several previous studies with various conclusions. Santoso et al<sup>3</sup> performed a randomized trial comparing 3 groups of patients: saline infusion alone, saline infusion with furosemide, and saline infusion with mannitol. The patients were diagnosed with gynecologic cancers. In this study, the group receiving saline and mannitol infusion had the poorest nephroprotective results. Similar conclusions were made in the study by Leu and Baribeault.<sup>2</sup> This was a retrospective trial comparing saline infusion with saline and mannitol infusion in

patients receiving cisplatin treatment. More recently, Morgan et al<sup>5</sup> found significant nephroprotective effect of mannitol in a retrospective study of patients receiving cisplatin (in low or high dose) as the only chemotherapeutic agent. McKibbin et al<sup>6</sup> also found a nephroprotective effect of mannitol in their study of SCCHN patients receiving high dose of cisplatin.

The aim of this study was to compare changes in <sup>51</sup>Cr-EDTA clearance and estimated glomerular filtration rate (eGFR) in head and neck cancer patients receiving either saline hydration with mannitol or saline hydration alone during treatment with cisplatin.

## Methods

The study was a single center, retrospective cohort study performed at the Department of Oncology, Head and Neck Unit, Copenhagen University Hospital, Herlev. The mannitol group received 2.5 L of isotonic (9%) saline infusion as well as 500 mL of 15% mannitol infusion during chemotherapy, whereas the non-mannitol group received saline hydration therapy only.

All patients had SCCHN (divided between oropharynx, hypopharynx, and larynx carcinomas). They had stage III or IV



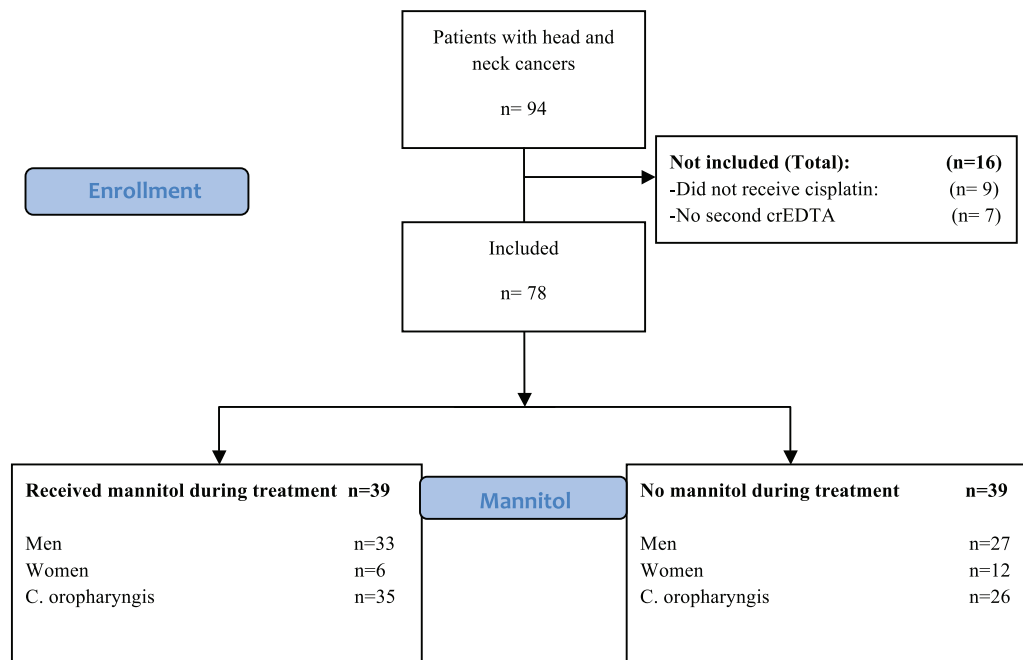


Figure 1. Flowchart.

disease and were treated according to the Danish DAHANCA guidelines. The guidelines recommend concomitant radiochemotherapy with cisplatin once a week to patients with locally advanced disease. Cisplatin is given once weekly at a dose of 40 mg/m<sup>2</sup> intravenously for 5 or 6 weeks. The recommended total radiotherapy dose is 66 to 68 Gy in 2 Gy fractions, 6 fractions per week. All patients additionally received nimorazole 1200 mg/m<sup>2</sup> orally 90 min before each fraction, as hypoxic radiosensitizer.<sup>7</sup>

Data were collected from November 1, 2013, to March 31, 2014 (mannitol group), and from April 1, 2014, to December 31, 2014 (non-mannitol group). Kidney function was monitored by weekly eGFR and <sup>51</sup>Cr-EDTA clearance measurements; the first measurements were performed prior to receiving any treatment and the comparative measurements were performed after the third treatment with cisplatin. The cisplatin treatment would be discontinued in case of <sup>51</sup>Cr-EDTA clearance decreasing below 50 mL/min.

Data on the following variables were recorded: age, sex, diagnosis, height, weight, mannitol treatment, cisplatin treatment (number of treatments and absolute dose), hypertension (current antihypertensive treatment), diabetes, use of acetylsalicylic acid, use of angiotensin-converting enzyme (ACE)-inhibitors, tobacco use, exposure to intravenous contrast during computed tomography/magnetic resonance imaging (CT/MRI), plasma creatinine/eGFR, and <sup>51</sup>Cr-EDTA clearance. Dates for blood sampling, <sup>51</sup>Cr-EDTA clearance, and chemotherapy were also recorded. Nonsteroidal anti-inflammatory drugs (NSAID) were all converted to other analgesic substances before starting treatment.

Patients with documented, compromised kidney function at referral were not considered eligible for treatment with cisplatin and were not included in the selection process.

Baseline characteristics were examined using descriptive statistics. Means with 1 standard deviation were reported for all continuous variables. Absolute numbers and percentages were reported for discrete data. The groups were compared using *t* tests and Fisher's exact tests. Exact *P* values are reported.

Multivariable linear regression models were fitted with the use of purposeful selection of variables. An inclusion criterion of *P* value < .5 was used, identified in univariable regression analyses.<sup>8</sup> To guard against Lord's paradox, both the change in the response variable (change score) and an analysis of covariance (ANCOVA) approach were examined. Control of the final model was done as recommended elsewhere.<sup>9</sup> All analyses and graphics were made using R statistical software, version 3.2.3, and the packages "car"<sup>9</sup> and "tableone."<sup>10</sup>

## Results

A total of 94 head and neck cancer patients were scheduled for cisplatin treatment. During the first part of the inclusion period, both mannitol and saline infusions were applied during treatment with cisplatin. In the last part of the inclusion period, only saline infusion was administered during treatment. In all, 16 patients were excluded due to missing values of <sup>51</sup>Cr-EDTA clearance (7 patients) or because they did not receive cisplatin (9 patients). Thus, 78 patients were included in the study. A total of 39 patients received additional mannitol and saline infusions, whereas 39 patients received only an additional saline infusion (Figure 1).

**Table 1.** Patients' characteristics.

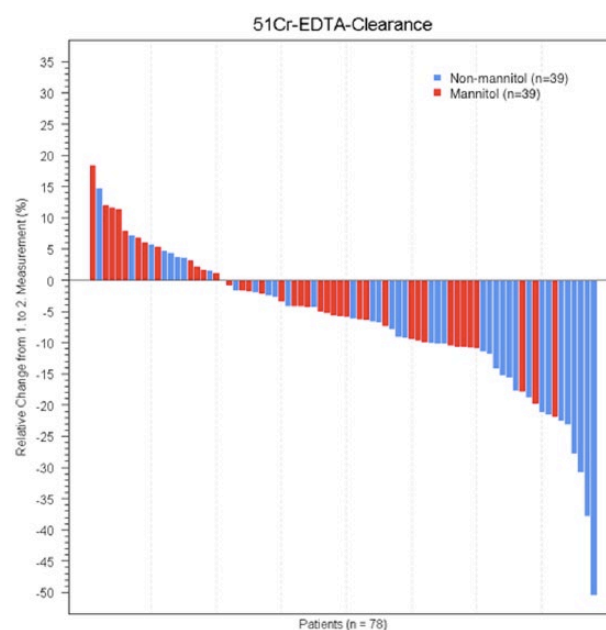
	NON-MANNITOL	MANNITOL	P VALUE
No. of patients	39	39	
<sup>a</sup> Age in years	61.6 (7.2)	62.6 (7.6)	.56
<sup>a</sup> Sex (men/women)	33/6	27/12	.18
<sup>a</sup> Diagnosis (%)			.04
Oropharynx	35 (89.7)	26 (66.7)	
Hypopharynx	3 (7.7)	12 (30.8)	
Larynx	1 (2.6)	1 (2.6)	
Height in cm	177.1 (7.4)	175.4 (8.3)	.35
Weight in kg	83.3 (21.9)	81.0 (15.1)	.59
<sup>a</sup> BMI in kg/m <sup>2</sup>	26.4 (6.0)	26.3 (4.4)	.93
<sup>a</sup> Hypertension (%)	10 (25.6)	17 (43.6)	.15
<sup>a</sup> Diabetes mellitus (%)	2 (5.1)	6 (15.4)	.26
<sup>a</sup> Smoking: pack years	24.4 (22.4)	31.5 (28.2)	.23
CT with contrast performed (%)	32 (94.1)	28 (96.6)	1.00
MR with contrast performed (%)	39 (100.0)	38 (97.4)	1.00
<sup>a</sup> Days from CT/MR to <sup>51</sup> Cr-EDTA clearance	-1.7 (3.9)	-2.2 (4.3)	.57
Baseline <sup>51</sup> Cr-EDTA clearance (mL/min/1.73m <sup>2</sup> )	102.2 (17.8)	99.7 (19.9)	.57
Baseline plasma creatinine (μmol/L)	71.7 (15.1)	68.2 (18.5)	.37
Baseline estimated GFR (mL/min)	93.4 (12.3)	93.7 (14.1)	.93
Baseline estimated GFR, weight corrected	96.4 (20.7)	98.8 (23.5)	.64
Days between first and second measurement	24.3 (4.8)	24.0 (5.4)	.80

Abbreviations: BMI, body mass index; CT, computed tomography; GFR, glomerular filtration rate; MR, magnetic resonance.

<sup>a</sup>Besides mannitol these variables were included in the multivariable linear regression models as predictor variables.

Table 1 shows the two groups to be very similar with the exception of distribution between cancer subgroup diagnoses. Most patients had oropharyngeal cancer, 35 patients in the mannitol group and 26 patients in the non-mannitol group. All patients were Caucasian. After the third series of cisplatin, the mean value of <sup>51</sup>Cr-EDTA clearance had declined to 92.3 mL/min (23.1) in the non-mannitol group and to 96.4 mL/min (20.8) in the mannitol group. The corresponding results for eGFR were 93.1 mL/min (11.4) and 91.9 mL/min (14.7).

The waterfall plot (Figure 2) shows that 57 patients had a decline in <sup>51</sup>Cr-EDTA clearance, 27 of whom received mannitol. However, the largest declines were observed in patients not receiving mannitol. In 12 patients receiving mannitol and 8 non-mannitol patients, <sup>51</sup>Cr-EDTA clearance increased. In 1 patient, <sup>51</sup>Cr-EDTA clearance was unchanged. In 1 patient, <sup>51</sup>Cr-EDTA clearance decreased below the limit for discontinuing treatment with cisplatin. None of the patients had a decrease in eGFR below 50 mL/min.

**Figure 2.** Changes in kidney function.

**Table 2.** Result of linear regression analyses (n=78 patients).

UNIVARIABLE MODELS	COEFFICIENT	P VALUE	95% CONFIDENCE INTERVAL	
Mannitol (no/yes)	6.54	.019	1.12	11.96
Age (years)	-0.074	.70	-0.46	0.31
Sex (men/women)	4.88	.14	-1.70	11.46
Diagnosis (oropharynx/other)	2.99	.38	-3.78	9.77
BMI (kg/m <sup>2</sup> )	0.057	.84	-0.49	0.60
Hypertension (no/yes)	1.45	.63	-4.45	7.35
Diabetes mellitus (no/yes)	-3.95	.49	-13.18	5.27
Smoking (pack years)	-0.028	.63	-0.14	0.087
Days from CT/MR to <sup>51</sup> Cr-EDTA clearance	0.29	.49	-0.56	1.14
Final multivariable model				
Mannitol (no/yes)	7.54	.0069	2.14	12.95
Sex (men/women)	6.52	.047	0.10	12.93
$R^2=0.12$	Adjusted $R^2=0.10$			

Abbreviations: BMI, body mass index; CT, computed tomography; GFR, glomerular filtration rate; MR, magnetic resonance.

None of the patients had an initial renal clearance below 50 mL/min when estimated with <sup>51</sup>Cr-EDTA. However, this was the case for 1 patient when renal clearance was estimated with eGFR.

Table 2 shows the results of the linear regression analysis. Treatment with mannitol and sex were identified to be significantly associated with the difference between the second and the first measurement when using the change in <sup>51</sup>Cr-EDTA clearance as the response variable and the highlighted variables in Table 1 as predictors. There was no detectable interaction between the predictors, nor was there any detectable interaction between body mass index (BMI) and sex. The result did not differ when modeled as either change scores or ANCOVA models (thus, the risk of Lord's paradox seems minimal). Accordingly, the final model is presented as a change score model as recommended elsewhere for nonrandomized studies.<sup>11</sup>

There was no significant association between treatment with mannitol or the other predictor variables using the same modeling strategy with plasma creatinine and eGFR as response variables, with the exception of an association with sex (*P* values: .02 and .04, respectively).

## Discussion

Descriptive statistics suggest and simple comparisons show a statistically significant difference between the mannitol and non-mannitol groups with a smaller decline in <sup>51</sup>Cr-EDTA clearance in the mannitol group (3.3% decrease in the mannitol group vs 9.7% in the non-mannitol group).

The multiple linear regression analysis shows an association with the change in <sup>51</sup>Cr-EDTA clearance and mannitol

treatment corrected for sex. No other collected covariates are associated with the outcome variable. The possibility of Lord's paradox does not seem to be a problem as the ANCOVA-like regression and the change score-regression show almost identical results. In "the final statistical change score model," mannitol and sex explain ~10% of the variation in the change of <sup>51</sup>Cr-EDTA clearance.

There was no corresponding significant difference in the change in eGFR between the groups, indicating that <sup>51</sup>Cr-EDTA clearance is a more sensitive and reliable method to detect changes in kidney function. This is also investigated in the Lindberg et al<sup>12</sup> study.

When comparing these results with earlier studies, there are some possible explanations for discrepancies in the conclusions. In the Santoso et al<sup>3</sup> study, a nephroprotective effect of mannitol could not be found. All patients were diagnosed with gynecologic cancers and received a higher dose of cisplatin (75 mg/m<sup>2</sup>). A majority was also treated with an additional chemotherapeutic agent such as 5-fluorouracil or paclitaxel. These agents are not known to have nephrotoxic side-effects, but commonly induce nausea, dehydration, diarrhea, and edema, thus serving as possible confounders. Moreover, the study involved patient-dependent data (24-h urine sampling) and was both underpowered and prematurely terminated. Subsequently, a nephroprotective effect of mannitol may have been missed. Similarly, the Leu et al<sup>2</sup> study found no significant nephroprotective effect of mannitol. The study consisted of a selected patient group with different malignancies, where SCCHN only accounted for 28% in the saline group and 4% in the mannitol group. Although there was no difference in the

mean cisplatin dose between the groups, the individual dose varied greatly between 40 and 100 mg/m<sup>2</sup>. An effect could have been missed, since the kidney function was measured with eGFR.

This study only included SCCHN patients receiving radiotherapy with concomitant cisplatin, which could explain the similar findings of a nephroprotective effect of mannitol in 2 other studies. In the study by Morgan et al,<sup>5</sup> the mannitol group consisted of 95.3% SCCHN patients and all of the patients in the non-mannitol group had SCCHN. Apart from a higher percentage of treatment with concomitant nephrotoxic drugs in the mannitol group, demographics were otherwise similar. Patients were treated with low (40 mg/m<sup>2</sup>) or high (100 mg/m<sup>2</sup>) dose cisplatin. There was a significant correlation between acute kidney injury (AKI) and treatment without mannitol. In the study by McKibbin et al,<sup>6</sup> 139 SCCHN patients receiving 100 mg/m<sup>2</sup> cisplatin were divided into a mannitol and a saline group. Cisplatin treatment was administered as a triweekly regimen, which differs from this study where weekly, low-dose treatment was used. There was a significantly increased risk of grade 3 increase in serum-creatinine (3.0 to 6.0 times the upper limit of normal serum-creatinine) in the saline group. There was no significant difference in risk of lower grades of serum-creatinine increase and no patients in either groups experienced higher grade increase.

This indicates that studies investigating the nephroprotective effect of mannitol can be difficult not only to evaluate but also to compare if the patients are not uniform regarding diagnosis and treatment. Also, this study has shown that the choice of kidney function measurement is of importance.

In this study, the patients were not randomized, but the baseline characteristics were very similar in the 2 groups. Only the distribution of subdiagnoses differed between the two groups, where the number of patients diagnosed with SCCHN other than oropharyngeal cancer is larger in the mannitol group. However, the statistical analysis did not show a significant influence of sub-diagnosis.

None of the patients in the non-mannitol group experienced a decrease of <sup>51</sup>Cr-EDTA clearance below the predefined limit of 50 mL/min. In other words, there were no direct clinical consequences for this group, as no planned cisplatin treatment was discontinued due to declining kidney function. No long-term data of the kidney function has been collected.

Although the results of this study show a significant nephroprotective effect of mannitol, it should be emphasized that only patients receiving low-dose cisplatin treatment were included. This brings up the question, if mannitol will have the same effect in patients receiving higher doses of cisplatin. The

Morgan et al and McKibbin et al studies indicate that a corresponding nephroprotective effect should be expected in patients treated with higher cisplatin dose, but this study will not provide an answer to this question. Thus, it would be of interest to investigate this further in a similar study.

## Conclusions

The group receiving saline and mannitol infusion had a significantly lower decline in <sup>51</sup>Cr-EDTA clearance compared with the group treated with saline hydration alone, indicating that mannitol has a nephroprotective effect. A similar study of patients receiving higher dose of cisplatin would be of interest.

## Author Contributions

EH conceived draft of manuscript, collected data, corresponding author. LL contributed in drafting and revising manuscript. JB supervised data-collection, contributed in drafting manuscript. KB contributed in drafting and revising manuscript. BZ contributed in collecting data, drafting and revising manuscript. BK conceived the statistical methods, performed the statistical analysis and analyzed the data.

## ORCID iD

Erik Hägerström  <https://orcid.org/0000-0002-8938-5917>

## REFERENCES

1. De Conti RC, Toftness BR, Lange RC, Creasey WA. Clinical and pharmacological studies with cis-diamminedichloroplatinum (II). *Cancer Res J.* 1973;33:1310–1315.
2. Leu L, Baribeault D. A comparison in the rates of cisplatin-induced nephrotoxicity associated with sodium loading or sodium loading with forced diuresis as a preventative measure. *J Oncol Pharm Pract.* 2010;16:167–171.
3. Santoso JT, Lucci JA, Coleman RL, Schafer I, Hannigan E. Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: a randomized trial. *Cancer Chemother Pharmacol.* 2003;52:13–18.
4. Morgan KP, Buie LW, Savage SW. The role of mannitol as a nephroprotectant in patients receiving cisplatin therapy. *Ann Pharmacother.* 2012;46:276–281.
5. Morgan KP, Snavelly AC, Wind LS, et al. Rates of renal toxicity in cancer patients receiving cisplatin with and without mannitol. *Ann Pharmacother.* 2014;48:864.
6. McKibbin T, Cheng LL, Kim S, et al. Mannitol to prevent cisplatin-induced nephrotoxicity in patients with squamous cell cancer of the head and neck (SCCHN) receiving concurrent therapy. *Support Care Cancer.* 2016;24:1789–1793.
7. Bentzen J, Toustrup K, Eriksen JG, Primdahl H, Andersen LJ, Overgaard J. Locally advanced head and neck cancer treated with accelerated radiotherapy, the hypoxic modifier nimorazole and weekly cisplatin. Results from the DAH-ANCA 18 phase II study. *Acta Oncol.* 2015;54:1001–1007.
8. Hosmer DW Jr, Lemeshow S, Sturdivant RX. *Applied Logistic Regression.* 3rd ed. London, England: Wiley; 2013.
9. Fox J, Weisberg S. *An {R} Companion to Applied Regression.* 2nd ed. Thousand Oaks, CA: SAGE; 2011.
10. Yoshida K, Bohn J. tableone: create “Table1” to describe baseline characteristics (R package version 0.7.3). <http://CRAN.R-project.org/package=tableone>. Published 2015.
11. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis.* 2nd ed. London, England: Wiley; 2011.
12. Lindberg L, Brødbæk K, Hägerström EG, Bentzen J, Kristensen B, Zerahn B. Comparison of methods for estimating glomerular filtration rate in head and neck cancer patients treated with cisplatin. *Scand J Clin Lab Invest.* 2017;77:237–246.