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Research Article

Evaluating the Effectiveness of N-Acetylcysteine in the Prevention of Cisplatin-Induced Nephrotoxicity: A Randomized Controlled Clinical Trial

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Abstract

Objectives: Nephrotoxicity is a major and dose-limiting side effect of cisplatin chemotherapy. There are conflicting reports in the literature regarding the possible benefit of N-acetylcysteine (NAC) for the prevention of cisplatin-induced nephrotoxicity (CINT). The purpose of this study was to determine the incidence of cisplatin-induced nephrotoxicity in our population and to evaluate the impact of NAC on the development of CINT.

Methods: This was a single-centre, two-arm, parallel, open-label randomized controlled trial conducted at the Medical Oncology Department of Fauji Foundation Hospital, Pakistan. Female patients with adequate baseline renal function who were scheduled to receive cisplatin-based chemotherapy were recruited for the trial. Those in the intervention (NAC) arm (n=35), in addition to the standard intravenous hydration protocol, received oral N-acetylcysteine 1200 mg starting 1 day before chemotherapy until 5 days after the chemotherapy infusion. Patients in the control arm (n=35) only received standard intravenous hydration. This protocol was followed for four consecutive cycles of cisplatin. Serum creatinine and blood urea nitrogen were serially measured. Creatinine clearance or estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI formula. Cisplatin-induced nephrotoxicity was defined as ≥25% decrease in eGFR from baseline value.

Results: Baseline characteristics were comparable between both arms. Out of 70 patients, 25 (35.71%) developed cisplatin-induced nephrotoxicity. 11 of 35 patients (31.43%) in the NAC arm and 14 of 35 patients (40%) in the control arm developed cisplatin-induced nephrotoxicity at the end of 4 cycles of cisplatin chemotherapy (p-value=0.51). A comparison of both groups across 4 chemotherapy cycles was done, and the increase in serum creatinine and subsequent decline in the patient's eGFR was found to be less pronounced in the NAC arm. Nevertheless, the difference between both arms was found to be statistically insignificant.

Conclusion: Oral N-acetylcysteine in a dose of 1200 mg/day when given in addition to the standard hydration protocol does not appear to have any significant beneficial role in the prevention of cisplatin-induced nephrotoxicity. Studies on an inclusive population set and with a longer follow-up are suggested to determine if NAC has any substantial long-term effect on cisplatin-induced renal toxicity.

Keywords: Cisplatin, N Acetylcysteine, nephrotoxicity, prevention, randomized controlled clinical trial

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Cisplatin is a highly effective and potent agent with broad utility against various solid cancers, both as a single agent and in combination with other chemotherapeutic agents or immunotherapy.[1] Its widespread use is limited by nephrotoxicity, which is a cumulative and relatively common adverse effect.[2] Cisplatin tends to preferentially accumulate in kidneys, where it causes structural and functional damage to nephrons.[3] Though there is a paucity of local data on the subject, international studies show that up to one-third of cancer patients receiving cisplatin develop renal impairment, which is manifested by progressively increasing serum creatinine levels and reduced creatinine clearance and occasionally may even lead to acute renal failure.[4,5]

Cisplatin-induced nephrotoxicity (CINT) is a complex multifactorial process. Certain membrane transporters (for instance, Megalin) are responsible for the accumulation of cisplatin within the proximal tubular epithelial cells (PTEC), followed by cellular injury via multiple mechanisms hypothesized as:[6-12]

a) Increased oxidative stress: Cisplatin gives rise to toxic metabolites, which not only deplete the intracellular antioxidants, namely superoxide dismutase, catalase, and glutathione, but also drive mitochondria to increase the production of reactive oxygen species (ROS). These processes result in an atmosphere of high oxidative stress. Increased oxidative stress leads to damage to cellular DNA and alteration of cellular proteins, thus impairing renal tubular cell structure and function.
b) Impaired renal flow dynamics: leading to reduced renal plasma flow.
c) Activation of multiple signalling pathways in renal tubular cells, leading to apoptosis.
d) Inflammation-mediated cellular damage: Cisplatin is known to activate nuclear factor κB (NF-κB), leading to increased production of inflammatory cytokines in renal tubular cells, most importantly tumour necrosis factor α (TNF-α). TNF-α triggers a cascade of inflammation, leading to cellular damage.

Various strategies employed to counter CINT include vigorous intravenous hydration, magnesium supplementation, and, in selected cases (hypertensive patients or those receiving high-dose cisplatin), mannitol-forced diuresis.[4,13-15]

Multiple past studies have been aimed at exploring the role of antioxidants in CINT, notably curcumin, amifostine, N-acetylcysteine, and sodium thiosulfate.[16-17] N-acetylcysteine (NAC) is a sulphur-containing cysteine analogue with antioxidant action that has traditionally been used as a mucolytic agent and also has an established role in paracetamol toxicity.[18-19] The role of N-acetylcysteine in countering CINT has been explored in several animal studies and showed the benefit of NAC in ameliorating nephrotoxicity.[20]

The postulated mechanisms for NAC's nephroprotection are:

a) NAC has antioxidant action by virtue of its free radical scavenging effect. In higher doses, it has been found to directly bind the cisplatin molecule due to its free thiol chain. In smaller doses, it increases the reducing capacity of the cell by replenishing the glutathione and sulfhydryl stores in the renal tubular cells. NAC can also reduce malondialdehyde (MDA) formation in the kidney via reduced lipid peroxidation.[21-24]
b) NAC, via nitrous oxide production, exerts a vasodilator effect and improves renal blood flow.[25]
c) NAC prevents the activation of the cell apoptosis pathway in renal tubules not only by reducing oxidative stress but also via deactivation of the P53 protein and inhibition of the apoptotic signalling cascade (MAPK, p58, caspase-3, and NF-κB).[26,27]
d) NAC also possesses anti-inflammatory properties, as evidenced by reduced production of pro-inflammatory cytokines, inhibition of the C5a-C5aR pathway, and NF-κB, which is responsible for mediating the cascade of inflammation.[28,29]

Due to the above actions, NAC can be regarded as a potential chemoprotectant. Different doses and routes are being explored in the literature for using NAC for protection against CINT. There is a paucity of literature regarding the use of NAC in humans for the said condition. As per our knowledge, only one randomized control trial was conducted in head and neck cancer patients to see the effect of NAC on cisplatin-induced nephrotoxicity.[30]

In this context, our study was aimed at:

(i) Documenting the incidence of renal impairment in our population receiving cisplatin.
(ii) Studying the efficacy of N-acetylcysteine for the prevention of cisplatin-induced nephrotoxicity.

Methods

Study Design

This two-arm prospective, open-label randomized controlled clinical trial was conducted from August 2023 to March 2024 at the Medical Oncology Department, Fauji Foundation Hospital, Rawalpindi, Pakistan. The study was approved by the Ethical Review Committee of Foundation University (Ref No.508/RC/FFH/RWP) and was carried out in compliance with the Declaration of Helsinki. Before being enrolled in the trial, all patients gave their informed consent. The trial was registered in Clinicaltrials.gov under the

name "Role of N-Acetylcysteine for Prevention of Cisplatin-induced Nephrotoxicity," and its identifier is: NCT06019520.

Inclusion criteria comprised adult female patients diagnosed with non-haematological malignancies having Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤2 who had never received platinum-based chemotherapy in the past and were now eligible to receive cisplatin-based chemotherapy. Patients were required to have normal bone marrow function (ANC >1500 per microliter, platelet count >100 × 10^9/L), adequate liver function (serum total bilirubin <17 µmol/L), and renal function (creatinine <97 µmol/L).

Exclusion criteria included patients with a solitary kidney and those taking potentially nephrotoxic drugs, e.g., non-steroidal anti-inflammatory agents (NSAIDs), loop diuretics, or aminoglycosides. Patients having a history of allergy to N-acetylcysteine and those expressing unwillingness to take part in the study were also excluded.

Sample Size

Based on data from the previous study that had evaluated the incidence of cisplatin-induced nephrotoxicity in the native female population,[31] the analysis showed that a minimum of 74 would be necessary, with 37 in each group, to find a mean difference of 23.6 µmol/L, the CI at 95%, and the power of the study at 80%. The sample size was also reviewed and approved by the Ethical Review Committee after checking alignment with the study's objectives and regulatory requirements.

Study Protocol

A total of 87 female patients planned to receive single agent/combination cisplatin chemotherapy were screened for eligibility, and out of these, 75 patients were enrolled in the study. Patients were randomized using the simple randomization technique of allotting even and odd numbers to drug and control groups, respectively. A consort flow diagram of the studied population is shown in Figure 1.

Data regarding patients' characteristics were sourced through interviews with patients and electronic medical records (as and where required). Information regarding age, comorbidities, ECOG-PS, TNM stage of tumours, and intent of treatment was noted. Baseline investigations were done, including serum creatinine and blood urea nitrogen (BUN). Body mass index (BMI) was calculated as per Quetelet's equation, and baseline creatinine clearance (CrCl)/estimated glomerular filtration rate (eGFR) was calculated as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[32,33] All these details were entered in a pre-made data collection form.

All participants received intravenous hydration and magnesium supplementation as per the standard protocol of hydration with cisplatin.[34] Additionally, patients in the NAC arm received oral NAC (1200 mg) in a water-soluble granule preparation dissolved in water and administered once daily at night for 7 consecutive days (starting 1 day before chemotherapy and continuing till 5 days after chemotherapy). This protocol was followed for four to five consecutive cycles of cisplatin chemotherapy, each separated by 21 days.

Before each cisplatin chemotherapy cycle, 5 ml of blood was collected for testing. Samples were clotted in a plain tube and then centrifuged to obtain serum. Serum was analysed for creatinine value using the Beckman Coulter Chemistry autoanalyzer (DXE 700 AU). Serial estimation of GFR was done using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[35] This equation was validated by Inker et al.[36] and found to be more accurate than the antecedent MDRD Equation/Cockroft-Gault formula for monitoring creatinine clearance, especially in patients receiving cisplatin chemotherapy.[37]

Primary outcomes of the study were to compare the incidence of cisplatin-induced nephrotoxicity, i.e., acute renal failure risk defined as ≥25% decrease in eGFR from baseline.[38,39] In addition, we assessed serial changes in serum creatinine, CrCl, and BUN across 4-5 consecutive cycles of cisplatin chemotherapy.

Data Analysis

Data were evaluated using SPSS version 26. Continuous data were reported as mean±SD, whereas categorical data were reported as frequencies and percentages. Data were checked for normality (through the Shapiro-Wilk test and graphical representation via histogram and Q-Q plot). In instances where the normality assumption for continuous variables was upheld, independent t-tests were conducted to compare the means of serum creatinine and BUN between the control and intervention groups; conversely, non-parametric tests were employed where necessitated. All statistical tests were two-sided and interpreted at a 0.05 significance level.

Results

The final analysed population comprised 70 adult females. The normality of data was confirmed by a Shapiro-Wilk value of 0.216 and is graphically depicted in Figure 2.

The baseline characteristics of the study population are shown in Table 1. This table also shows the acceptable stratification of all characteristics across the study arms, as shown by the insignificant p-value of the student's t-test among all the variables.

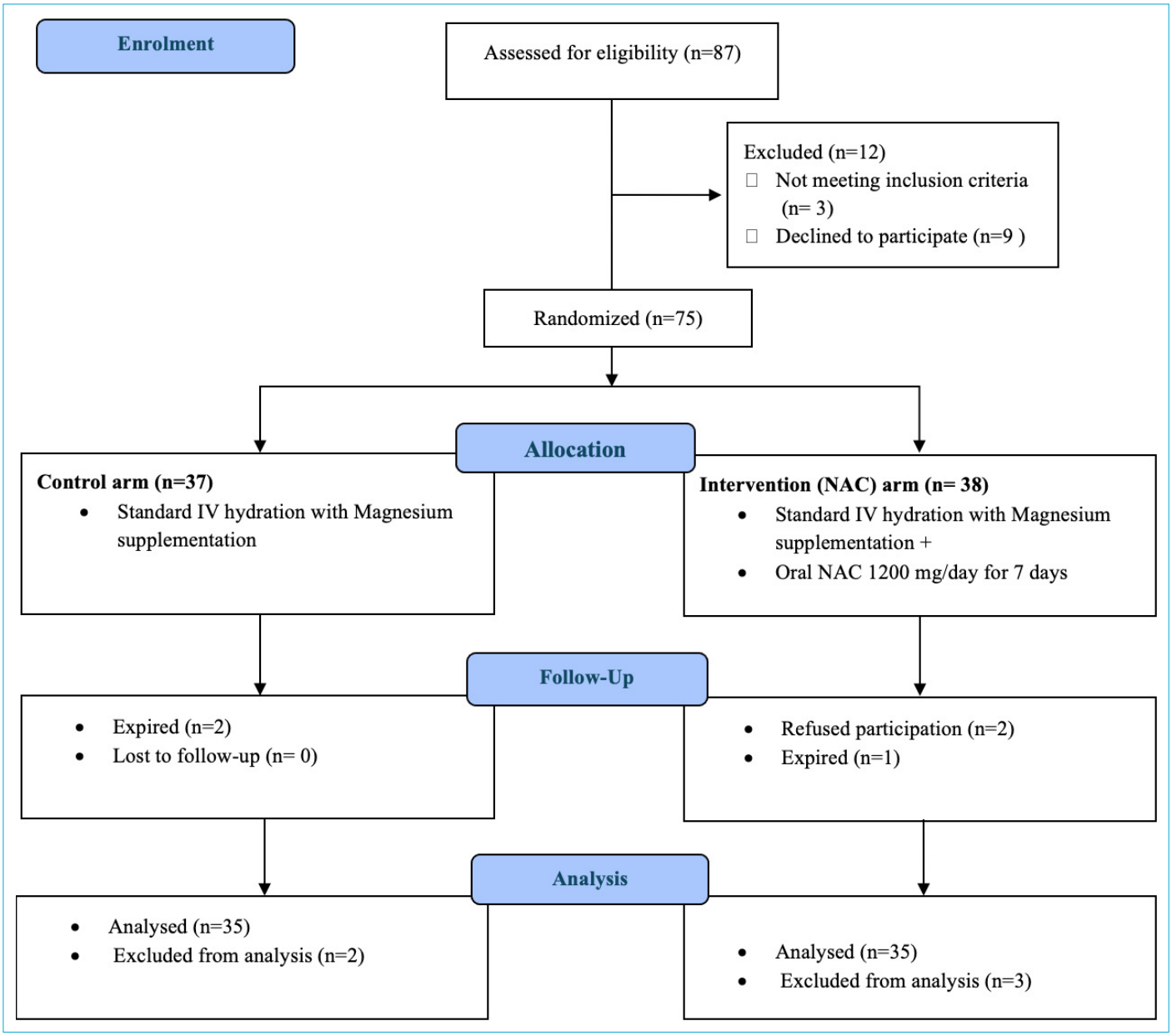

Figure 1. CONSORT flow diagram of the studied population.

IV: Intravenous; NAC: N-Acetylcysteine.

The impact of cisplatin on kidney function of the studied population is shown via a comparison of renal function tests at baseline and post-4 cycles of cisplatin in Table 2. As shown, cisplatin negatively affected serum BUN, creatinine, and CrCl across all 4 cycles in a significant manner.

These findings are reinforced in Figure 3, which shows that mean serum creatinine and BUN values significantly and steadily increased, while mean eGFR/CrCl significantly decreased in both groups over a period of four cycles with focus on change after each cycle. The serum creatinine rise and eGFR decline was less pronounced in the NAC arm; however, as per the statistical analysis, the p-value was insignificant.

As shown in Table 3, a total of 25 out of 70 patients (35.71%) developed cisplatin-induced nephrotoxicity. In the control arm, 14 patients (40%) and 11 patients in the NAC arm (31.4%) developed CINT. Though a small protective effect of NAC was noticed, the difference in incidence of CINT was not statistically significant among both groups.

Discussion

Nephrotoxicity is a major adverse effect of cisplatin chemotherapy and is commonly encountered in clinical settings. [40] In some cases, early discontinuation of this otherwise

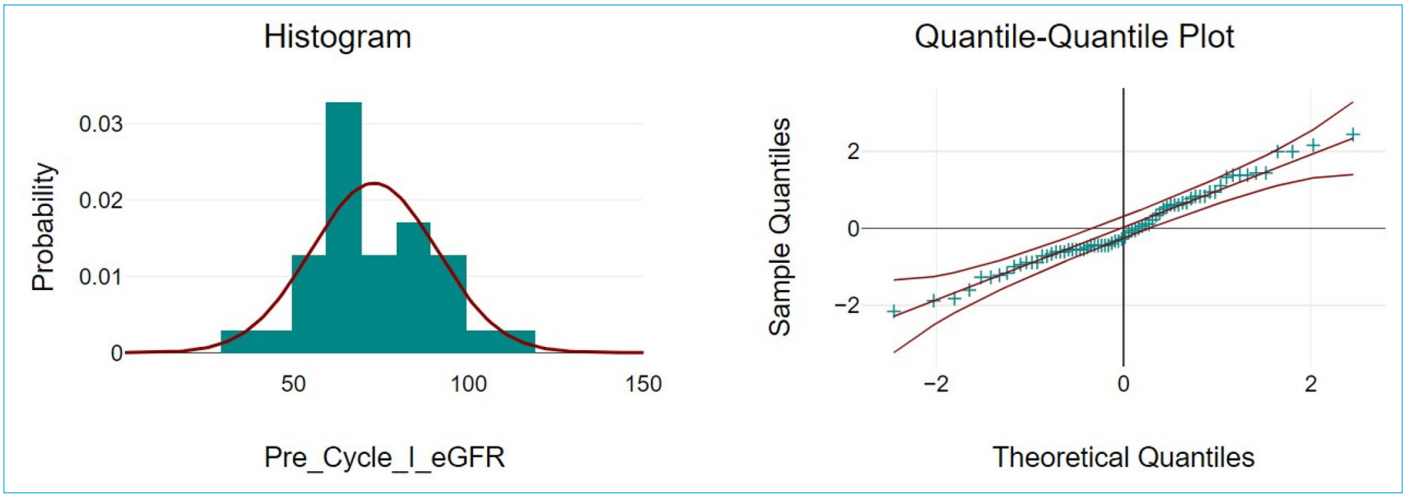

Figure 2. Histogram and Quantile-Quantile (Q-Q) plot showing normality of data of the studied population.

Table 1. Stratification of demographic and clinical characteristics of the studied population

Baseline Characteristics	Control Arm (n=35)	NAC Arm (n=35)	p
Age (mean±SD) years	55.14±8.87	51.17±13.95	0.160[a]
BMI (mean±SD) kg/m^2	23.49±4.61	21.43±4.93	0.076[a]
ECOG PS, n (%)			
0-1	26 (74)	30 (86)	0.371[b]
2	9 (26)	5 (14)	
Stage, n (%)			
I	0 (3)	3 (9)	0.232[b]
II	2 (6)	2 (6)	
III	12 (34)	11 (31)	
IV	21 (60)	19 (54)	
Comorbidities	n=16	n=11	
Systemic arterial hypertension	5	4	0.129[c]
Diabetes mellitus	6	0	
Both hypertension and diabetes	1	2	
Other[†]	4	5	

Data mentioned as number (%) or mean±standard deviation; n=number; BMI=Body mass index; ECOG PS=Eastern cooperative oncology group performance status; [a]Independent Sample t-test; [b]Chi square test; [c]Fisher's exact test; [†]Other comorbidities: Arrythmia, Acid peptic disease, hypothyroidism, Asthma, COPD, hepatitis B/C, dyslipidaemia.

highly effective chemotherapy agent is unavoidable to prevent long-term morbidity, as this toxicity is not only cumulative but also frequently irreversible.

As per our study findings, 35.7% of our studied population, after being exposed to cisplatin, developed CINT. Notably, our study participants were female only, as our institution caters primarily to the wives/dependent children of retired personnel of the organization. A large retrospective cohort study suggested that gender-based differences exist as regards the incidence of cisplatin-induced nephrotoxicity and the response of CINT to nephroprotective agents. Higher CINT incidence was found in perimenopausal women when compared with men of similar age or premenopausal women.[41] In the study by Inamullah et al., the incidence of CINT was 29% in females and 46% in males. Our study findings are comparable with a study by Praja et al., according to which female gender and age ≥50 were linked with a relatively higher incidence of CINT.[31,42]

Our study documented minimal yet statistically insignificant improvement in serum creatinine and CrCl with oral NAC 1200 mg/day. Past literature has indicated a varying degree of benefit of NAC for the prevention of nephrotoxicity. A case report by Hamad et al. mentioned accidental overdosage of cisplatin resulting in severe kidney damage. Although the patient did not survive the event, the benefit of NAC was suggested by a reduction in the patient's serum

Figure 3. Graphical representation of changes in serum creatinine, BUN and eGFR over time and across both arms.

BUN: Blood urea Nitrogen; NAC: N-acetylcysteine; eGFR: Estimated Glomerular Filtration rate.

BUN and creatinine levels, improved creatinine clearance, and urine output. Also, some improvement in the patient's liver damage was observed. The postulated reason behind this clinical benefit was the replenishment of the patient's glutathione and sulfhydryl stores by NAC.[43] Another case report by Emir et al., describing the use of NAC in a similar dose for accidental cisplatin overdose in a paediatric patient, reported complete normalization of renal functions and no long-term renal damage on delayed follow-ups.[44] The dose used in both instances and the protocol of administration was the same as that used for paracetamol toxicity, i.e., 140 mg/kg initially, then 70 mg/kg 4 hourly for the next 4 days.

Oral administration of NAC leads to bioavailability of around 5-10% owing to its extensive first-pass metabolism.[45] It has been postulated that an oral NAC dose of a minimum of 800 mg/day is required to achieve sufficient plasma levels of NAC for a significant antioxidant effect via GSH production (indirect antioxidant effect).[46] For this reason, we used Tepel's regimen for NAC in our study.[46] The same regimen was successfully used in two studies involving chronic kidney disease (CKD) patients. Trimarchi et al. observed that NAC in a dose of 600 mg BD given for 30 days improved oxidative stress in haemodialysis (HD) patients. This was evident by the reduced levels of malondialdehyde (MDA: a marker of oxidative stress) in HD patients receiving NAC.[47] Nascimento et al. studied the effect of oral NAC on 30 CKD cases undergoing peritoneal dialysis. NAC in a dose of 600 mg BD for 8 weeks was found to be well-tolerated as well as efficacious for reducing oxidative stress and inflammation, as evidenced by lower levels of the inflammatory marker (IL-6) in the intervention arm.[48] In both studies, the route and dosage were the same as those used in our study, and a significant antioxidant and anti-inflammatory effect of NAC was indirectly determined by the measurement of markers of inflammation.

Table 2. Effect of cisplatin on renal functions of studied population (by comparing renal function tests at baseline and post 4 cisplatin cycles)

Parameter	Control arm		NAC arm		p
	Baseline	Post Cisplatin	Baseline	Post Cisplatin	
Serum creatinine (µmol/L)	68.43±14.04	90.29±16.56	71.17±11.90	86.32±12.55	p<0.001[a] p<0.001[b]
Serum BUN (mmol/L)	4.01±0.39	4.71±0.46	4.05±0.24	4.60±0.34	p<0.005[c] p<0.001[d]
eGFR (mL/min/1.73m^2)	74.06±16.29	58.57±13.27	71.94±19.97	62.11±19.46	p<0.001[c] p<0.001[d]

Values expressed as mean±standard deviation; NAC: N-Acetylcysteine; BUN: Blood Urea Nitrogen; eGFR: estimated GFR; [a]Wilcoxon-Signed rank test on control arm; [b]Wilcoxon-Signed rank test on intervention arm; [c]Paired-Sample t-test on control arm, d Paired-Sample t-test on intervention arm.

Table 3. Comparison of the frequency of cisplatin induced nephrotoxicity between two groups

Parameter	Control arm (n=35) n (%)	NAC arm (n=35) n (%)	p
Number of CINT# cases	14 (40.0)	11 (31.43)	0.509[a]

#CINT/Acute renal failure risk, defined as a ≥25% decrease in eGFR from baseline; [a]Chi-square test for both control and NAC arms.

Differing from our protocol, a higher dosage of 2400 mg/day was used alongside the standard 1200 mg/day dose in a randomized controlled study involving 75 patients receiving paclitaxel. Reduced oxidative stress, thereby leading to lesser chemotherapy-induced neurotoxicity, was observed in the NAC group, particularly in the higher dose (2400 mg/day) group as compared with the lower dose (1200 mg/day) group.[49]

In our study, chemotherapy and NAC administration were separated spatiotemporally, i.e., both agents were given via different routes and at different times of the day. This was done to address a concern expressed in some older studies about the probability of reduced chemotherapy efficacy with NAC administration.[50] More recent studies have suggested a lesser probability of chemotherapy resistance with the use of antioxidant agents.[51]

Our study was most closely matched to the randomized placebo-control trial on 57 head and neck cancer patients conducted by Visacri et al., in which 600 mg/day NAC was given starting 2 days before till 5 days after cisplatin administration, and the difference in chemotherapy-induced toxicities, levels of oxidative stress markers, and tumour response was studied and compared across both groups. Analysis showed no difference in cisplatin-induced renal, GI, or haematological toxicity between both groups. The dosage of NAC used in our study was higher compared to the aforementioned study, yet results were comparable as regards the efficacy of NAC for CINT.

We measured serum creatinine in our patients for serial estimation of renal function. This lab parameter was used due to its easy accessibility and low cost in our resource-constrained setup. In some other related studies, serum cystatin and novel markers of kidney injury, e.g., kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), etc., have been used to assess renal tubular injury owing to the greater sensitivity of these parameters.[52]

Although our study did not yield a statistically significant impact of NAC for the prevention of CINT, minimal benefit was suggested, which may be more pronounced on a longer follow-up and with a larger sample size. Some limitations of our study are selection (gender) bias, non-availability of a placebo due to the difficulty of manufacturing a similar granular preparation as commercially available NAC, and the inability to follow-up on day 5-7 post-cisplatin, when the maximum oxidative damage/renal injury is expected.

We are humbled to present some suggestions for future studies. Different dosing and alternative routes of NAC can be explored in a wider, larger, and more diverse population set. Novel sensitive and specific markers of renal injury may be used, and follow-up periods may be modified to look for meaningful results.

Disclosures

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Ethics Committee Approval: The study was approved by the Ethical Review Committee of Foundation University (Ref No.508/RC/FFH/RWP) and was carried out in compliance with the Declaration of Helsinki (Date: 28.10.2021).

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Conflict of Interest: None declared.

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References

1. Brown A, Kumar S, Tchounwou PB. Cisplatin-based chemotherapy of human cancers. J Cancer Sci Ther 2019;11(4):97.
2. Hoek J, Bloemendal KM, van der Velden LA, van Diessen JN, van Werkhoven E, Klop WM, et al. Nephrotoxicity as a dose-limiting factor in a high-dose cisplatin-based chemoradiotherapy regimen for head and neck carcinomas. Cancers (Basel) 2016;8(2):21.
3. Perazella MA, Rosner MH. Drug-induced acute kidney injury. Clin J Am Soc Nephrol 2022;17(8):1220–1233.
4. Ben Ayed W, Ben Said A, Hamdi A, Mokrani A, Masmoudi Y, Toukabri I, et al. Toxicity, risk factors and management of cisplatin-induced toxicity: A prospective study. J Oncol Pharm Pract 2020;26(7):1621–1629.

5. Manohar S, Leung N. Cisplatin nephrotoxicity: A review of the literature. J Nephrol 2018;31:15–25.
6. Holditch SJ, Brown CN, Lombardi AM, Nguyen KN, Edelstein CL. Recent advances in models, mechanisms, biomarkers, and interventions in cisplatin-induced acute kidney injury. Int J Mol Sci 2019;20(12):3011.
7. Huang G, Zhang Q, Xu C, Chen L, Zhang H. Mechanism of kidney injury induced by cisplatin. Toxicol Res 2022;11:385–390.
8. Iwakura T, Zhao Z, Marschner JA, Devarapu SK, Yasuda H, Anders HJ. Dipeptidyl peptidase-4 inhibitor teneligliptin accelerates recovery from cisplatin-induced acute kidney injury by attenuating inflammation and promoting tubular regeneration. Nephrol Dial Transplant 2019;34(10):1669–1680.
9. Pabla N, Dong Z. Cisplatin nephrotoxicity: Mechanisms and renoprotective strategies. Kidney Int 2008;73:994–1007.
10. Sánchez-González PD, López-Hernández FJ, López-Novoa JM, Morales AI. An integrative view of the pathophysiological events leading to cisplatin nephrotoxicity. Crit Rev Toxicol 2011;41:803–821.
11. Watanabe M, Oe Y, Sato E, Sekimoto A, Sato H, Ito S, et al. Protease-activated receptor 2 exacerbates cisplatin-induced nephrotoxicity. Am J Physiol Renal Physiol 2019;316:F654–659.
12. Zhang L, Zhu Z, Liu J, Zhu Z, Hu Z, et al. Protective effect of N-acetylcysteine (NAC) on renal ischemia/reperfusion injury through Nrf2 signaling pathway. J Recept Signal Transduct Res 2014;34:396–400.
13. Crona DJ, Faso A, Nishijima TF, McGraw KA, Galsky MD, Milowsky MI. A systematic review of strategies to prevent cisplatin-induced nephrotoxicity. Oncologist 2017;22:609–619.
14. Desilets A, Adam JP, Soulières D. Management of cisplatin-associated toxicities in bladder cancer patients. Curr Opin Support Palliat Care 2020;14(3):286–292.
15. Sainamthip P, Saichaemchan S, Satirapoj B, Prasongsook N. The effect of intravenous mannitol combined with normal saline in preventing cisplatin-induced nephrotoxicity: A randomized, double-blind, placebo-controlled trial. JCO Glob Oncol 2022;8:e2100275.
16. Aldini G, Altomare A, Baron G, Vistoli G, Carini M, Borsani L, et al. N-Acetylcysteine as an antioxidant and disulphide breaking agent: The reasons why. Free Radic Res 2018;52:751–762.
17. Casanova AG, Harvat M, Vicente-Vicente L, Pellicer-Valero ÓJ, Morales AI, López-Hernández FJ, et al. Regression modeling of the antioxidant-to-nephroprotective relation shows the pivotal role of oxidative stress in cisplatin nephrotoxicity. Antioxidants (Basel) 2021;10(9):1355.
18. Pei Y, Liu H, Yang Y, Yang Y, Jiao Y, Tay FR, Chen J. Biological activities and potential oral applications of N-acetylcysteine: Progress and prospects. Oxid Med Cell Longev 2018;2018:2835787.
19. Tenório MCDS, Graciliano NG, Moura FA, Oliveira ACM, Goulart MOF. N-Acetylcysteine (NAC): Impacts on Human Health. Antioxidants (Basel) 2021;10(6):967.
20. Zavala-Valencia AC, Velasco-Hidalgo L, Martínez-Avalos A, Castillejos-López M, Torres-Espíndola LM. Effect of N-Acetylcysteine on cisplatin toxicity: A review of the literature. Biologics 2024;18:7–19.
21. Güntürk I, Yazici C, Köse SK, Dağli F, Yücel B, Yay AH. The effect of N-acetylcysteine on inflammation and oxidative stress in cisplatin-induced nephrotoxicity: A rat model. Turk J Med Sci 2019;49:1789–1799.
22. Moreira MA, Irigoyen MC, Saad KR, Saad PF, Koike MK, Montero EF, et al. N-acetylcysteine reduces the renal oxidative stress and apoptosis induced by hemorrhagic shock. J Surg Res 2016;203(1):113–20.
23. Raghu G, Berk M, Campochiaro PA, Jaeschke H, Marenzi G, Richeldi L, et al. The multifaceted therapeutic role of N-Acetylcysteine (NAC) in disorders characterized by oxidative stress. Curr Neuropharmacol 2020;19:1202–1224.
24. Gibson KR, Neilson IL, Barrett F, Winterburn TJ, Sharma S, MacRury SM, et al. Evaluation of the antioxidant properties of N-acetylcysteine in human platelets: Prerequisite for bioconversion to glutathione for antioxidant and antiplatelet activity. J Cardiovasc Pharmacol 2009;54:319–326.
25. Conesa EL, Valero F, Nadal JC, Fenoy FJ, López B, Arregui B, et al. N-acetyl-L-cysteine improves renal medullary hypoperfusion in acute renal failure. Am J Physiol Regul Integr Comp Physiol 2001;281(3):R730–7.
26. Dong XQ, Chu LK, Cao X, Xiong QW, Mao YM, Chen CH, et al. Glutathione metabolism rewiring protects renal tubule cells against cisplatin-induced apoptosis and ferroptosis. Redox Rep 2023;28(1):2152607.
27. Gong X, Duan Y, Zheng J, Wang Y, Wang G, Norgren S, et al. Nephroprotective effects of N-Acetylcysteine amide against contrast-induced nephropathy through upregulating thioredoxin-1, inhibiting ASK1/p38MAPK pathway, and suppressing oxidative stress and apoptosis in rats. Oxid Med Cell Longev 2016;2016:8715185.
28. Gao X, Lampraki EM, Al-Khalidi S, Qureshi MA, Desai R, Wilson JB. N-acetylcysteine (NAC) ameliorates Epstein-Barr virus latent membrane protein 1 induced chronic inflammation. PLoS One 2017;12:1–20.
29. Tanaka S, Tanaka T, Kawakami T, Takano H, Sugahara M, Saito H, et al. Vascular adhesion protein-1 enhances neutrophil infiltration by generation of hydrogen peroxide in renal ischemia/reperfusion injury. Kidney Int 2017;92:154–164.
30. Visacri MB, Quintanilha JCF, de Sousa VM, Amaral LS, de F L Ambrósio R, Calonga L, et al. Can acetylcysteine ameliorate cisplatin-induced toxicities and oxidative stress without decreasing antitumor efficacy? A randomized, double-blind, placebo-controlled trial involving patients with head and neck cancer. Cancer Med 2019;8:2020–2030.
31. Inamullah M, Khalid AM, Mehdi RS, Mehmood E, Alvi ZA. Fre-

quency of cisplatin-induced severe renal injury in patients with solid tumours on renal scintigraphy. Pak J Nucl Med 2015;5(1):51–57.
32. Gadzik J. 'How much should I weigh?'--Quetelet's equation, upper weight limits, and BMI prime. Conn Med 2006;70:81–88.
33. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612.
34. Nitipir C, Popa AM, Motatu P, Popescu B, Cristian I, Olaru M, et al. Important aspects to take into consideration when administering cytotoxic chemotherapy. A review. Modern Medicine 2017;24:185–189.
35. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate Ann Intern Med 2011;155(6):408.
36. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367(1):20–9.
37. Klöckl MC, Kasparek AK, Riedl JM, Moik F, Mollnar S, Stotz M, et al. Estimation versus measurement of the glomerular filtration rate for kidney function assessment in patients with cancer undergoing cisplatin-based chemotherapy. Sci Rep 2020;10(1):11219.
38. Thomas ME, Blaine C, Dawnay A, Devonald MA, Ftouh S, Laing C, et al. The definition of acute kidney injury and its use in practice. Kidney Int 2015;87:62–73.
39. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8(4):R204–12.
40. Qi L, Luo Q, Zhang Y, Jia F, Zhao Y, Wang F. Advances in toxicological research of the anticancer drug cisplatin. Chem Res Toxicol 2019;32(8):1469–1486.
41. Chen WY, Hsiao CH, Chen YC, Ho CH, Wang JJ, Hsing CH, et al. Cisplatin nephrotoxicity might have a sex difference. an analysis based on women's sex hormone changes. J Cancer 2017;8:3939–3944.
42. Prasaja Y, Sutandyo N, Andrajati R. Incidence of cisplatin-induced nephrotoxicity and associated factors among cancer patients in Indonesia. Asian Pac J Cancer Prev 2015;16:1117–1122.
43. Sheikh-Hamad D, Timmins K, Jalali Z. Cisplatin-induced renal toxicity: Possible reversal by N-acetylcysteine treatment. J Am Soc Nephrol 1997;8(10):1640–1644.
44. Emir S, Özyörük D, Arman Ö, Özbek N, Tunç B. Accidental cisplatin overdose in a child: Successful management with repetitive plasmapheresis and use of chemoprotective agents. Turk J Pediatr 2016;58(3):315–317.
45. Liu YM, Liu Y, Lu C, Jia JY, Liu GY, Weng LP, et al. Relative bioavailability of generic and branded acetylcysteine effervescent tablets: A single-dose, open-label, randomized-sequence, two-period crossover study in fasting healthy chinese male volunteers. Clin Ther 2010;32:2097–2105.
46. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000;343:180–184.
47. Trimarchi H, Mongitore MR, Baglioni P, Forrester M, Freixas EA, Schropp M, et al. N-acetylcysteine reduces malondialdehyde levels in chronic hemodialysis patients - A pilot study. Clin Nephrol 2003;59:441–446.
48. Nascimento MM, Suliman ME, Silva M, Chinaglia T, Marchioro J, Hayashi SY, et al. Effect of oral N-acetylcysteine treatment on plasma inflammatory and oxidative stress markers in peritoneal dialysis patients: A placebo-controlled study. Perit Dial Int 2010;30(3):336–342.
49. Khalefa HG, Shawki MA, Aboelhassan R, El Wakeel LM. Evaluation of the effect of N-acetylcysteine on the prevention and amelioration of paclitaxel-induced peripheral neuropathy in breast cancer patients: A randomized controlled study. Breast Cancer Res Treat 2020;183(1):117–125.
50. Dickey DT, Muldoon LL, Doolittle ND, Peterson DR, Kraemer DF, Neuwelt EA. Effect of N-acetylcysteine route of administration on chemoprotection against cisplatin-induced toxicity in rat models. Cancer Chemother Pharmacol 2008;62(2):235–241.
51. Ilghami R, Barzegari A, Mashayekhi MR, Letourneur D, Crepin M, Pavon-Djavid G. The conundrum of dietary antioxidants in cancer chemotherapy. Nutr Rev 2020;78:65–76.
52. Rossiter A, La A, Koyner JL, Forni LG. New biomarkers in acute kidney injury. Crit Rev Clin Lab Sci 2024;61:23–44.