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Research Article

The Effect of Antioxidants Uses with Aminoglycosides Antibiotics on Serum Creatinine and Urea Levels

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Abstract
Aminoglycosides are older-generation antibiotics used to treat infectious diseases like tuberculosis and urinary tract infections. While they improve multidrug resistant tuberculosis treatment success, their nephrotoxicity hinders optimal therapy. This study investigated the concomitant use of aminoglycosides (streptomycin, gentamicin, and kanamycin) and antioxidants to mitigate nephrotoxicity, as measured by serum creatinine and urea levels. Using a retrospective, descriptive analytical design, we analyzed medical records of 32 patients treated with aminoglycoside antibiotics at dr. Wahidin Sudirohusodo Hospital, Makassar, from January 2017 to November 2018. Patients were grouped based on antioxidant treatment: N-acetylcysteine (NAC), N-acetylcysteine and Curcuma (NAC+Cur), vitamin C (Vit C), Curcuma and vitamin C (Cur+Vit C), and a control group (X) receiving no antioxidants. All antioxidant groups showed decreased creatinine and urea levels with streptomycin, except the control group, which exhibited increased levels. With gentamicin, only vitamin C decreased urea. For kanamycin, NAC, NAC+Cur, and Cur+Vit C decreased urea, while NAC+Cur also decreased creatinine. NAC alone and the NAC+Cur combination showed the greatest ability to reduce serum creatinine and urea levels for both streptomycin and kanamycin. These findings suggest that antioxidant supplementation, particularly NAC and NAC+Cur, may play a crucial role in mitigating aminoglycoside-induced nephrotoxicity. Reduced creatinine and urea levels with antioxidant use could translate to improved renal function and potentially better patient outcomes during aminoglycoside therapy. Further research is needed to confirm these findings and explore optimal antioxidant dosing strategies in clinical practice.

Keywords: aminoglycoside, antioxidant, nephrotoxicity, renoprotection

Efek Penggunaan Antioksidan dengan Antibiotik Aminoglikosida terhadap Kadar Kreatinin dan Ureum Serum

Abstrak
Aminoglikosida merupakan antibiotik generasi tua yang umum digunakan untuk penyakit infeksi seperti tuberkulosis dan infeksi saluran kemih. Meskipun efektif, terutama untuk tuberkulosis *multidrug resistant*, nefrotoksisitas aminoglikosida membatasi penggunannya secara optimal. Antioksidan yang umum digunakan di lingkungan klinis, seperti N-asetilsistein, asam askorbat, dan kurkumin, telah dibuktikan secara *in vivo* berpotensi sebagai nefroprotektor. Penelitian ini menganalisis pengaruh pemberian aminoglikosida (streptomisin, gentamisin, kanamisin) bersama antioksidan terhadap kadar kreatinin dan urea serum. Desain penelitian yang digunakan adalah deskriptif retrospektif, dengan populasi berupa rekam medis 32 pasien yang diterapi dengan aminoglikosida di RSUP dr. Wahidin Sudirohusodo Makassar, Januari 2017–November 2018. Pasien dikelompokkan berdasarkan penggunaan antioksidan: N-asetilsistein (NAC), N-asetilsistein dan Curcuma (NAC+Cur), vitamin C (Vit C), Curcuma dan vitamin C (Cur+Vit C), dan kelompok kontrol (X) tanpa antioksidan. Semua kelompok antioksidan menunjukkan penurunan kadar kreatinin dan urea dengan streptomisin, kecuali kelompok kontrol yang menunjukkan peningkatan. Pada gentamisin, hanya vitamin C yang menurunkan urea. Untuk kanamisin, NAC, NAC+Cur, dan Cur+Vit C menurunkan urea, dengan NAC+Cur juga menurunkan kreatinin. Hasil ini menunjukkan suplementasi antioksidan, terutama NAC dan NAC+Cur, berpotensi mengurangi nefrotoksisitas aminoglikosida, meningkatkan fungsi ginjal, dan berpotensi memberikan nefroproteksi bagi pasien. Penelitian lebih lanjut diperlukan untuk mengonfirmasi hasil ini dan menentukan strategi dosis antioksidan yang optimal dalam praktik klinis.

Kata Kunci: aminoglikosida, antioksidan, nefrotoksisitas, renoproteksi

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Introduction

Aminoglycosides are a class of antibiotics primarily prescribed to treat severe bacterial infections, especially those caused by gram-negative bacteria. Known for their potent bactericidal properties, these antibiotics disrupt protein synthesis in bacteria, which effectively halts their growth and eliminates the infection. Commonly used aminoglycoside drugs include streptomycin, amikacin, capreomycin, kanamycin, and gentamicin, each of which plays a crucial role in treating different types of infections, from tuberculosis to hospital-acquired infections.[1] These antibiotics belong to Group C therapy for rifampicin-resistant tuberculosis (RR-TB) and multidrug-resistant TB (MDR-TB). This antibiotic group usually increases the chance of successful treatment of MDR-TB.[2,3]

Even though these aminoglycoside antibiotics have high efficacy for tuberculosis treatment, these antibiotics have several side effects which could lead to ineffective therapy. A cohort study by Shibesi *et al.* (2019) in Ethiopia revealed that nephrotoxicity and ototoxicity occurred in 62 (6.7%) and 42 (4.8%) individuals, respectively, out of 900 participants receiving injectable aminoglycosides for MDR-TB.[4] Further research by Perumal *et al.* (2018) demonstrated a significant decrease in estimated glomerular filtration rate (eGFR) following aminoglycoside use (kanamycin/capreomycin), both with and without concomitant antiretroviral therapy.[5] Both ototoxicity and nephrotoxicity are best known side effect of aminoglycosides, which are attributed to their ability to be readily taken up by renal proximal tubule cells and cochlear cells.[6,7] The accumulation of aminoglycosides in these cells stimulates the production of reactive oxygen species (ROS) by mitochondria, leading to increased oxidation of various cellular molecules, including proteins and lipids. This oxidative stress ultimately results in dysfunction and death of renal tubule and cochlear cells.[8]

Hence this toxicity of aminoglycosides becomes an obstacle to the optimal use of this antibiotic for RR-TB and MDR-TB cases, because it takes about 6–7 months for intensive phase and total length of therapy could reach 18–20 months.[3] Research by Paquette *et al.* (2015) showed that since 2001, the incidence of aminoglycoside-induced acute kidney injury has remained constant, reaching 56% for stage 1 acute kidney injury (AKI), 29% for stage 2 AKI, and 12% for stage 3 AKI, out of 562 patients.[9] After all, the nephrotoxic effect of aminoglycosides is primarily due to its dosage and therapy duration.[10,11] This nephrotoxicity can be manifested as an non-oliguric AKI and clinically noticeable after 5 to 7 days of drug therapy.[12] Hence, although their nephrotoxic side effects, aminoglycoside exhibit a notably lower resistance rate compared to other antibiotic classes, such as fluoroquinolones and penicillins.[13] If we can mitigate their nephrotoxic effects, the potential to utilize aminoglycosides as a treatment for infections caused by multidrug-resistant (MDR) organisms could be significantly enhanced.

By addressing and minimizing toxicity, aminoglycosides could become a more viable option for combating MDR infections, where limited treatment alternatives often present significant challenges in clinical settings. A new strategy is essential to mitigate the nephrotoxicity of aminoglycosides during long-term therapy. A suggested approach is to use aminoglycoside together with antioxidants. The use of antioxidants is based on the study that proves the manifestation of nephrotoxicity of aminoglycosides involves inflammation reactions caused by the increased production of ROS.[14] A systemic review and meta-analysis by Kranzer

et al. (2015) showed that NAC reduced aminoglycoside induced-ototoxicity in 146 end-stage renal failure patients.[15] Another pre-clinical meta-analysis by Vicente *et al.* (2017) showed that the concomitant use of aminoglycoside and antioxidants yields a renoprotection effect.[16] A systematic review by Birjan *et al.* (2020) demonstrated that the use of antioxidants can reduce the nephrotoxic potential of aminoglycosides.[17] Similarly, a randomized clinical trial by Vural *et al.* (2017) showed the potential of NAC as a protective agent against amikacin-induced ototoxicity and inflammation. Based on thse findings and the lack of clinical studies specifically investigating vitamin C, this study analyzed the effect of concomitant use of aminoglycosides and antioxidants.[18] Based on these facts and the lack of clinical study, this study analyzed the effect of the concomitant use of aminoglycoside and antioxidants.

Methods

This study is nonexperimental, utilizing a descriptive analytical design and a retrospective data collection method. Data were obtained from the medical records of patients who received aminoglycoside antibiotic therapy (streptomycin, gentamicin and kanamycin) at dr. Wahidin Sudirohusodo Hospital between January 2017 and November 2018. The therapy data from these medical records were processed using Microsoft Excel to calculate the average values for each therapy group and were presented in bar charts to facilitate the comparison of creatinine (Cr) and urea (Ur) levels among the therapy groups. The study included patients whose medical records indicated infection which treated with aminoglycoside antibiotics for more than two days. This inclusion criterion was based on the definition of AKI as an increase in serum creatinine by ≥0.3 mg/dl (26.5 μmol/L) within 48 hours, or a 1.5-fold increase from baseline serum creatinine level.[19] Patients were excluded if they were not prescribed aminoglycosides, received them for less than two days, had pre-existing chronic kidney disease, or lacked at least two serum creatinine and urea measurements for monitoring changes during aminoglycoside and antioxidant therapy. Medical records, selected based on aminoglycoside therapy data from the dr. Wahidin Sudirohusodo Hospital Pharmacy's medication monitoring system, were retrieved, sorted according to predetermined criteria (inclusion and exclusion criteria), and tabulated. Statistical analysis was performed using SPSS for Windows version 23, employing paired sample *t*-tests and one-way ANOVA as appropriate. Ethical approval was obtained from the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University (Recommendation letter number 569/H4.8.4.5.31/PP36-KOMETIK/2018).

Results

The total sample is 32 patients who received aminoglycosides (streptomycin, gentamicin and kanamycin) and antioxidant drugs, like N-acetylcysteine, Curcuma, and vitamin C (Table 1). The streptomycin and kanamycin subject groups were given the therapy intramuscularly, and the gentamicin group received it intravascularly. This study investigated the potential of various antioxidants to mitigate the nephrotoxic effects of aminoglycosides (streptomycin, gentamicin, and kanamycin). Subjects were divided into five groups based on the type of antioxidant administered: NAC group (received N-acetylcysteine only), NAC+Cur group (received both NAC and Curcuma), Vit C group (received vitamin C), Cur+Vit C group (received both

Table 1 Subject Characteristics

	Streptomycin n=19 (59.38%)	Gentamicin n=6 (18.75%)	Kanamycin n=7 (21,87%)	Total n=32
Sex				
Male	15	2	4	21 (65,62%)
Female	4	4	3	11 (34,38%)
Age				
16–40 years	10	5	4	19 (59,38%)
41–62 years	9	1	3	13 (40,62%)
Antioxidants				
NAC	6	-	1	7 (21,87%)
NAC+Cur	8	2	3	13 (40,62%)
Cur+Vit C	1	-	1	2 (6,25%)
Curcuma	-	1	1	2 (6,25%)
Vitamin C	1	2	-	3 (9,37%)

NAC: N-acetylcysteine; NAC+Cur: N-acetylcysteine and Curcuma; Cur+Vit C: Curcuma and vitamin C

Curcuma and vitamin C), and X (received no antioxidant treatment). The impact of these antioxidants on kidney function was assessed by measuring serum creatinine and urea levels before and after aminoglycoside treatment, presented in diagram figures. The figures illustrate the changes in these parameters between the groups, highlighting the differences observed with and without antioxidant administration.

The results show that patients receiving streptomycin and kanamycin therapy, treated with either NAC alone or the NAC+Cur combination, demonstrated a greater reduction in serum creatinine (Figures 1 and 5) and urea levels (Figure 2). However, no significant difference in urea levels was observed in the kanamycin+NAC group (Figure 6). Conversely, cotreatment with NAC+Cur in the gentamicin group showed

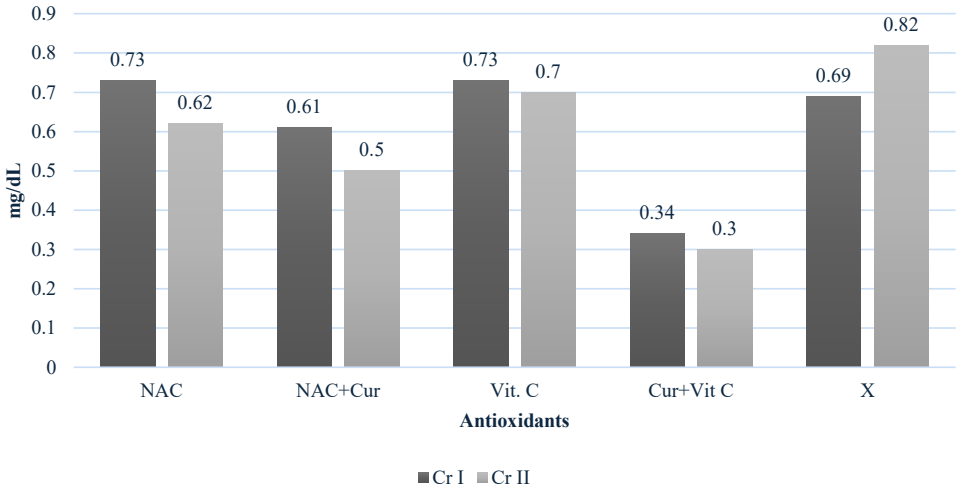

Figure 1 Comparison of the Antioxidants' Effect on the Average Serum Creatinine Level in the Streptomycin Therapy Group

NAC: N-acetylcysteine; NAC+Cur: N-acetylcysteine and Curcuma; Vit C: vitamin C; Cur+Vit.C: Curcuma and vitamin C; X: without antioxidant; Cr: creatinine

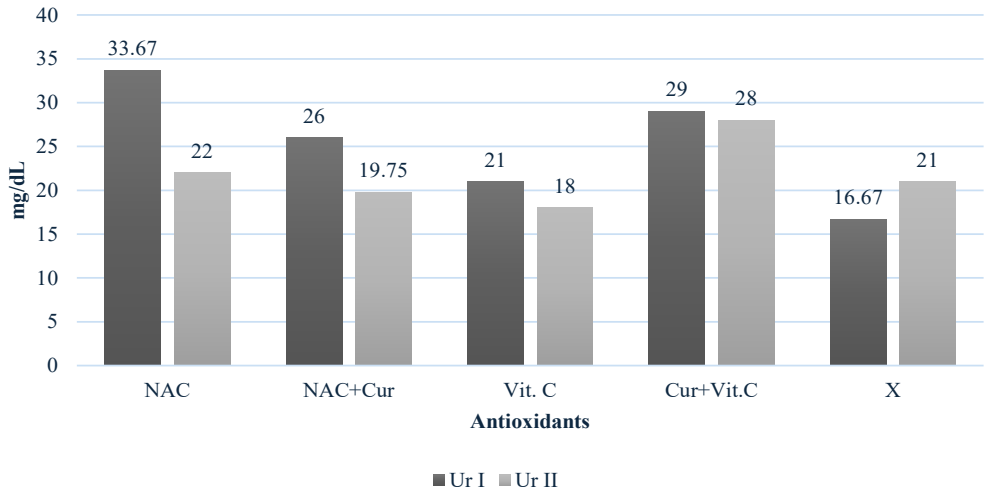

Figure 2 Comparison of the Antioxidants' Effect on the Average Serum Urea Level in the Streptomycin Therapy Group

NAC: N-acetylcysteine; NAC+Cur: N-acetylcysteine and Curcuma; Vit C: vitamin C; Cur+Vit.C: Curcuma and vitamin C; X: without antioxidant; Ur: urea

increased serum creatinine and urea levels, from 0.8 mg/dL to 1.09 mg/dL and 10 mg/dL to 11 mg/dL, respectively (Figure 3 and 4). However, these values remained within the normal ranges for creatinine (male <1.3 mg/dL and female <1.1 mg/dL) and serum urea (10-50 mg/dL). Curcuma-only therapy in the kanamycin group showed a rise in creatinine (Cr I 0.6 mg/dL to Cr II 0.7 mg/dL) (Figure 5) and urea (Ur I 25mg/dL to Ur II 33mg/dL) serum levels (Figure 6). The streptomycin and kanamycin groups who received Cur+vit. C combination showed a decrease in serum creatinine and urea levels (Figure 1,2, and 5), except for the kanamycin group (Figure 6), who showed a decrease in serum urea levels. The group without antioxidant therapy (group X) tended to exhibit a rise in serum creatinine

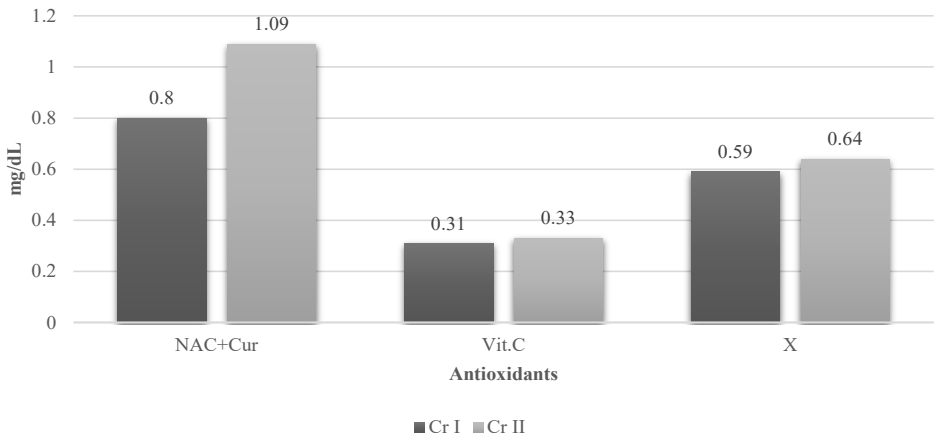

Figure 3 Comparison of the Antioxidants' Effect on the Average Serum Creatinine Level in the Gentamicin Therapy Group

NAC+Cur: N-acetylcysteine and Curcuma; Vit C: vitamin C; X: without antioxidant; Cr: creatinine

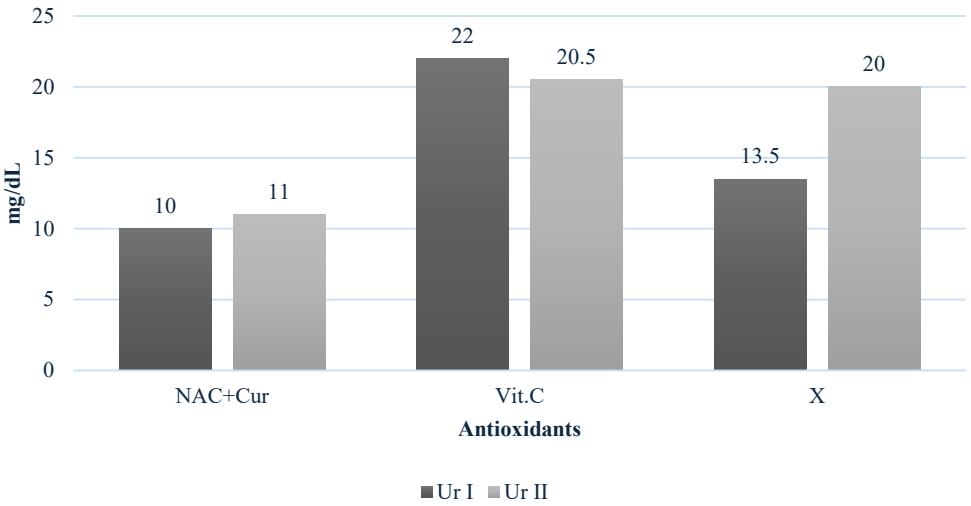

Figure 4 Comparison of the Antioxidants' Effect on the Average Serum Urea Level in the Gentamicin Therapy Group
NAC+Cur: N-acetylcysteine and Curcuma; Vit C: vitamin C; X: without antioxidants; Ur: urea

and urea levels, in streptomycin group the Cr value rose from 0,69 to 0,82 mg/dL and the Ur value from 16,67 to 21 mg/dL; gentamicin group the Cr value rose from 0,59 to 0,64 mg/dL and the Ur value from 13,5 to 20 mg/dL; and kanamycin group the Cr value rose from 0,75 to 0,88 mg/dL and Ur value from 16 to 22 mg/dL.

The statistical analysis of paired samples t-test revealed a significant difference in urea levels before and after streptomycin administration (p=0.039), indicating that average urea levels were significantly different between these two time points. However, creatinine levels did not differ significantly before and after streptomycin administration (p=0.077). For gentamicin, the paired samples t-test showed no significant difference in either urea (p=0.387) or creatinine (p=0.258) levels. Similarly, no significant difference was observed for kanamycin in urea (p=0.710) or creatinine (p=0.909) levels. A one-way ANOVA revealed no significant differences in urea (p=0.133) or creatinine (p=0.246) levels among the three aminoglycoside antibiotics (streptomycin, gentamicin, and kanamycin).

Discussion

There are three mechanisms of aminoglycoside nephrotoxicity manifestation. The first and most common mechanism is renal tubular toxicity due to the accumulation of aminoglycosides in tubular epithelial cells that will lead to apoptosis and necrosis.[8] The clinical manifestations are hypocalcemia, hypomagnesemia, and proteinuria, and eventually, will exhibit an increase in the excretion of potassium, sodium, and blood creatinine levels. Other mechanisms are the induction of mesangial contractions and secondary renal blood flow reduction. Both of these mechanisms will result in a decrease in the glomerular filtration rate (GFR).[20]

Aminoglycoside effect on ROS

This study shows that the coadministration of antioxidants with aminoglycoside antibiotics gave varied outcomes on serum creatinine and urea levels. The combination of NAC+Cur showed better protection against kidney damage than other antioxidant

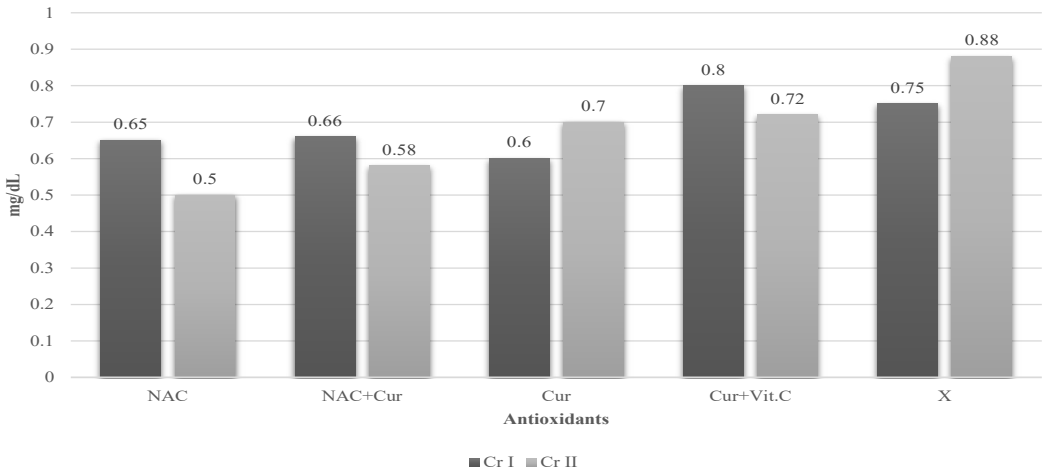

Figure 5 Comparison of the Antioxidants' Effect on the Average Serum Creatinine Level in the Kanamycin Therapy Group

NAC: N-acetylcysteine; NAC+Cur: N-acetylcysteine and Curcuma; Cur: Curcuma; Cur+Vit C: Curcuma and vitamin C; X: without antioxidant; Cr: creatinine

treatments, except in the group treated with gentamicin. This difference in the gentamicin group could be attributed to the multiple daily doses of gentamicin administered, as aminoglycosides exhibit concentration-dependent killing and a post-antibiotic effect, meaning their bactericidal activity increases with concentration and persists even after drug levels are no longer detectable.[21] Due to its low excretion and high reabsorption rates in the kidneys, Gentamicin is the most nephrotoxic aminoglycoside. Additionally, research by Ishikawa *et al.* (2019) and Jospe-Kaufman *et al.* (2020) indicates that gentamicin has a more significant ototoxic effect compared to neomycin and paromomycin.[22,23] Aminoglycosides, particularly gentamicin, can lead to kidney damage through a cascade of events: they induce apoptosis and inflammation, causing

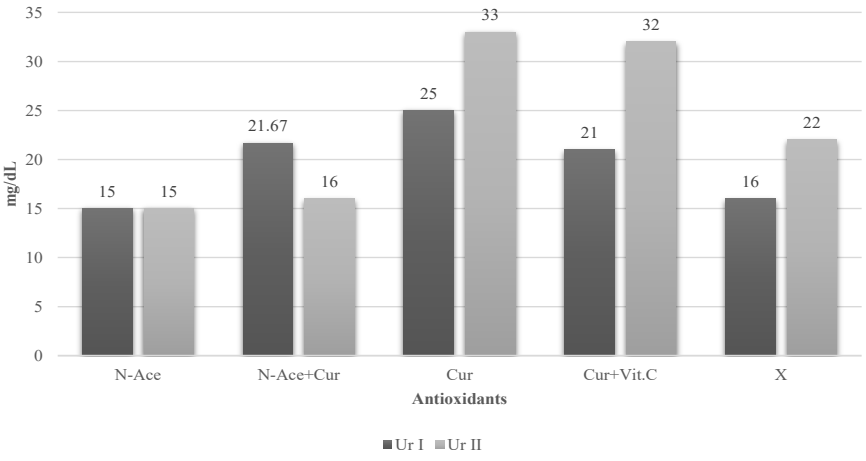

Figure 6 Comparison of the Antioxidants' Effect on the Average Serum Urea Level in the Kanamycin Therapy Group

NAC: N-acetylcysteine; NAC+Cur: N-acetylcysteine and Curcuma; Cur: Curcuma; Cur+Vit C: Curcuma and vitamin C; X: without antioxidant; Ur: urea

mesangial contraction. This contraction restricts renal blood flow due to the overproduction of nitric oxide by inducible nitric oxide synthase (iNOS). Excess nitric oxide (NO) forms peroxynitrite, inhibiting endothelial nitric oxide synthase, ultimately increasing superoxide anions and causing vascular oxidative stress.[24]

Antioxidant as renoprotective agents

The antioxidants provide a renoprotective effect against the nephrotoxicity of aminoglycosides. N-acetylcysteine, a thiol compound, works as an antioxidant through several mechanisms: a direct antioxidant, an indirect antioxidant (as the precursor of natural antioxidant, reduced-glutathione or GSH), and restoring the natural thiol content to regulate the cellular redox state.[25] Vural *et al.* (2018) showed that N-acetylcysteine reduces the toxic effect of long-term amikacin therapy.[18] Similar results are visible in the streptomycin+NAC and kanamycin+NAC therapy groups, showing serum creatinine decrease compared to group X (Figures 1, 2, 5, and 6). And although the kanamycin+NAC group did not show a difference between the first and second urea levels, both of which were 15 mg/dL, this indicates that NAC alone may help maintain a stable urea level within the standard range (10–50 mg/dL). While serum creatinine is generally a more accurate assessment of renal function compared to urea, urea levels tend to increase earlier in renal disease.[26] Therefore, these results suggest that NAC can stabilize serum urea levels.

Meanwhile, vitamin C, also known as ascorbic acid, was given as a single antioxidant therapy only to streptomycin and gentamicin groups. Figures 1 and 2 showed that vitamin C reduced the serum creatinine and urea levels in the streptomycin group. Figures 3 and 4 show that the coadministration gentamicin+Vit C only reduced blood urea levels, and although creatinine levels increased, the Cr I and Cr II levels difference in gentamicin+Vit C group was only 0.02 mg/dL, smaller than the creatinine level increase in the NAC+Cur group that increased by 0.29 mg/dL (Cr I 0.8 mg/dL; Cr II 1.09 mg/dL). This is slightly differ with studies conducted by Moreira *et al.* (2014) and Derakhshanfar (2013), which showed that the combination of gentamicin and vitamin C could prevent elevation of both serum creatinine and urea levels, reduce blood NO levels, and minimize lesion formation in the proximal tubules.[27, 28] Vitamin C scavenges free radicals to minimize oxidative damage caused by ROS.[29]

Another antioxidant used in this study was Curcuma tablets containing *Curcuma xanthorrhiza* extract. *C.xanthorrhiza* contains active metabolites from the terpenoid and curcuminoid groups.[30] Ojha *et al.* (2016) proved that xanthorrhizol (terpenoid) and curcumin (curcuminoid) have renoprotective abilities against cisplatin nephrotoxicity.[31] Curcumin maintains and increases the expression of erythroid-derived nuclear factor 2 (Nrf2), a natural antioxidant enzyme production regulator, and prevents damage to antioxidant enzymes such as catalase (CAT) and glutathione reductase, reduces the protein tyrosine nitration level and renal tubular necrosis.[32,33] The other compound, xanthorrhizol, increases the activity of antioxidant enzymes (CAT and superoxide dismutase [SOD]) and exhibits anti-inflammatory activities by inhibiting COX-2 and iNOS activation and suppressing the production of proinflammatory cytokines such as IL-6, IL-1β, TNF-α, and C reactive protein.[30,34,35]

Antioxidants as a potential strategy to mitigate aminoglycoside-induced nephrotoxicity

Antibiotic resistance is increasing due to the frequent use of antibiotics and the

administration of broad-spectrum antibiotics without antibiotic susceptibility tests, resulting in resistance to broad-spectrum antibiotics such as the cephalosporin class.[36] Therefore, older-generation antibiotics, like aminoglycosides, have become the choice for handling resistant microorganisms.[1] However, the ototoxic and nephrotoxic effects of aminoglycosides limit their optimal use. A study by Sutanto *et al.* (2016) at dr. Moewardi Hospital demonstrated that high-dose, long-term kanamycin therapy for MDR-TB resulted in hearing loss in patients.[37] Similarly, Purnasari et al. (2019) found that increased dosage and duration of aminoglycoside therapy can heighten their nephrotoxic effects. Consequently, the use of aminoglycosides is often avoided or replaced with newer antibiotics, potentially contributing to the rise of antibiotic resistance.[10]

In Indonesia, there are no specific therapeutic efforts to reduce the nephrotoxic effects of aminoglycosides. The administration of antioxidants along with antibiotics is generally only used in tuberculosis patients because antituberculosis drugs have hepatotoxic effects and also to aid patient recovery.[38] However, a study by Ulya *et al.* (2024) at the RSPON Jakarta showed that the use of high doses of NAC was able to improve kidney conditions in patients with AKI.[39] Another study by Simatupang *et al.* (2017) proved that the administration of NAC and hydration successfully reduced the incidence of contrast-induced nephropathy in patients undergoing percutaneous coronary intervention procedures.[40]

Based on this study and prior researches, antioxidants present a potential strategy for mitigating the risk of side effects associated with aminoglycoside-class antibiotics. This study shows that NAC or NAC+Cur have good chance to prevent nephrotoxicity in patients whom received streptomycin or kanamycin, and vitamin C for gentamicin-received patients. This study aims to provide insights for pharmacists, particularly clinical pharmacists, to advocate for the administration of antioxidants in patients undergoing aminoglycoside antibiotic therapy.

This study had several limitations. Patients received various uninvestigated drug therapies besides aminoglycosides and antioxidants. These other medications could have interacted with the aminoglycosides or antioxidants, potentially influencing the observed nephrotoxicity. Future research should carefully track and analyze potential drug interactions to determine if these medications alter aminoglycosides' nephrotoxic effects. Additionally, the impact of age and sex on nephrotoxicity and antioxidant effectiveness requires further investigation, as these demographic factors can influence outcomes.[41] Larger, more diverse studies, considering age, sex, and antioxidant dosages, are needed to better understand how these factors influence aminoglycoside nephrotoxicity and antioxidant effectiveness. Older patients may have a higher toxicity risk regardless of antioxidant use, and effectiveness may differ between sexes. Finally, this study's focus on only the presence or absence of antioxidants, without considering dosage, complicates interpretation. Antioxidants have dose-dependent effects; their impact varies significantly based on the amount administered.[28] Future research should investigate the dose-dependent effects of different antioxidants in mitigating aminoglycoside nephrotoxicity to better understand the relationship between these drugs. Addressing these limitations will lead to a more comprehensive understanding of aminoglycoside nephrotoxicity and the potential role of antioxidants, ultimately contributing to more effective strategies for

preventing and managing aminoglycoside-induced kidney damage.

Conclusions

This study investigated the potential of various antioxidants to mitigate aminoglycoside-induced nephrotoxicity in 32 patients receiving streptomycin, gentamicin, or kanamycin. While NAC and the NAC+Cur combination showed promise in reducing serum creatinine and urea levels in patients receiving streptomycin and kanamycin, the same combination unexpectedly increased these markers in the gentamicin group, albeit within normal ranges. Curcuma alone also elevated creatinine and urea levels in the kanamycin group. The combination of Cur+Vit C generally decreased these markers, except for urea in the kanamycin group. The control group, receiving no antioxidants, consistently showed increased creatinine and urea levels across all aminoglycoside treatments. Statistical analysis revealed a significant difference in urea levels before and after streptomycin administration, but not for creatinine. No significant differences were found for either marker with gentamicin or kanamycin, nor were there significant differences in urea or creatinine levels among the three aminoglycosides.

These findings suggest a complex dynamic between aminoglycoside type and antioxidant treatment. While NAC, alone or with Curcuma, may offer nephroprotective benefits in streptomycin and kanamycin-treated patients, this effect is not observed with gentamicin, warranting further investigation into the underlying mechanisms. The differential effects of Curcuma alone and in combination with vitamin C also highlight the need for careful consideration of antioxidant combinations. The lack of statistically significant differences between the aminoglycosides themselves, despite the observed trends, may be due to the small sample size and underscores the need for larger, more powered studies.

The clinical relevance of these findings lies in the potential for antioxidant supplementation to improve patient outcomes during aminoglycoside therapy. By mitigating nephrotoxicity, antioxidants could reduce the risk of AKI and potentially allow for higher or longer durations of aminoglycoside treatment, which could be particularly important in serious infections. Future research should focus on larger clinical trials to validate these findings, explore optimal antioxidant dosing strategies for different aminoglycosides, and investigate the specific mechanisms by which these interactions occur. This research could ultimately lead to personalized antioxidant therapies and dosage that maximize the efficacy and safety of aminoglycoside treatment. Furthermore, exploring the impact of these interventions on long-term renal health is crucial.

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Conflict of Interest

The author declares no conflict of interest.

References

1. Krause KM, Serio AW, Kane TR, Connolly LE. Aminoglycosides: An Overview. Cold Spring Harb Perspect Med. 2016 Jun 1;6(6):a027029. https://doi.org/10.1101/cshperspect.a027029
2. Reeves AZ, Campbell PJ, Sultana R, Malik S, Murray M, Plikaytis BB, et al. Aminoglycoside Cross-Resistance in Mycobacterium tuberculosis Due to Mutations in the 5′ Untranslated Region of whiB7. Antimicrob Agents Chemother. 2013 Apr;57(4):1857–65. https://doi.org/10.1128/aac.02191-12
3. WHO Global TB Programme. WHO Operational Handbook on Tuberculosis. Modul 4: Treatment - drug-resistant tuberculosis treatment, 2022, update. 2022nd ed. World Health Organization, editor. Vol. 4. Geneva: World Health Organization; 2022.
4. Shibeshi W, Sheth AN, Admasu A, Berha AB, Negash Z, Yimer G. Nephrotoxicity and ototoxic symptoms of injectable second-line anti-tubercular drugs among patients treated for MDR-TB in Ethiopia: a retrospective cohort study. BMC Pharmacol Toxicol. 2019 Dec 23;20(1):31. https://doi.org/10.1186/s40360-019-0313-y
5. Perumal R, Abdelghani N, Naidu N, Yende-Zuma N, Dawood H, Naidoo K, et al. Risk of Nephrotoxicity in Patients With Drug-Resistant Tuberculosis Treated With Kanamycin/Capreomycin With or Without Concomitant Use of Tenofovir-Containing Antiretroviral Therapy. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2018;78(5):536–42. https://doi.org/10.1097/QAI.0000000000001705
6. Le TA, Hiba T, Chaudhari D, Preston AN, Palowsky ZR, Ahmadzadeh S, et al. Aminoglycoside-Related Nephrotoxicity and Ototoxicity in Clinical Practice: A Review of Pathophysiological Mechanism and Treatment Options. Adv Ther. 2023;40(4):1357–65. https://doi.org/10.1007/s12325-023-02436-x
7. Jiang M, Karasawa T, Steyger PS. Aminoglycoside-Induced Cochleotoxicity: A Review. Front Cell Neurosci. 2017;11. https://doi.org/10.3389/fncel.2017.00308
8. Casanova AG, Vicente-Vicente L, Hernández-Sánchez MT, Pescador M, Prieto M, Martínez-Salgado C, et al. Key role of oxidative stress in animal models of aminoglycoside nephrotoxicity revealed by a systematic analysis of the antioxidant-to-nephroprotective correlation. Toxicology. 2017;385:10–7. https://doi.org/10.1016/j.tox.2017.04.015
9. Paquette F, Bernier-Jean A, Brunette V, Ammann H, Lavergne V, Pichette V, et al. Acute Kidney Injury and Renal Recovery with the Use of Aminoglycosides: A Large Retrospective Study. Nephron. 2015;131(3):153–60. https://doi.org/10.1159/000440867
10. Purnasari C, Manggau MA, Kasim H. Studi Pengaruh Dosis Dan Lama Penggunaan Terapi Aminoglikosida Terhadap Fungsi Ginjal. Majalah Farmasi dan Farmakologi. 2019;22(3):76–80.
11. Picard W, Bazin F, Clouzeau B, Bui HN, Soulat M, Guilhon E, et al. Propensity-Based Study of Aminoglycoside Nephrotoxicity in Patients with Severe Sepsis or Septic Shock. Antimicrob Agents Chemother. 2014;58(12):7468–74. https://doi.org/10.1128/aac.03750-14
12. Caires RA, da Costa e Silva VT, Burdmann EA, Coelho FO, Costalonga EC. Drug-Induced Acute Kidney Injury. In: Critical Care Nephrology. Elsevier; 2019. p. 214-221.e2. https://

doi.org/10.1016/B978-0-323-44942-7.00039-X
13. Rosenberg CR, Fang X, Allison KR. Potentiating aminoglycoside antibiotics to reduce their toxic side effects. PLoS One. 2020;15(9):e0237948. https://doi.org/10.1371/journal.pone.0237948
14. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. Kidney Int. 2011;79(1):33–45. https://doi.org/10.1038/ki.2010.337
15. Kranzer K, Elamin WF, Cox H, Seddon JA, Ford N, Drobniewski F. A systematic review and meta-analysis of the efficacy and safety of N -acetylcysteine in preventing aminoglycoside-induced ototoxicity: implications for the treatment of multidrug-resistant TB. Thorax. 2015;70(11):1070–7. https://doi.org/10.1136/thoraxjnl-2015-207245
16. Vicente-Vicente L, Casanova AG, Hernández-Sánchez MT, Pescador M, López-Hernández FJ, Morales AI. A systematic meta-analysis on the efficacy of pre-clinically tested nephroprotectants at preventing aminoglycoside nephrotoxicity. Toxicology. 2017;377:14–24. https://doi.org/10.1016/j.tox.2016.12.003
17. Mahi-Birjand M, Yaghoubi S, Abdollahpour-Alitappeh M, Keshtkaran Z, Bagheri N, Pirouzi A, et al. Protective effects of pharmacological agents against aminoglycoside-induced nephrotoxicity: A systematic review. Expert Opin Drug Saf. 2020;19(2):167–86. https://doi.org/10.1080/14740338.2020.1712357
18. Vural A, Koçyiğit İ, Şan F, Eroğlu E, Ketenci İ, Ünal A, et al. Long-Term Protective Effect of N-Acetylcysteine against Amikacin-Induced Ototoxicity in End-Stage Renal Disease: A Randomized Trial. Perit Dial Int. 2018;38(1):57–62. https://doi.org/10.3747/pdi.2017.00133
19. McWilliam SJ, Antoine DJ, Smyth RL, Pirmohamed M. Aminoglycoside-induced nephrotoxicity in children. Pediatric Nephrology. 2017;32(11):2015–25. https://doi.org/10.1007/s00467-016-3533-z
20. Wargo KA, Edwards JD. Aminoglycoside-Induced Nephrotoxicity. J Pharm Pract. 2014;27(6):573–7. https://doi.org/10.1177/0897190014546836
21. Beauduy CE, Winston LG. Chapter 45 Aminoglycosides & Spectinomycin. In: Katzung BG, editor. Basic and Clinical Pharmacology 14th Edition. 14th Edition. McGraw-Hill Education; 2018. p. 826–33.
22. Ishikawa M, García-Mateo N, Čusak A, López-Hernández I, Fernández-Martínez M, Müller M, et al. Lower ototoxicity and absence of hidden hearing loss point to gentamicin C1a and apramycin as promising antibiotics for clinical use. Sci Rep. 2019;9(1):2410. https://doi.org/10.1038/s41598-019-38634-3
23. Jospe-Kaufman M, Siomin L, Fridman M. The relationship between the structure and toxicity of aminoglycoside antibiotics. Bioorg Med Chem Lett. 2020;30(13):127218. https://doi.org/10.1016/j.bmcl.2020.127218
24. Randjelovic P, Veljkovic S, Stojiljkovic N, Sokolovic D, Ilic I. Gentamicin nephrotoxicity in animals: Current knowledge and future perspectives. EXCLI J. 2017;16:388–99. https://doi.org/10.17179/excli2017-165
25. 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(7):751–62. https://doi.org/10.1080/10715762.2018.1468564

26. Gounden V, Bhatt H, Jialal I. Renal Function Tests. [Updated 2024 Jul 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK507821/
27. Moreira MA, Nascimento MA, Bozzo TA, Cintra A, da Silva SM, Dalboni MA, et al. Ascorbic acid reduces gentamicin-induced nephrotoxicity in rats through the control of reactive oxygen species. Clinical Nutrition. 2014;33(2):296–301. https://doi.org/10.1016/j.clnu.2013.05.005
28. Derakhshanfar A, Roshanzamir M, Bidadkosh A. Dose-related protecting effects of vitamin C in gentamicin-induced rat nephrotoxicity: a histopathologic and biochemical study. Comp Clin Path. 2013;22(3):441–7. https://doi.org/10.1007/s00580-012-1430-9
29. Omotoso DR, Olajumoke JM. Ameliorative Effects of Ascorbic Acid and Allium sativum (Garlic) Ethanol Extract on Renal Parenchyma of Gentamicin-induced Nephropathic Rats. Journal of Complementary and Alternative Medical Research. 2020;1–8. https://doi.org/10.9734/jocamr/2020/v9i430146
30. Rahmat E, Lee J, Kang Y. Javanese Turmeric (Curcuma xanthorrhiza Roxb.): Ethnobotany, Phytochemistry, Biotechnology, and Pharmacological Activities. Evidence-Based Complementary and Alternative Medicine. 2021;2021:1–15. https://doi.org/10.1155/2021/9960813
31. Ojha S, Venkataraman B, Kurdi A, Mahgoub E, Sadek B, Rajesh M. Plant-Derived Agents for Counteracting Cisplatin-Induced Nephrotoxicity. Oxid Med Cell Longev. 2016;2016:1–27. https://doi.org/10.1155/2016/4320374
32. Ma Q. Role of Nrf2 in Oxidative Stress and Toxicity. Annu Rev Pharmacol Toxicol. 2013;53(1):401–26. https://doi.org/10.1146/annurev-pharmtox-011112-140320
33. Trujillo J, Molina-Jijón E, Medina-Campos ON, Rodríguez-Muñoz R, Reyes JL, Loredo ML, et al. Curcumin prevents cisplatin-induced decrease in the tight and adherens junctions: relation to oxidative stress. Food Funct. 2016;7(1):279–93. https://doi.org/10.1039/C5FO00624D
34. Salim Said SA. A study of hepatoprotective effects of Curcuma Xanthorrhiza and Ipomoea Aquatica on thioacetamide-induced liver cirrhosis in rats [Thesis (PhD)]. [Kuala Lumpur]: University of Malaya; 2013.
35. Kim MB, Kim C, Song Y, Hwang JK. Antihyperglycemic and Anti-Inflammatory Effects of Standardized Curcuma xanthorrhiza Roxb. Extract and Its Active Compound Xanthorrhizol in High-Fat Diet-Induced Obese Mice. Evidence-Based Complementary and Alternative Medicine. 2014;2014:1–10. https://doi.org/10.1155/2014/205915
36. Rhee C, Kadri SS, Dekker JP, Danner RL, Chen HC, Fram D, et al. Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated With Inadequate and Broad-Spectrum Empiric Antibiotic Use. JAMA Netw Open. 2020;3(4):e202899. https://doi.org/10.1001/jamanetworkopen.2020.2899
37. Sutanto M, Harsini, Reviono, Aphridasari, Eko V. Relationship Between Kanamycin Injection Treatment and Evaluation of Hearing Loss in MDR-TB Patients in Dr. Moewardi Hospital. [cited 2024 Jul 8]; Available from: https://pulmonologi.fk.uns.ac.id/wp-content/uploads/2016/11/Abstrak-

full-text-dr.Magda-revisi.pdf
38. Ramírez-Marroquín OA, Jiménez-Arellanes MA. Hepato-Protective Effect from Natural Compounds, Biological Products and Medicinal Plant Extracts on Antitubercular Drug-Induced Liver Injuries: A Systematic Review. Med Aromat Plants (Los Angel). 2019;08(05). https://doi.org/ 10.35248/2167-0412.19.8.339
39. Ulya N, Sumarny R, Arozal W, Musridharta E. Analisis Pemberian N-acetylcysteine Dosis Tinggi Terhadap Fungsi Ginjal Pasien yang Didiagnosis Acute Kidney Injury Periode Januari – Desember 2021 di RSPON Jakarta. Syntax Literate ; Jurnal Ilmiah Indonesia. 2024; 9(8):3970–82. https://doi.org/10.36418/syntax-literate.v9i8
40. Simatupang LD, Susalit E, Wijaya IP. Peran Kombinasi Hidrasi dan N-Acetyl Cysteine terhadap Nefropati akibat Kontras 48 Jam Pasca Percutaneous Coronary Intervention pada Pasien Penyakit Ginjal Kronik Stadium 3. Jurnal Penyakit Dalam Indonesia. 2017;3(3):125. https://doi.org/10.7454/jpdi.v3i3.22
41. Wu H, Huang J. Drug-Induced Nephrotoxicity: Pathogenic Mechanisms, Biomarkers and Prevention Strategies. Curr Drug Metab. 2018;19(7):559–67. https://doi.org/10.2174/1389200218666171108154419

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