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Effect of N-acetylcysteine in the prevention of ototoxicity caused by vancomycin in the treatment of peritonitis in patients undergoing peritoneal dialysis

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A B S T R A C T

Peritonitis is currently one of the leading complications of continuous ambulatory peritoneal dialysis (CAPD) treatment. Vancomycin is used in the treatment of CAPD peritonitis despite its potential risk for ototoxicity. N-Acetyl Cysteine (NAC) is a molecule used in the treatment and prophylaxis of many diseases related to oxidative stress. The aim of this study was to examine whether ototoxicity due to Vancomycin used in the treatment of CAPD peritonitis can be prevented by NAC. Sixty patients, who developed CAPD peritonitis from September 2012 to November 2013, were included in this study. Patients were divided into two groups, those taking an additional NAC treatment (n = 30) and a control group (n = 30). Low and high-frequency hearing function tests were performed on the two groups before treatment (baseline), and 9±2 days after the treatment (follow-up). Total doses of Vancomycin were recorded. There was no statistically significant difference between the groups in terms of hearing functions at the beginning. However, patients taking NAC had better hearing function test results after the treatment compared with those of the control group (P < 0.05). There were no statistical differences between post treatment low-frequency hearing function tests conducted at the baseline and follow-up in control group and patients taking NAC but NAC may also have a curative effect on impaired low-frequency hearing functions in case group. In follow-up, high-frequency hearing functions worsened when compared with the baseline high-frequency results in the control group (P =0.006). It was found that NAC had a protective effect against ototoxicity on high-frequency hearing functions. In follow-up, high-frequency hearing functions improved when compared with baseline high-frequency hearing functions in patients taking NAC (P ≤ 0.001). The present study suggests that intraperitoneal Vancomycin administration in CAPD patients may cause high-frequency hearing loss, and this ototoxic effect is related to the dose given. It was found that when the antioxidant NAC is administered alone, it prevents ototoxicity associated with intraperitoneal Vancomycin in patients with CAPD peritonitis. In addition, it was revealed that NAC may also have a curative effect on impaired low frequency hearing functions.

Introduction

Peritonitis is a common complication of CAPD (1-5). Peritonitis not only results in

the technical disorders but also leads to significant morbidity and mortality. It

should be noted that its incidence varies considerably between centers which caused death in 3% of patients during the episodes (6). Many patients have been hospitalized and treated for the CAPD peritonitis (7). According to the recommendations of the international community in order to peritoneal dialysis treatment, the empirical antibiotic therapy should be immediately started following the culturing as soon as the patient with peritonitis hospitalized (8-11). The gram-positive and gram-negative microorganisms should be covered by the empirical treatment. The efficacy and the sensitivity of the microorganisms that are induced peritonitis in a patient population should be recognized by each peritoneal dialysis center, in order to identify the appropriate antibiotics for empirical treatment. The gram-positive and gram-negative organisms are respectively covered by the (Vancomycin or cephalosporin) and (the third-generation of cephalosporin or aminoglycosides).

In a study conducted by Tokgoz et al it has been proved that the hearing loss is the most common complication observed in the patients treated with CAPD (12). In the same paper it has been shown that peritoneal dialysis patients with a history of peritonitis had a higher incidence of high frequencies hearing loss compared with the cases with no peritonitis history. Furthermore the antibiotics (Vancomycin and aminoglycosides) is directly associated with hearing loss in these patients.

The most recommended mechanism which is responsible in ototoxicity induced by Vancomycin and aminoglycosides is the various type of the reactive oxygen. In the studies conducted on animals, the ototoxicity has been improved by

simultaneous administration of antioxidants (13).

NAC is a drug prescribed in the treatment and prophylaxis of many diseases related to oxidative stress. It is believed that NAC could prevent hearing loss caused by bacterial meningitis (14) and cisplatin-induced damage of auditory hair cells (15). It has been shown that NAC could improve the aminoglycosides-induced nephrotoxicity (16). The aim of our study was whether NAC could be effective in the prevention and treatment of ototoxicity induced by Vancomycin or not?

Materials and Methods

In a randomized and controlled open-label clinical trial on patients undergoing CAPD which was performed in nephrology section at the Department of internal medicine in Tabriz University of medical sciences in Iran, the effect of NAC in the prevention and treatment of ototoxicity of the Vancomycin was evaluated.

In this study, 60 patients with ESRD undergoing CAPD and had inclusion criteria of the study were selected and studied in two groups of intervention and control.

All the patients with conditions of inclusion during the 2012-2013 intervals were evaluated in two groups of control and intervention. Patients in this study were used for random sampling using Rand list software.

All patients with CAPD and subsequently peritonitis were treated with intraperitoneal ceftazidime and Vancomycin in accordance with the protocol of ISPD.

The patients were randomly divided into two groups containing 30 members. In one group treatment of peritonitis was done with oral NAC twice a day in addition to antibiotics and control group have received no additional drug except for antibiotics. At first, all patients went under basic audiometer at frequencies of 250, 500, 1000, 2000, 4000, 6000, and 8000 Hz. The total period of the treatment was 21 days.

After about 9-11 days from the completion of the treatment, patients were under the audiometer again and were actually examined in terms of the amount of acoustic injuries. Threshold values for hearing were determined via pure-tone audiometer instrument. Measured frequencies were divided into two separate and pure-tone-PTA mediocrity groups as follows:

- Low frequencies (1-PTA): 250, 500, 1000, 2000 and 4000 Hz.
- High - frequencies, (2-PTA): 6000 and 8000 Hz.

Auditory function tests were performed before starting treatment (basic amount) on two groups.

Hearing injuries were evaluated on the basis of ASHA criteria. Hearing loss was defined as increasing the threshold of hearing at least 20dB in each frequency or at least 10 db in two adjacent frequency or lack of response in the three consecutive frequencies in baseline assessment and follow up in affected ear.

Inclusion criteria included having advanced renal failure disease, who are under peritoneal dialysis due to this problem; additionally, patients with peritoneal dialysis who has been proven to suffer from

peritonitis and the patients who consumed no other ototoxic drug; as well, the patients with no previous hearing problem (physical, convective and nervous problems, etc.) and accepted the conditions of participation in treatment with NAC finally.

The exclusion criteria of the study also included patients with hearing injuries or under the treatment with another ototoxic drug before the intervention in audiometer. Patients who had not the ability to do audiometric testing appropriately or the ones who did not accepted the research conditions of study were set aside.

The data obtained from the study were evaluated by descriptive statistical methods (standard deviation \pm mean) and frequency-percent and Paired samples T-Test, the Independent samples T-Test, Chi square, Fisher and data distribution being normal by klmogrov-Smirnov.

The data were analyzed using SPSS software and P-Value less than 0.05 has been considered statistically significant.

Ethical considerations

In this study, no additional intervention therapeutic has been done for the patients. All information about patients in this study will remain confidential. Each of the necessary tests conducted were based on reputable sources and studies of routine diagnostic methods which are performed commonly by various physicians to patients. There exists no special moral prohibition except prescription of medicines, especially NAC, which is based on reference and articles. Nevertheless, informed consent has been

obtained from each patient before carrying out the study.

Result and Discussion

In sum, 26 (43.3%) patients were male and 34 (56.7%) were female. In the experimental group 11 (36.66%) were male while in the control group 15 (50%) were male ($P=0.297$).

The average age of patients in the intervention group was 40.70 ± 10.40 years and that of the control group was 40.27 ± 11.15 years ($P=0.88$). As shown in Table (1), in this study, patients in both groups were fully equal in terms of the following characteristics: age, gender, CAPD duration, WBC serum, Hb, serum albumin, residual urine volume, cumulative dose of ceftazidime, cumulative dose of vancomycin, K_t/v_{urea} , and base hearing level at low and high frequencies.

Results of peritoneal fluid culture and culture of microorganisms obtained from the two groups are shown in Table (2). A significant difference was observed between the two groups at high frequencies (Table 3). In the follow-up, at PTA-1, 10 patients (33.3%) from the control group and 3 (10%) in the intervention group met the ototoxicity criteria. In addition, at PTA-2, 21 patients (70%) from the control group and 1 (3.3%) patient from the intervention group also satisfied the aforementioned criteria ($P=0.03$, $P<0.001$) (Table 4).

The mean hearing loss at PTA-2 in patients from the control and intervention groups was 5.30 ± 1.78 and -3.76 ± 0.55 , respectively ($P=0.001$) (Table 5). No significant statistical difference was observed between groups in hearing performance tests performed in the beginning of the study. In sum, patients

receiving NAC performed better in the performance tests at the end of the treatment course compared to the control group patients ($P<0.05$). These results suggest that NAC not only prevents the development of ototoxicity, but also can have curative properties as well.

Vancomycin has traditionally been considered as the ototoxic drug (17). The prominent toxic response of Vancomycin would commonly effect on cochlea. However, this problem could be reduced by monitoring the serum levels of the drug, especially in patients with renal dysfunction (18). High frequencies-induced hearing impairment and tinnitus is the common and known side effects of Vancomycin (19) which usually could lead to deafness (20). According to previous studies, the incidence of ototoxicity induced by the Vancomycin is highly variable (21) which would frequently occur for the following three reasons: the variety of methods to evaluate these patients, Heterogeneity in the current population survey and the different treatment regimes with Vancomycin.

The high-frequency sensorineural hearing loss is the first audiological finding in the cochlea toxicity. It should be noted that the tinnitus have been reported in many patients before the hearing loss. Despite the normal serum levels of Vancomycin, the clinical findings of hearing impairment have been reported in some case-reports (22-24). The rank of 11 out of 15 is considered for Vancomycin compared with other ototoxic drugs by Fried Lander who reports the major contribution of toxicity related to cochlea (versus vestibular).

Gorge and Debora is argued that the ototoxicity is not a common side effect of Vancomycin (25) and also its true incidence is probably low and unknown. Gendew and

colleagues reported that the transient exposure levels of Vancomycin (up to 40-30 $\mu\text{g}/\text{mL}$) does not lead to the acute effects (26).

The ototoxic effects of Vancomycin are dose dependent (18) which occurs at the serum levels between 100-80 $\mu\text{g}/\text{mL}$. (27-28). Vancomycin serum concentrations were not measured, especially in such articles that reported the Vancomycin ototoxicity (9). There is no accurate and precise mechanism to explain how the Vancomycin impacts on the auditory system of patients who consumed single or repeated doses.

the Vancomycin-induced hearing loss would firstly affects the high frequency hair cells in cochlea via auditory nerve damage then the moderate and low frequency hair cells would be involved which could ultimately lead to the complete hearing loss. Whereas the hair cells generation is irreversible so the hearing loss will be permanent in these patients (25). The ototoxicity followed by the maximum drug concentration consumption (up to 80 $\mu\text{g}/\text{mL}$) are associated with the renal failure (18) which could be often irreversible in patients .

The high frequencies hearing loss with reversible tinnitus would be occur while the serum concentration peak of the drug is less than 38-40 $\mu\text{g}/\text{mL}$ (23). Gendew and colleagues demonstrated that Vancomycin could cause the hearing impairment in patients with CAPD, especially when combined with an aminoglycoside and also they stated that hearing loss might be due to the synergistic effects of the two drugs (29). Since hearing damage leaves negative effects on the individual's life, use of unnecessary or repetitive doses of ototoxic medicine has to be stopped or limited. Patients with CAPD, who are treated by ototoxic drugs, have to be examined for

complications of hearing damage (e.g. tinnitus, vertigo, and lightheadedness). In the present study, no significant statistical difference was observed between the performances of patients in the control group at base low frequencies and low frequencies measured after administration of Vancomycin ($p=0.657$). In other words, it was found out that patients receiving a fixed dose of Vancomycin demonstrated no hearing loss at low frequencies.

In addition, a significant statistical difference was observed between the performances patients in the control group at base high frequencies and high frequencies measured after treatment with Vancomycin ($P=0.006$). In other words, the control group treated with a fixed dose of Vancomycin demonstrated hearing loss at high frequencies.

One of the mechanisms involved in the development of ototoxicity as a result of consumption of Vancomycin and aminoglycosides is reactive oxygen (in its different forms), which damages the inner ear [30]. NAC, as a thiol containing antioxidants, was originally used as a mucolytic for the treatment of pulmonary diseases. Later on, NAC was used for the treatment of acute toxicity with acetaminophen [31]. Recently, NAC has been also used for the treatment of such ischemic and toxic damages caused to the heart, kidneys, liver and lungs as well [16, 32-34]. In each of the aforementioned conditions, it is assumed that this drug (NAC) affects body through its antioxidant properties(32-34). According to the theory of development of free radicals causing autotoxicity as a result of the use of Vancomycin and aminoglycoside, it is argued that NAC is more effective in the case of uremic patients than in ordinary people.

Table.I Studied variables in two groups

	Group		P
	Case	Control	
Age	40.70 ± 10.40	40.27 ± 11.15	0.88
CAPD duration(month)	28.20 ± 10.72	31.10 ± 15.39	0.40
WBC	8056.67 ± 2352.94	7483.33 ± 2734.09	0.39
Hb(g/dL)	10.81 ± 1.55	10.22 ± 1.15	0.10
Alb(g/dL)	3.92 ± .42	4.02 ± .37	0.33
Residual urine volume (ml/day)	6.20 ± 3.99	6.33 ± 3.92	0.90
Cumulative dose of ceftazidime (g)	17.13 ± 3.23	17.27 ± 3.28	0.87
Cumulative dose Vancomycin (g)	4.77 ± .43	4.53 ± .51	0.06
Kt/Vurea (dB)	1.91 ± .17	1.97 ± .13	0.11
PTA-1	24.73 ± 8.52	23.22 ± 12.53	0.59
PTA-2	31.21 ± 9.12	32.32 ± 17.48	0.76

Table.II Microorganisms obtained from peritoneal fluid culture

	Group	
	Case	Control
Gram Positive		
Staphylococcus epidermidis	4(13.3%)	3(10%)
Staphylococcus aureus	8(26.7%)	6(20%)
Streptococcus	0(0%)	1(3.3%)
Gram Negative	6(20%)	9(30%)
Culture Negative	12(40%)	11(36.7%)

Table.III Evaluation of Hearing level between two groups

	Group		P
	Case	Control	
PTA-1	22.27 ± 6.86	23.13 ± 9.74	0.07
PTA-2	23.51 ± 8.34	37.62 ± 17.98	0.008

Table.IV Patients with Ototoxicity

	Group		P
	Case	Control	
PTA-1	3(10%)	10(33.3%)	0.03
PTA-2	1(3.3%)	21(70%)	<0.001

Table.V Mean hearing loss in two groups of patients

	Group		P
	Case	Control	
PTA-1	-2.47 ± 0.96	-0.09 ± 1.71	0.23
PTA-2	-3.76 ± 0.55	5.30 ± 1.78	0.001

This can be ascribed to the high levels of oxidative stresses in such patients. Okur et al. examined the ototoxicity caused in animals by the use of carboplatin and stated that this drug increases the levels of No and thus leads to a decrease in hearing. They also stated that if NAC is added 30 minutes before administration of carboplatin, production of No reduces and the body is protected against ototoxicity [35]. Thenesh Kumar et al. stated that intraperitoneal NAC prevents the development of ototoxicity caused by cisplatin in animals [36].

Thomas Dickey et al expressed that at NAC infusion into NS has helpful effects in improving hearing tests conducted after 7 days in low frequencies due to ototoxicity created by Cisplatin in animal models (37). Sinswat et al suggested that concurrent administration of intraperitoneal antioxidants leads to prevention of ototoxicity caused by aminoglycosides (13). According to results of Low et al, NAC administration leads to decreased apoptosis in cochlea cells, as well as reduction of free oxygen radicals induced after radiation in the internal ear (38).

Feghail et al indicated that NAC has protective effects either against injury of auditory neural cells induced by Cisplatin or auditory hair cells (15). Feldman et al showed that NAC has otoprotective effects in high frequencies in ototoxicity caused by gentamicin in ESRD patients (39).

Tokgoz et al considered NAC as a cheap, effective and safe material to prevent ototoxicity caused by Vancomycin and aminoglycosides in patients with CAPD.

In our study, there exist a significant differences between low base frequency and lower frequencies after treatment with

Vancomycin in patients who treated with low frequencies ($p = 0.016$).

In other words, in our study it was observed that patients who were located in the face of a constant dose of Vancomycin showed better hearing function in low frequencies after receiving NAC since there was no significant ototoxicity in these frequencies in the control group, despite failing to receive NAC. So, it seems that patients in the intervention group have been improved in terms of hearing after receiving NAC. Also, in our study there was a significant difference between high base frequency and measured higher frequencies after treatment with Vancomycin in patients of intervention group who treated with high frequencies ($P < 0.001$).

In our study it was observed that patients exposed to a constant dose of Vancomycin did not show auditory injury after receiving NAC at high frequency. This drug probably has therapeutic and protective effects in ototoxicity caused by Vancomycin.

Conclusion

According to the obtained results, hearing injury as a result of Vancomycin is negligible in low frequencies and significant in high frequencies.

In addition, the use of NAC in low and high frequencies has therapeutic and protective properties in ototoxicity of Vancomycin in patients with peritonitis in the field of CAPD.

Suggestions

In our study there were some limitations and the following may be suggested to overcome these restrictions:

A similar study should be performed on patients with higher sample sizes, blood levels of ototoxic drugs such as Vancomycin and aminoglycosides should be checked, audiometer studies should be performed on peritonitis population in two steps of early stage (approximately the first week after the completion of treatment) and late one (around 4 weeks after cessation of therapy). Laboratory methods such as electronistagmography could be used for the evaluation of vestibular ototoxicity and OAE measurement could be carried out to evaluate cochlea performance.

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