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Effect of prehydration solution on hearing threshold after chemotherapy in patients with head and neck cancers: a retrospective study

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Background: The study aimed to evaluate the effect of prehydration solution on hearing thresholds after cisplatin chemotherapy.
Methods: In this retrospective cohort study, we reviewed the data of patients who underwent ≥3 courses of cisplatin-based chemotherapy for locally advanced head and neck cancers at a tertiary referral center (n=64). The dextrose solution (DW) group (n=26) received 2 L of normal saline and 1 L of 5% dextrose. The Hartmann solution (HS) group (n=38) received 2 L of normal saline and 1 L of HS. Hearing data were measured 1 day before starting the first course of chemotherapy, and again 20 days after the first, second, and third courses of chemotherapy. The severity of hearing loss was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE).
Results: Thresholds at all frequencies after chemotherapy were greater in the DW group than in the HS group. The increase in thresholds in 1 to 4 kHz after the third course of chemotherapy was greater in the DW group than in the HS group. CTCAE grades after the second and third courses of chemotherapy were greater in the DW group than in the HS group. Logistic regression showed that the odds ratio for CTCAE grade 3 or 4 after the third course of chemotherapy in the DW group was 4.84 on univariate analysis.
Conclusion: Prehydration using a solution with salt was associated with a decrease in change in hearing thresholds after cisplatin chemotherapy in patients with head and neck cancers.

Keywords: Cisplatin; Drug therapy; Hearing; Solutions

Introduction

Cisplatin is a classic chemotherapeutic drug discovered by Rosenberg et al. [1] in 1965. It is currently one of the most commonly used chemotherapeutic drugs in locally advanced head and neck cancers. Nephrotoxicity and ototoxicity are considered the most important complications associated with cisplatin use as a chemotherapeutic drug; cisplatin induces or leads to oxidative stress, inflammation, and outer and inner hair cell apoptosis [2-4]. Consequently, cisplatin is associated with progressive and irreversible sensorineural hearing loss. Breglio et al. [4] showed that approximately 40% to 80% of patients who underwent cisplatin chemotherapy experienced permanent hearing loss. Previous studies have investigated the protective effects of several agents on cisplatin-in-

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duced ototoxicity (CIO). However, despite their promising effects in experimental studies, strong evidence regarding the favorable effects of these agents in clinical studies is scarce [5].

Nephrotoxicity is another complication of cisplatin-induced tubular injury. Clinical practice guidelines strongly recommend vigorous hydration to reduce the cisplatin-induced nephrotoxicity [6]. Hydration is associated with volume expansion, leading to an increase in the rate of cisplatin excretion. In addition, the prehydration solution with salt has a high concentration of chloride and prevents the dissociation of the chloride ions from the platinum molecule, thereby reducing the formation of the reactive species of cisplatin [7,8]. Previous studies have revealed that prehydration plays a role in decreasing cisplatin-induced nephrotoxicity and prehydration solutions with salts are more protective in preventing toxicity. This evidence suggests that prehydration using a salt fluid is strongly recommended to reduce nephrotoxicity. These hypotheses may be applicable to CIO, and prehydration using a salt fluid may be associated with protection of CIO. The aim of our study was to evaluate the effect of prehydration solution on hearing thresholds after cisplatin chemotherapy in patients with head and neck cancers.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Hospital (IRB No: KNUH 2020-04-009), and the requirement for informed consent was waived.

1. Study population and treatment

In this retrospective cohort study, we reviewed the data of patients who underwent at least three courses of cisplatin-based chemotherapy for locally advanced head and neck cancers at a medical center between May 2014 and September 2019. Among the initial 162 patients, the exclusion criteria included the following: having chronic otitis media or otitis media effusion, or missing data for hearing thresholds at the baseline or after the first, second, or third course of chemotherapy (n = 98). None of the enrolled participants were undergoing any additional therapy associated with ototoxicity during the follow-up period. In addition, other than cisplatin, none of the chemotherapeutic drugs were associated with ototoxicity.

The dose of cisplatin was modified as described in a previous study [9]. Briefly, cisplatin was injected every 3 weeks at doses of 50 to 100 mg/m^2. The cisplatin dose administered in each cycle was determined based on individual patient conditions (age, comorbidities, Eastern Cooperative Oncology Group performance status, and treatment-related toxicities) and tumor status (stage and early treatment response). All patients received concomitant radiotherapy at a dose of 60 to 70 Gy; the doses of radiotherapy were similar among the patients. Prehydration solution (3 L) was administered immediately before cisplatin injection. The dextrose solution (DW) group (n = 26) received 2 L of normal saline and 1 L of 5% dextrose. The Hartmann solution (HS) group (n = 38) received 2 L of normal saline and 1 L of HS. Selection of prehydration was randomly determined regardless of the clinician's decision.

2. Study variables

Clinical and laboratory data collected during the examination included the following: age, sex, hemoglobin (g/dL), serum albumin (g/dL), serum creatinine (mg/dL), body mass index (kg/m^2), location of cancer, cumulative dose of cisplatin, and hearing thresholds. Hearing data were measured 1 day before starting the first course of chemotherapy, and again at 20 days after the first, second, and third courses of chemotherapy. The hearing thresholds were measured using an automatic audiometer at 0.5, 1, 2, 3, 4, 6, and 8 kHz. Hearing thresholds at each frequency were averaged using both ears of each patient. The difference after chemotherapy was defined as postchemotherapy values minus the baseline. The severity of hearing loss was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), as previously described [10]. Briefly, grade 1 was defined as a threshold shift of 15 to 25 dB at two frequencies in at least one ear. Grade 2 was defined as a threshold shift > 25 dB at two contiguous frequencies. Grade 3 was defined as a threshold shift > 25 dB at three contiguous frequencies. Grade 4 was defined as non-serviceable hearing, > 80 dB at 2 kHz and above.

3. Statistical analysis

The data were analyzed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as counts (percentage), and continuous variables were expressed as means ± standard deviations (expressed as means ± standard errors for multivariate analysis). Pearson chi-square or Fisher exact test was used to analyzing the categorical variables. For continuous variables, means were compared using a Student *t*-test or a paired *t*-test. Logistic regression analyses were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs), which were then used to determine the correlation between prehydration solution and high CTCAE grade. Multivariate analyses were adjusted for age, sex, baseline hearing thresholds, and cumulative dose of cisplatin and performed using a forward selection method. The *p*-values

< 0.05 were considered statistically significant.

Results

1. Clinical characteristics

The mean age values in the DW and HS groups were 59.4 ± 8.0 and 59.8 ± 11.6 years, respectively ($p = 0.873$) (Table 1). The proportion of male sex in the DW and HS groups was 96.2% and 81.6%, respectively. There were no significant differences in age, sex, hemoglobin, albumin, creatinine, body mass index, and location of cancer between the two groups. The cumulative dose of cisplatin was similar at the first course of chemotherapy, but the cumulative dose of cisplatin at the second and third courses was higher in the DW group than in the HS group.

2. Changes in hearing thresholds after chemotherapy according to prehydration solution

Fig. 1 shows the trends of hearing thresholds according to chemotherapy. Baseline 0.5 and 3 kHz values were greater in the DW group than in the HS group ($p = 0.027$ for 0.5 kHz and $p = 0.017$ for 3 kHz). There were no significant differences in 1, 2, 4, 6, and 8 kHz at baseline between the two groups. However, thresholds at all frequencies after chemotherapy were greater in the DW group than in the HS group. In the DW group, the thresholds in all frequencies after the third course of chemotherapy were greater than each baseline value. In the HS group, those in 3, 4, 6, and 8 kHz after the third course of chemotherapy were greater than each baseline value, but there were no significant differences in 0.5, 1, and 2 kHz between values on baseline and after the third course of chemotherapy.

Table 2 shows the difference between values on baseline and after chemotherapy. The increase in thresholds in 0.5, 1, 2, 3, and 6 kHz after the first course of chemotherapy was greater in the DW group than in the HS group. Those in 0.5, 1, 2, 3, 4, and 6 kHz after the second course of chemotherapy were greater in the DW group than in the HS group. Those in 1, 2, 3, and 4 kHz after the third course of chemotherapy were greater in the DW group than in the HS group. Multivariate analysis showed the same trend for those after the first or second course of chemotherapy. Those after the third course of chemotherapy were greater in the DW group than in the HS group, but statistical significance was not obtained.

We have divided the two groups according to median cumulative dose (260 mg/m^2) in the third chemotherapy. The numbers of patients with median cumulative dose of < 260 mg/m^2 (low dose group) were 9 and 24 in the DW and HS groups, respectively. The numbers of patients with median cumulative dose of ≥ 260 mg/m^2 (high dose group) were 17 and 14 in the DW and HS groups, respectively. In the low dose group, patients with grade 3 or 4 after the third chemotherapy were 3 (33.3%) and 3 (12.5%) in the DW and HS groups, respectively ($p = 0.309$). In the high dose group, patients with grade 3 or 4 after the third chemotherapy were 8 (47.1%) and 2 (14.3%) in the DW and HS groups, respectively

Table 1. Participant clinical characteristics according to hydration solution

Characteristic	DW group (n = 26)	HS group (n = 38)	*p*-value[a]
Age (yr)	59.4 ± 8.0	59.8 ± 11.6	0.873
Male sex	25 (96.2)	31 (81.6)	0.128
Hemoglobin (g/dL)	13.2 ± 1.5	13.4 ± 1.9	0.765
Albumin (g/dL)	4.1 ± 0.4	4.3 ± 0.3	0.094
Creatinine (mg/dL)	0.9 ± 0.3	0.8 ± 0.2	0.115
Body mass index (kg/m^2)	22.9 ± 3.3	23.0 ± 2.7	0.851
Location of cancer			0.955
Nasal cavity, nasopharynx	6 (23.1)	7 (18.4)	
Oral cavity (tonsil, tongue, BOT), oropharynx	8 (30.8)	11 (28.9)	
Larynx	10 (38.5)	17 (44.7)	
The others (LN, EAC, unknown primary)	2 (7.7)	3 (7.9)	
Cumulative dose of cisplatin (mg/m^2)			
First chemotherapy	94.4 ± 12.6	91.1 ± 17.1	0.393
Second chemotherapy	182.7 ± 23.2	168.4 ± 28.2	0.037
Third chemotherapy	262.1 ± 34.8	235.0 ± 34.5	0.003

Values are presented as mean ± standard deviation or number (%).
DW, dextrose solution; HS, Hartmann solution; BOT, base of tongue; LN, lymph node; EAC, external auditory canal.
[a]The continuous variables were compared using Student *t*-test and the categorical variables were compared using Pearson chi-square or Fisher exact tests.

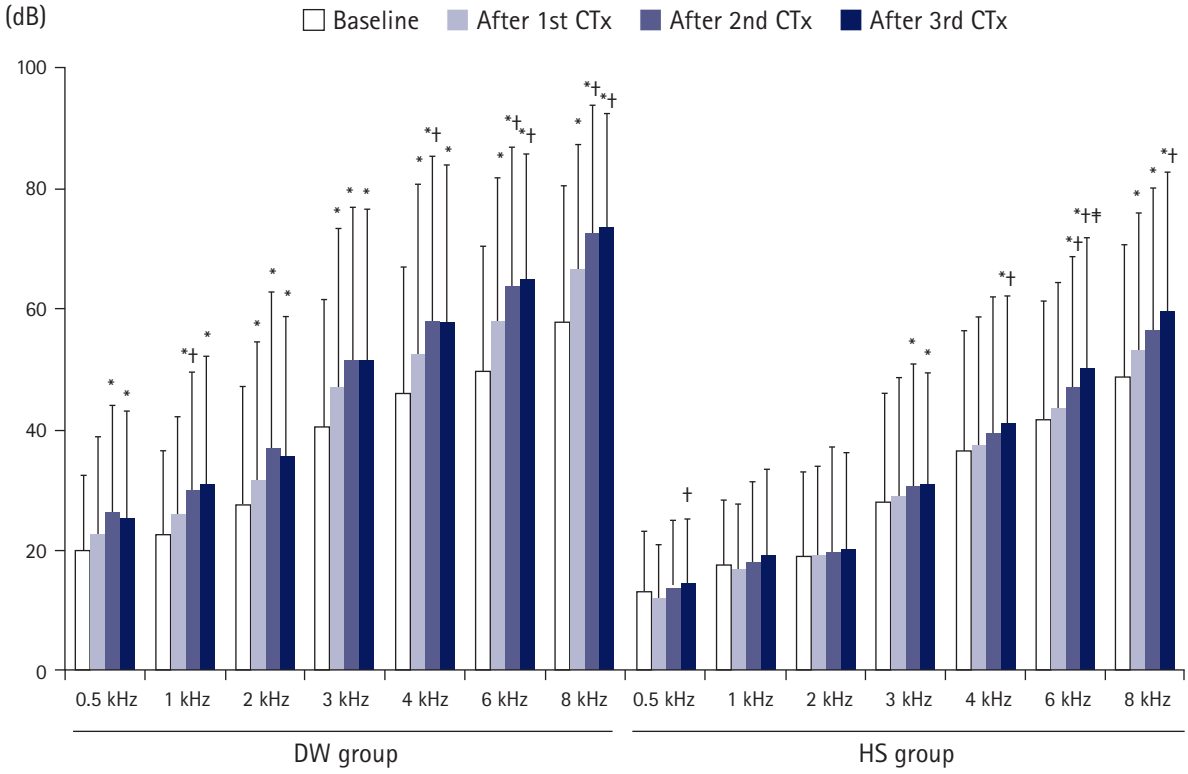

Fig. 1. Hearing thresholds after CTx according to prehydration solution. The mean 0.5 kHz values at baseline, and after the first CTx, second CTx, and third CTx were 19.8±12.6, 22.5±16.3, 26.2±17.7, and 25.3±17.7 dB for the DW group and 13.0±10.0, 11.8±9.2, 13.5±11.5, and 14.5±10.7 dB for the HS group, respectively. The mean 1 kHz values at baseline, after the first CTx, second CTx, and third CTx were 22.9±13.5, 25.8±16.3, 29.8±19.7, and 30.8±21.4 dB for the DW group and 17.4±10.8, 16.6±11.1, 17.9±13.3, and 19.0±14.3 dB for the HS group. The mean 2 kHz values at baseline, after the first CTx, second CTx, and third CTx were 27.4±19.8, 31.5±23.0, 36.9±25.9, and 35.4±23.2 dB for the DW group and 18.9±14.0, 18.9±15.1, 19.5±17.6, and 20.1±16.0 dB for the HS group. The mean 3 kHz values at baseline, after the first CTx, second CTx, and third CTx were 40.5±21.0, 47.0±26.2, 51.4±25.4, and 51.3±25.3 dB for the DW group and 28.0±18.1, 28.7±19.9, 30.4±20.5, and 30.8±18.5 dB for the HS group. The mean 4 kHz values at baseline, after the first CTx, second CTx, and third CTx were 45.9±21.0, 52.4±28.4, 57.9±27.4, and 57.6±26.3 dB for the DW group and 36.4±19.9, 37.3±21.3, 39.3±22.6, and 40.9±21.2 dB for the HS group. The mean 6 kHz values at baseline, after the first CTx, second CTx, and third CTx were 49.4±21.0, 57.8±23.9, 63.7±23.2, and 64.7±21.0 dB for the DW group and 41.6±19.6, 43.5±20.8, 46.9±21.7, and 50.2±21.6 dB for the HS group. The mean 8 kHz values at baseline, after the first CTx, second CTx, and third CTx were 57.9±22.5, 66.6±20.6, 72.2±21.5, and 73.4±18.8 dB for the DW group and 48.8±21.8, 53.3±22.7, 56.3±23.6, and 59.4±23.3 dB for the HS group. CTx, chemotherapy; DW, dextrose solution; HS, Hartmann solution. *$p<0.05$ vs. the value at baseline; †$p<0.05$ vs. the value after the first CTx; ‡$p<0.05$ vs. the value after the second CTx.

($p=0.068$). Although the differences were not statistically significant, the development of grade 3 or 4 in the HS group was lower than that in the DW group in both the low- and high-dose groups.

Lesions owing to radiotherapy can influence hearing impairment more than that with cisplatin or prehydration. In our study, there were 32 and 27 patients with nasopharyngeal or oropharyngeal cancer (NOPCa) and glottic or laryngeal cancer (GLCa), respectively. The numbers of patients with grade 3 or 4 after the third chemotherapy were 10 (31.3%) and 5 (18.5%) in the NOPCa and GLCa groups, respectively ($p=0.263$). There was no significant difference in the development of grade 3 or 4 between the two groups; however, the trend showed a greater proportion of grade 3 or 4 in patients with NOPCa than that in patients with GLCa. Patients with NOPCa were more prone to high risk for radiation than those with GLCa, which may be associated with a greater proportion of hearing impairment in patients with NOPCa.

3. Change in CTCAE grades after chemotherapy according to prehydration solution

CTCAE grade after the first course of chemotherapy in the DW and the HS groups was 15 (57.7%) and 29 (76.3%) in grade 0, 5 (19.2%) and 6 (15.8%) in grade 1, 1 (3.8%) and 1 (2.6%) in grade

Table 2. Change in hearing thresholds after chemotherapy according to hydration solution

Analysis	After the first chemotherapy from baseline			After the second chemotherapy from baseline			After the third chemotherapy from baseline		
	DW group	HS group	*p*-value[a]	DW group	HS group	*p*-value[a]	DW group	HS group	*p*-value[a]
Univariate									
0.5 kHz	2.7 ± 8.0	−1.3 ± 4.5	0.014	6.3 ± 11.1	0.5 ± 5.6	0.007	5.5 ± 13.0	1.5 ± 5.8	0.102
1 kHz	2.9 ± 8.3	−0.7 ± 4.7	0.031	6.9 ± 12.1	0.5 ± 5.9	0.007	7.9 ± 14.4	1.6 ± 7.6	0.028
2 kHz	4.1 ± 10.1	0.1 ± 5.7	0.045	9.5 ± 19.3	0.6 ± 7.5	0.012	8.0 ± 17.2	1.2 ± 7.9	0.036
3 kHz	6.5 ± 15.0	0.7 ± 7.0	0.041	11.0 ± 17.8	2.4 ± 6.9	0.009	10.8 ± 18.4	2.8 ± 8.5	0.023
4 kHz	6.5 ± 14.8	0.9 ± 5.6	0.060	12.0 ± 17.2	2.9 ± 9.8	0.009	11.7 ± 15.8	4.5 ± 12.7	0.048
6 kHz	8.4 ± 14.4	1.9 ± 8.3	0.026	14.2 ± 15.9	5.3 ± 10.6	0.009	15.3 ± 15.2	8.6 ± 13.4	0.069
8 kHz	8.8 ± 15.3	4.5 ± 9.6	0.181	14.3 ± 15.6	7.6 ± 13.4	0.068	15.5 ± 15.7	10.7 ± 16.8	0.251
Multivariate									
0.5 kHz	3.2 ± 1.3	−1.6 ± 1.0	0.009	6.3 ± 1.8	0.5 ± 1.4	0.018	5.2 ± 2.1	1.7 ± 1.7	0.221
1 kHz	3.4 ± 1.2	−1.0 ± 1.0	0.010	6.6 ± 1.8	0.7 ± 1.5	0.019	7.0 ± 2.3	2.2 ± 1.9	0.129
2 kHz	4.5 ± 1.4	−0.2 ± 1.1	0.014	10.0 ± 2.8	0.2 ± 2.3	0.012	7.9 ± 2.7	1.2 ± 2.1	0.070
3 kHz	6.8 ± 2.2	0.6 ± 1.8	0.042	10.6 ± 2.7	2.7 ± 2.2	0.037	9.4 ± 2.8	3.8 ± 2.3	0.152
4 kHz	6.2 ± 2.1	1.1 ± 1.7	0.078	11.1 ± 2.7	3.5 ± 2.2	0.041	10.1 ± 2.9	5.7 ± 2.3	0.263
6 kHz	8.4 ± 2.1	1.9 ± 1.8	0.026	13.3 ± 2.6	6.0 ± 2.1	0.038	13.4 ± 2.8	9.9 ± 2.2	0.349
8 kHz	9.2 ± 2.3	4.2 ± 1.9	0.110	13.6 ± 2.8	8.1 ± 2.2	0.143	13.7 ± 3.0	11.8 ± 2.4	0.647

Values are presented as mean ± standard deviation for univariate analysis and mean ± standard error for multivariate analysis. Values were calculated from values obtained after each chemotherapy minus baseline.

DW, dextrose solution; HS, Hartmann solution.

[a]The *p*-values were tested by Student *t*-test for univariate analysis and analysis of covariance for multivariate analysis. All regimens of chemotherapy were the same excluding doses of cisplatin and radiotherapy. Changes in hearing thresholds after the first, second, and third chemotherapy were compared between the DW and HS groups. The dependent variable was difference in hearing threshold between the baseline and after each cycle of chemotherapy. Covariates were age and baseline hearing thresholds before first chemotherapy, sex, and cumulative dose of cisplatin at the time of audiogram.

2, 2 (7.7%) and 2 (5.3%) in grade 3, and 3 (11.5%) and 0 in grade 4 ($p = 0.241$), respectively. CTCAE grade after the second course of chemotherapy in the DW and the HS groups was 10 (38.5%) and 27 (71.1%) in grade 0, 5 (19.2%) and 5 (13.2%) in grade 1, 0 and 1 (2.6%) in grade 2, 4 (15.4%) and 5 (13.2%) in grade 3, and 7 (26.9%) and 0 in grade 4 ($p = 0.007$), respectively. CTCAE grade after the third course of chemotherapy in the DW and the HS groups was 9 (34.6%) and 22 (57.9%) in grade 0, 4 (15.4%) and 7 (18.4%) in grade 1, 2 (7.7%) and 4 (10.5%) in grade 2, 5 (19.2%) and 4 (10.5%) in grade 3, and 6 (23.1%) and 1 (2.6%) in grade 4 ($p = 0.007$), respectively. CTCAE grades after the second and third courses of chemotherapy were greater in the DW group than in the HS group.

Logistic regression showed that the OR for CTCAE grade 3 or 4 after the third course of chemotherapy in the DW group was 4.84 (95% CI, 1.43–16.41; $p = 0.011$) on univariate analysis. Multivariate analysis was performed using a forward selection method with age, sex, all hearing thresholds, and cumulative dose of cisplatin. The analysis showed that, among the covariates, only prehydration solution was statistically significant. The results of multivariate analysis matched those of univariate analysis.

Discussion

Our study showed that prehydration with a salt solution alone was more effective in protecting the increase in hearing thresholds in patients who received cisplatin chemotherapy for head and neck cancers. All hearing thresholds after cisplatin chemotherapy increased compared with values on the baseline. The amount of increase in hearing thresholds after chemotherapy was greater in the DW group than in the HS group. CTCAE grade as a categorical variable after chemotherapy was higher in the DW group than in the HS group. Logistic regression analyses showed similar trends.

CIO is a well-known complication that appeared in early clinical studies of cisplatin. Previous studies demonstrated that factors such as old age, noise exposure, male sex, hypertension, and high cumulative dose of cisplatin are associated with the incidence of hearing impairment after cisplatin chemotherapy [11]. Various experimental studies have investigated mechanisms of CIO. Previous studies showed that cochlear influx of cisplatin is developed by the copper transporter 1, which results in the production of reactive oxygen species [12-14]. These lead to injuries to various cells in the auditory systems and irreversible hearing impairment. Many

interventional drugs targeting these mechanisms have been investigated for the protection of CIO. Experimental studies have shown favorable results of sulfhydryl compounds (alpha-lipoic acid, amifostine, sodium thiosulfate) or antioxidant/anti-apoptotic agents (NOX inhibitor, allicin, epicatechin, dexamethasone, and vitamin E) for protection of CIO [5]. Meta-analysis has shown a trend toward decreased ototoxicity in patients receiving amifostine, but statistical significance was not obtained [15]. Sodium thiosulfate has shown consistently favorable results in non-metastatic hepatoblastoma, but the data were available for children or adolescents alone [16]. In addition, many clinical studies for mechanism-targeted therapies showed inconsistent results regarding the protective effect, and there is no otoprotective agent routinely recommended for the prevention of CIO [17,18].

The association between vigorous hydration and protection of nephrotoxicity is well known. Although there have been few randomized trials, vigorous hydration (≥ 3 L/day) during cisplatin administration is strongly recommended to maintain a balance between benefits and risks. A previous study has shown that fluid with salt is superior to osmotic agents such as mannitol [19]. The difference between HS and 5% DW should be considered. HS or DW is the two most used crystalloid solutions. HS includes 130 mEq/L of sodium, 109 mEq/L of chloride, 28 mEq/L of bicarbonate, 4 mEq/L of potassium, and 3 mEq/L of calcium in water. The 5% DW includes 50 g/L of glucose in water. The increase in intravascular volume by 1 L supplementation was approximately 85 mL for 5% DW and 250 mL for HS, respectively. The effect of volume expansion is 2.9 times greater in HS than in the 5% DW. The renoprotective effect by volume expansion may be an extension of difference in otoprotective effect according to hydration solution. In addition, fluid therapy with salt influences chloride entrapment for platinum above volume expansion. Therefore, prehydration using fluid with salt may be superior to fluid with glucose alone. However, there are few data regarding association between fluid types and ototoxicity.

In this study, hearing thresholds in two frequencies (0.5 and 3 kHz) were greater in the DW group than in the HS group. This was an inherent limitation of our study. The changes in hearing thresholds after chemotherapy would be influenced by the sensitivity of chemotherapy beyond prehydration fluid. Therefore, our results should be carefully interpreted due to difference in baseline hearing thresholds. However, we tried to attenuate this limitation using multivariate analysis or comparison of delta values in hearing thresholds between two groups. These results revealed favorable trends for the HS group compared to that of the DW group. Our study is a pilot rather confirmative design and insufficient to confirm between prehydration solution and hearing, and the generalization of our results. Therefore, further studies with larger sample size and similar hearing threshold are needed to overcome this limitation. If baseline hearing was different despite large sample size, propensity score-matched cohort would be useful in matching hearing levels.

Our results showed that the change in hearing threshold was increased as frequency increased. The preservation of the hearing threshold by prehydration was better in low-frequency lesion than in high-frequency lesions. The preventive effect by prehydration was attenuated as cycles of chemotherapy increased. Cisplatin ototoxicity can cause cochlear injury. This injury initiates from outer hair cells adjacent to the cochlear base and progresses to the apical cells with increasing dose [20]. Therefore, hearing impairment progresses from high frequency to low frequency, and becomes worse with the increasing cumulative dose of cisplatin. In our study, only 1 L of the total 3 L of hydration solution was different, and this small difference may be difficult to induce a large difference in preventive effect. This small difference between the two groups would be associated with less improvement in high-frequency lesion (highly injurious lesion) than in low-frequency lesions (low injurious lesion). In addition, toxicity accumulates according to the cycle of chemotherapy, which would attenuate preventive effect.

The change in hearing thresholds after the third chemotherapy was lesser than those after the first or second chemotherapy. Two issues were associated with these changes. First, it may be associated with a decreased dose of cisplatin according to cycles of chemotherapy. The dose of cisplatin according to cycles were 93.1 ± 14.8 mg/m^2 in the first, 83.4 ± 15.7 mg/m^2 in the second, and 73.1 ± 16.7 mg/m^2 in the third cycles. The dose of cisplatin decreased as the cycles of chemotherapy increased. A decrease in the dose of chemotherapy may be associated with attenuated ototoxicity of cisplatin despite increase in cumulative dose. Second, activation of resistant mechanism would be associated with decreased ototoxicity according to the cycles of chemotherapy. Resistance can be developed by decreased influx or increased efflux of drug, activation of antioxidant mechanisms, or drug detoxification [21]. Normal hair cells after chemotherapy may have improved resistance to cisplatin compared to that before chemotherapy, although information remains limited in this regard.

Cumulative dose of cisplatin would be a confounding factor for the effect of prehydration on hearing. In our study, based on 100 mg/m^2 as the standard dose, the initial dose of cisplatin was modified according to a patient's performance status. The second or third doses of cisplatin were modified according to toxicity grade, changes in a patient's performance status, and tumor response. Therefore, a low cumulative dose of the HS group may be associat-

ed with higher toxicity grade, changes in a patient's performance status, and poorer tumor response during cycles compared to that in the DW group. Our study did not include these data or adjust for these variables due to limitation of sample size. Adjustment for these variables would be helpful in identifying the independent effect of prehydration on hearing.

This study had several limitations. First, it was a retrospective, single-center study. Prehydration solutions were selected without randomized controlled methods. Second, baseline characteristics, including hearing thresholds and cumulative dose of cisplatin, were different between the two groups. Third, the number of participants was small and statistical significance was weak. In addition, other modifiable factors were not considered because of the small number of participants in our study. Fourth, causal relationship was obscure. In our study, the two groups were distinguished by solution type of 1 L within total 3 L of fluid in both groups. It is not clear whether these small differences can lead to significant changes in clinical outcome. Randomized controlled studies including a larger number of participants are warranted to overcome these limitations.

In conclusion, prehydration using a solution with salt was associated with a decrease in change in hearing thresholds after cisplatin chemotherapy in patients with head and neck cancers. Therefore, vigorous prehydration with a solution of salt may be helpful to prevent CIO in patients with head and neck cancers, except in circumstances in which overhydration would be a hazard.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: DJJ, MO, BJ; Investigation, Resources: EO, KYL; Data curation: DJJ, DA; Methodology: EO, DJJ; Formal analysis: DJJ, BJ; Supervision, Validation: MO; Funding acquisition: BJ, DA; Writing-original draft: DJJ; Writing-review & editing: KYL,DJJ, DA.

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