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Effect of high dose intravenous vitamin C on idiopathic sudden sensorineural hearing loss: a prospective single-blind randomized controlled trial

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Abstract The aim of this prospective single-blind randomized controlled study was to evaluate the therapeutic efficacy of high dose intravenous vitamin C (HDVC) added to systemic steroid in patients with idiopathic sudden sensorineural hearing loss (ISSNHL). Between August 2010 and August 2011, 72 ISSNHL patients who participated in this study were randomly allocated to two groups: 36 to a control group, members of which were given systemic steroid treatment for 15 days, and 36 to a HDVC group, members of which were given HDVC (200 mg/kg/day) for 10 days in addition to steroid therapy followed by oral vitamin C (2,000 mg) for 30 days after discharge. Finally, we analyzed each group: 35 as a control group and 32 as a HDVC group. Auditory evaluations were performed by pure tone audiometry (PTA) before and ~1 month after treatment using Siegel's criteria. HDVC group showed significantly greater complete and partial recovery improvement ($p = 0.035$). In addition, the complete recovery rate in the HDVC group was more than twice that of the control group ($p = 0.031$). In the HDVC group, PTA improved from 67.6 ± 19.8 dB HL before treatment to 37.1 ± 28.8 dB HL at 1 month after treatment, whereas in the control group, PTA improved from 70.3 ± 12.4 to 47.6 ± 25.2 dB HL, which represented a significant intergroup difference ($p = 0.030$). In conclusion, HDVC may enhance hearing recovery in ISSNHL patients, which suggests that HDVC reduces levels of reactive oxygen metabolites produced by inner ear ischemia or inflammation, and that HDVC could be considered for the treatment of ISSNHL.

Keywords Sudden hearing loss · Ascorbic acid · Antioxidants · Steroids

Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is defined as sensorineural hearing loss of 30 dB or more in three contiguous frequencies over a time course of 72 h or less. Many etiologies have been supposed but the exact cause of ISSNHL remains unclear [1].

Viral infection, vascular injuries, and membrane ruptures have been suggested as possible causative factors. Damage to the auditory nerve due to inflammation caused by viral infections and vascular incidents has also been suggested, and because such varying etiologies are believed to underlie the disease, many different therapeutic regimens have been employed. Typically, systemic steroids are administered, although vasodilators, diuretics, and antiviral agents have been recommended. Nevertheless, only a third of patients recover normal hearing, another third retain of hearing loss of 40–60 dB, and the remainder progress to complete loss of hearing [2].

Recently, a number of studies have suggested that free radicals, reactive oxygen species, and nitric oxide have toxic effects on the auditory system. In particular, several animal studies have concluded that free radical scavengers

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reduce outer hair cell loss caused by cisplatin, aminoglycoside, and loud noise [3].

Vitamin E, vitamin C, and coenzyme Q10 are representative biologic antioxidants, and vitamin C is known to be a powerful antioxidant. Furthermore, some have reported that these antioxidants ameliorate ISSNHL [1, 4]. Hatano et al. [1] reported that vitamin C and E have a beneficial effect on ISSNHL. However, only 1.2 g/day of vitamin C was administered [1], which we consider small amount because lower mammals like rodents synthesize the equivalent of 6–10 g of vitamin C per day in man under normal conditions, and the amount synthesize is increased 10–100 folds under stressful conditions [5]. Furthermore, vitamin C has been recently found to have anticancer effects to prolong life and to improve quality of life in terminal cancer patients, and according to these reports, intravenous vitamin C is harmless even when administered at 100 g/day for 8 weeks [5].

Accordingly, in the present study we administered much higher levels of intravenous vitamin C than those used in previous studies in combination with high doses of steroid to ISSNHL patients, and compared its effects on hearing recovery versus control patients not administered vitamin C.

Materials and methods

This prospective study was carried out on 74 ISSNHL patients who visited our tertiary referral clinic and treated with or without high dose vitamin C (HDVC) at the Department of Otolaryngology, Gyeongsang National University Hospital between August 2010 and August 2011. The institutional review board of our hospital approved the study protocol and written informed consent was obtained from each subject. The two patients were refused to the informed consent. This was a prospective single-blind randomized controlled study with an independent assessor. The 72 patients were randomly divided into two groups: 36 to a control group, members of which were given systemic steroid treatment (1 mg kg/day) for 15 days including 10-day hospitalization, and 36 to a HDVC group, members of which were given HDVC (200 mg/kg/day) for 10 days added to steroid therapy followed by oral vitamin C (2,000 mg) for 30 days after discharge. Finally, we analyzed each group: 35 as a control group and 32 as a HDVC group. The Consort flow chart is shown in Fig. 1.

The diagnostic criteria for sudden sensorineural hearing loss are acute onset of hearing loss of 30 dB in three contiguous frequencies occurring instantaneously or over several days. All patients fulfilled the following inclusion criteria: (1) sudden onset of sensorineural hearing loss, (2)

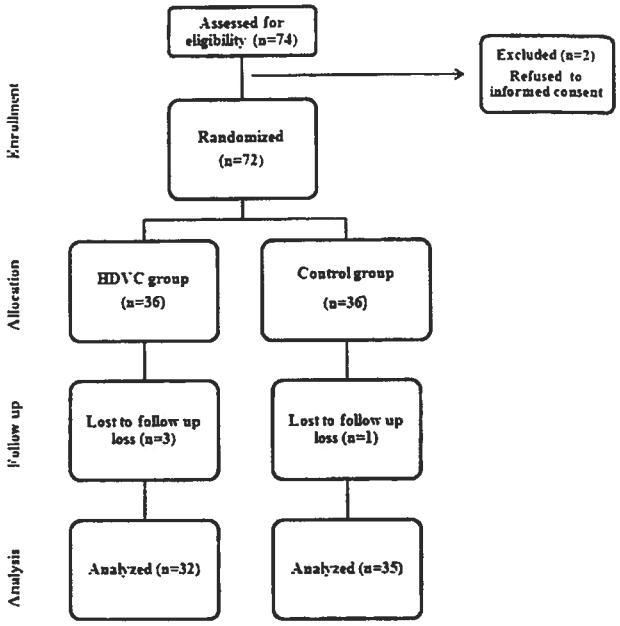

Fig. 1 Patients flow chart illustrating the progress of patients through the study. *HDVC* high dose vitamin C

cause of hearing loss unknown, (3) hearing loss did not fluctuate, and (4) treatment commencement within 14 days from onset. In addition, the exclusion criteria are also as follows: (1) chronic kidney disease, (2) congestive heart failure, (3) diabetes, (4) vestibular schwannoma, and (5) renal stone history. Patients with chronic kidney disease or congestive heart failure were excluded due to potential volume overload. In addition, diabetes mellitus was excluded because the accuracy of blood sugar level testing is adversely affected by the presence of vitamin C.

Pure tone audiometry (PTA) was performed on the initial day of hospital visit. A fixed hearing level was defined as the stable hearing level at 1 month or more after the treatment. Pure tone average was defined as the mean thresholds at 500, 1,000, 2,000, and 3,000 Hz. Final hearing improvements were classified using Siegel's criteria (Table 1). 'Complete recovery' was defined as final hearing better than 25 dB, 'partial recovery' as >15 dB hearing gain and final hearing between 25 and 45 dB, 'slight improvement' as >15 dB gain and final hearing poorer than 45 dB, and 'no improvement' as <15 dB gain and final hearing poorer than 75 dB. We defined hearing recovery as complete and partial recovery as defined by Siegel's criteria. Degree of initial hearing loss in affected ears was defined as moderate (41–55 dB loss), moderate–severe (56–70 dB loss), or severe (>71 dB loss).

Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). The unpaired *t* test was used to compare the HDVC and control groups with respect to initial and final PTA, age at onset, and symptom

Table 1 Criteria of hearing recovery according to Siegel's criteria

	Hearing recovery
Complete recovery	Final hearing better than 25 dB
Partial recovery	More than 15 dB gain and final hearing 25–45 dB
Slightly improvement	More than 15 dB gain and final hearing poorer than 45 dB
No improvement	Less than 15 dB gain or final hearing poorer than 75 dB

onset. Fisher's exact test was used to compare the two groups with respect to sex and lesion site distribution and hearing improvements according to Siegel's criteria. Statistical significance was accepted for p values of <0.05.

Results

Clinical characteristics of patients

No significant intergroup was observed between demographic and clinical features (Table 2). Degrees of hearing loss by initial PTA in the two groups are listed in Table 3. No significant difference in initial hearing was found between the HDVC and control groups ($p > 0.05$).

Hearing improvements using Siegel's criteria

When classified as complete recovery, partial recovery, slight recovery, and no improvement at 1 month after termination of the treatment, the HDVC group achieved 46.8, 18.7, 6.25, and 28 %, respectively, and the control group achieved 23.8, 18.2, 22, and 34 % (Fig. 2). In terms of patients that achieved more than partial recovery, 65.5 % achieved this level in the HDVC group and 42 % in the control group, and this difference was significant ($p = 0.035$) (Table 4). Furthermore, the complete recovery rate was more than twice as high in the HDVC group ($p = 0.031$).

PTA improvement

HDVC group showed a PTA improvement from 67.6 ± 19.8 dB HL to 37.1 ± 28.8 dB HL, whereas the control group showed an improvement from 70.3 ± 12.4 to 47.6 ± 25.2 dB HL, which was significantly different ($p = 0.030$) (Fig. 3). Figure 4 shows the hearing threshold outcome as a function of the initial PTA for both groups. Each case is plotted showing the initial PTA on the horizontal axis and the amount of improvement (at the ~1 month posttreatment PTA) on the vertical axis. This

Table 2 Demographic, clinical and audiologic features of patients with sudden sensorineural hearing loss

	HDVC group ($n = 32$)	Control group ($n = 35$)	p value
Age (years)	52 ± 15.3	50.3 ± 12.4	0.130
Male:female	15:17	18:17	0.270
Site (Rt:Lt)	17:15	15:20	0.380
Initial PTA (dB HL)	67.6 ± 19.8	70.3 ± 12.4	0.200
Onset to treatment (days)	2.4 ± 1.5	2.4 ± 1.3	0.163

HDVC high dose vitamin C, *PTA* pure tone audiometry

Table 3 Patients' distribution by degree of hearing loss of the initial pure tone averages

Degree of HL	HDVC group ($n = 32$)	Control group ($n = 35$)	All patients
Moderate	12 (37.5 %)	11 (31.4 %)	23
Moderate–severe	3 (9.3 %)	7 (20 %)	10
Severe	17 (53 %)	17 (48.5 %)	34

HL hearing loss, *HDVC* high dose vitamin C

allows appreciation of the likelihood and magnitude of recovery for each group, given the presenting severity of hearing loss of the patients.

Complications

No patient in either group experienced any complication related to steroid or vitamin C.

Discussion

ISSNHL is considered an otologic emergency requiring immediate and careful clinical intervention, and subsequently appropriate and specific treatment. Despite many proposed treatments, the prognosis of ISSNHL is not good, and the merits of many treatments are controversial. The anti-inflammatory effects of steroids have been proposed to be beneficial in patients with virus induced sudden hearing loss [6]. On the other hand, it has also been reported that steroid has no significant benefit in ISSNHL [7]. Antiviral agents [8], vasodilators, and fibrinogen apheresis have been applied in ISSNHL [9], but their efficacies have not been established.

Although the etiology of ISSNHL is unclear, oxidative damage to the inner ear probably contributes to its pathogenesis, in the same manner as it does in cases of ototoxicity and noise-induced hearing loss [3, 10]. James et al. [3]

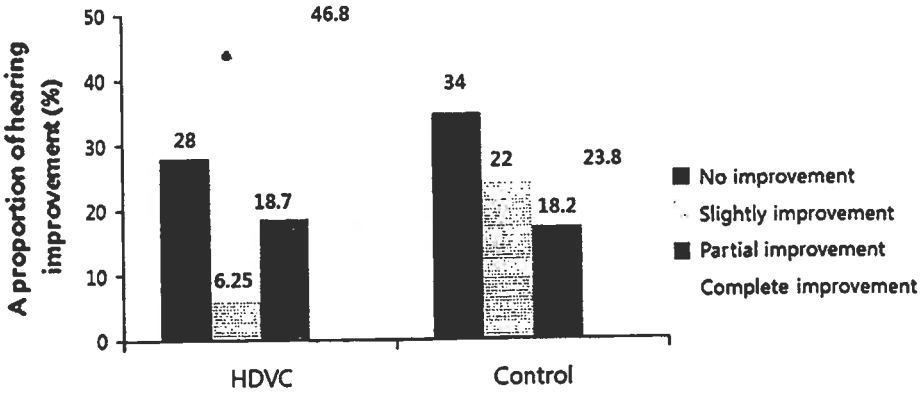

Fig. 2 It shows comparison of hearing recovery proportion using Siegel's criteria between HDVC group and control group. *HDVC* high dose vitamin C

Table 4 Hearing improvements based on the Siegel's criteria

	HDVC group ($n = 32$)	Control group ($n = 35$)	p value
Complete and partial recovery	21 (65.5 %)	15 (42 %)	0.035*

HDVC high dose vitamin C

* $p < 0.05$ in Fisher's exact test

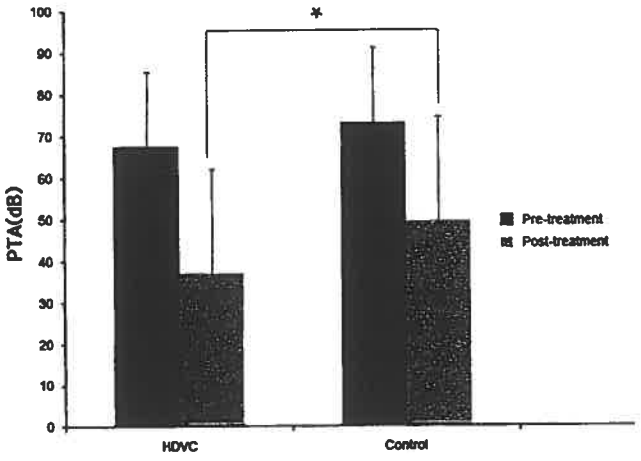

Fig. 3 Comparison of hearing improvement after treatment. The *asterisk* represents a significant difference between each group of posttreatment PTA level ($p = 0.030$). *HDVC* high dose vitamin C, *PTA* pure tone audiometry

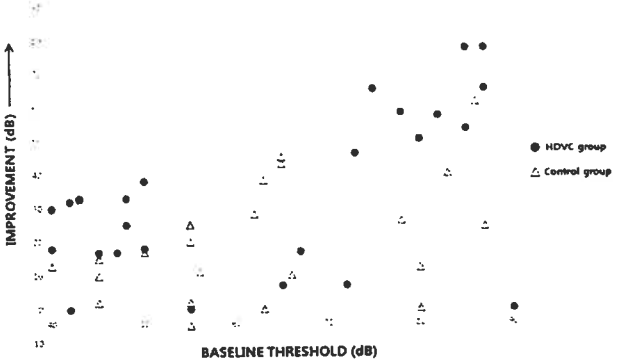

Fig. 4 Each individual case can be seen, plotted horizontally by the severity of hearing loss on entry and vertically by the amount of improvement (dB) seen at the ~1 month posttreatment evaluation. HDVC group is shown using *filled circles* and control group using *open triangles*. *HDVC* high dose vitamin C

concluded that vitamin E appears to have a protective effect against cisplatin-induced ototoxicity, and Takemoto et al. [11] suggested that edaravone (a free radical scavenger) protects the cochlear from acoustic trauma.

Vitamin C is known to accelerate hydroxylation reactions in a number of biosynthetic pathways. The best-known biochemical role of ascorbate is that of cofactor for prolyl and lysyl hydroxylase enzymes during the biosynthesis of collagen [12]. Vitamin C is present in most biological settings and is an essential vitamin for humans, and scurvy, the disease arising from vitamin C deficiency can be fatal [13]. Interestingly, most mammals synthesize vitamin C from glucose, but during evolution humans lost L-gluno-γ-lactone oxidase, which is required for the conversion of glucose to vitamin C, and thus, humans must obtain vitamin C from diet [14]. Vitamin C is water-soluble and does not accumulate in the body, and thus, high dose vitamin C is harmless in the human body. Furthermore, HDVC has long been used to treat bacterial infections, viral infections, and as adjuvant therapy in cancer [5, 15]. Vitamin C is considered one of the strongest reductants and radical scavengers in vivo and reduces unstable oxygen, nitrogen, and sulfur radicals [16]. Hatano et al. [1] reported that vitamins C and E affect ISSNHL, but only 1.2 g/day of vitamin C was used. We consider this level too small, because, for example, rodents synthesize the equivalent of 6–10 g of vitamin C per day on a pro rata basis as compared with humans. Accordingly, in the present study, we treated patients with 200 mg/kg/day of vitamin C, which meant that a 60 kg patient was administered 12 g/day, which is ten times as much as that administered by Hatano et al. [1]. According to a recent pharmacokinetic modeling study, even very large and frequent oral doses of vitamin C

increase plasma concentrations only modestly (to 70–220 μmol/L), whereas intravenous administration can increase plasma concentrations to as high as 14,000 μmol/L [12]. In the present study, we decided to administer vitamin C intravenously to achieve higher plasma concentrations.

Recommended daily vitamin C intakes vary from 100 to 200 g/day, and according to the Riordan clinic, which has treated 80,000 terminal cancer patients over 30 years, intravenous vitamin C is harmless even when administered at 100 g/day for 8 weeks [5]. In the present study, the dose use was 200 mg/kg/day, because our pediatric department has safely used this dose for 20 years to treat patients with inflammation, infection, hepatitis, etc.

When compared the two study groups, we found that a significantly greater proportion achieved more than partial recovery in the HDVC group (65.5 vs. 42 %; $p = 0.035$). Furthermore, the proportion of patients that achieved complete recovery was more than twice as high in the HDVC group ($p = 0.031$). In addition, in the HDVC group, PTA improved from 67.6 ± 19.8 dB HL to 37.1 ± 28.8 dB HL, whereas in the control group it improved from 70.3 ± 12.4 to 47.6 ± 25.2 dB HL, and this difference was significant ($p = 0.030$). This study result is difficult to compare accurately with the results obtained in Hatano study, because in this previous study, patients were treated with vitamins C and E and a different recovery classification method was used (the Sudden Deafness Research Committee of the Ministry of Health and Welfare, Japan) [1]. Accordingly, the present study was the first to administer vitamin C plus systemic steroid in ISSNHL.

The side effects of intravenous vitamin C are only rarely encountered, but there are contraindications and potential side effects that should be considered. Depending on the individual, a large oral dose of vitamin C can cause diarrhea, because non-absorption of vitamin C can change osmolarity in the colon [17]. Another report described acute oxalate nephropathy in a patient with bilateral ureteric obstruction and renal insufficiency administered 60 g of vitamin C intravenously, and although rare, intravascular hemolysis has been reported after massive vitamin C administration in individuals with a glucose-6-phosphate dehydrogenase deficiency [5].

Rivers [18] reported that HDVC is contraindicated in cases of renal insufficiency, chronic hemodialysis patients, unusual forms of iron overload, and in oxalate stone formers, although interestingly, two reports showed that magnesium oxide (300 mg/day, orally) and vitamin B6 (10 mg/day, orally) inhibit oxalate stone formation in recurrent stone formers [19, 20]. In the present study, patients with a renal stone history were excluded.

The fluid used as a vehicle for vitamin C can cause complications, and thus, patients with congestive heart failure, ascites, edema, or hypertension are relatively contraindicated. Vitamin C is preferably given by intravenous drip, and should never be administered by intravenous injection, because the osmolarities induced by high doses are capable of sclerosing peripheral veins. Furthermore, many intravenous solutions used for high dose vitamin C therapy are hypertonic, but this does not create problems as long as the infusion rate is low enough and the osmolarity does not exceed 1,200 mOsm. When infusing vitamin C up to 25 g, it should be mixed with Ringer's lactate solution and/or with sterile water when administered in larger amounts. In the present study, all patient infusions were made up in Ringer's lactate because no patient was administered more than 25 g at one time.

The limitations of the present study are as follows. Considering the importance of communication in social life, speech discriminating ability or the pattern of pure tone audiometry is very important in the quality of life. However, we did not perform speech audiometry or evaluation of hearing at different frequencies in the present study. Further study will be needed to include assessment for speech discriminating ability. In addition, the appropriate calculated sample size in the present study was more than 43 patients for each group. The sample size was a bit short in our study (each group 35 as a control group and 32 as a HDVC group). Therefore, further trials including a larger number of patients need to be conducted to confirm the efficacy of HDVC on ISSNHL.

Conclusions

This study shows that HDVC enhances hearing recovery in ISSNHL patients and that HDVC is a potential therapy for ISSNHL. HDVC may enhance hearing recovery in ISSNHL patients, which suggests that HDVC reduces levels of reactive oxygen metabolites produced by inner ear ischemia or inflammation, and that HDVC could be considered for the treatment of ISSNHL.

Conflict of interest The authors have no conflict of interest to disclose.

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