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Urografin in the Treatment of Sudden Sensorineural Hearing Loss

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Abstract: The present study was conducted to find out whether combined treatment of intravenous urografin and corticosteroid has a therapeutic advantage over oral corticosteroid therapy in the treatment of Sudden Sensorineural Hearing Loss (SSNHL). The design of the study was an interventional and controlled clinical trial. Between 2003 and 2005, patients with SSNHL were treated in our center in Tabriz, Iran. Patients were selected if they had a hearing loss of at least 30 dB in at least 3 frequencies on audiometric testing. Audiograms were performed before admission, 1 and 2 weeks and 1 and 2 months after treatment. Patients who were put on bed rest and received intravenous urografin and hydrocortisone were compared with outpatients treated with oral steroid alone. Various descriptive analytical calculations and both Chi-square and t-test were used to analyze the data. Sixty patients were included in this study. Fifty-one patients referred to the otological clinics for the appropriate treatment within the first two weeks after the onset of hearing loss. The overall improvement of both groups was 53.3%. Seventeen (56.6%) of 30 patients treated in the inpatient group who received intravenous urografin and intravenous corticosteroid had hearing improvement, while half of the outpatient group received oral corticosteroid responded positively to the treatment ($p > 0.05$). This study revealed no significant difference in hearing improvement between the hospitalized patients who received intravenous urografin and corticosteroid and the patients who received oral corticosteroid alone.

Key words: Sudden sensorineural hearing loss, urografin, treatment, corticosteroid

INTRODUCTION

Sudden Sensorineural Hearing Loss (SSNHL) is an uncommon otologic condition that is thought to affect 10 persons per 100,000 annually (Zadeh *et al.*, 2003). SSNHL, which accounts for about 1% of all cases of Sensorineural Hearing Loss (SNHL), is defined as hearing loss greater than 30 dB in at least three subsequent frequencies of sudden onset on audiometric testing or within maximum of 72 h (Penido Nde *et al.*, 2005; Chandrasekhar, 2003). Although extensive evaluations have been done, an etiology can only be found in 10 to 15% of patients (Zadeh *et al.*, 2003). Viral infection of the labyrinth or cochlear nerve, vascular insult, intralabyrinthine membrane rupture, perilymphatic fistula and autoimmunity are a few entities known to cause SSNHL (Yeo *et al.*, 2007). Apart from the high spontaneous recovery rate within two weeks after the onset (30 to 60% of patients), an unknown pathophysiology and the low incidence make the selection of treatment options difficult (Uri *et al.*, 2003).

Therefore, a cocktail therapy (combination therapy) including systemic corticosteroids, vasodilators, Hyper-Baric Oxygen therapy (HBO), diuretics, anticoagulants, carbogen inhalation and vitamins has been frequently used for two or more probable mechanisms, such as cochlear blood flow insufficiency (Kanzaki *et al.*, 2003; Psifidis *et al.*, 2006; Narozny *et al.*, 2004). Nowadays, the confirmed gold standard of treatment of SSNHL is steroid therapy (Chandrasekhar, 2003). However, vasodilator drugs such as urografin (Natrium-Meglumine-diatrizoat) which was first reported in 1976 as a treatment of SSNHL is still used as a therapeutic agent for the treatment of SSNHL in some otological clinics (Noi and Makimoto, 1998).

Not recently performed studies have shown controversial results regarding the therapeutic effects of urografin in the treatment of SSNHL. Therefore, we aimed to find out whether combined treatment of intravenous urografin and corticosteroid has a therapeutic advantage over oral corticosteroid therapy.

MATERIALS AND METHODS

The design of the study was an interventional and controlled clinical trial. Between 2003 and 2005, 60 patients with SSNHL were treated for SSNHL in the Department of Otolaryngology-Head and Neck Surgery at Imam Khomeini Hospital in Tabriz, Iran. Hearing loss was defined as a sensory hearing impairment of at least 30 dB in at least 3 frequencies on audiometric testing. Patients were selected if they were aged over 12 years and had a hearing loss of at least 30 dB in at least 3 frequencies on audiometric testing. Excluded from the study were patients with general medical condition necessitating a specific therapy as well as in compliance to the medications. The study was approved by the Institutional Board Review and Ethics Committee, a section of Research Deputy of Faculty of Medicine at Tabriz University of Medical Sciences, Iran. Audiograms were performed before admission, 1 and 2 weeks and 1 and 2 months after treatment. The Pure-Tone Average (PTA) was calculated as the average of thresholds at 250, 500, 1000, 2000, 4000 and 8000 Hz. The initial pretreatment audiogram was classified into 5 categories depending on the degree of SSNHL: mild (25 to 50 dB), moderate (51 to 70 dB), severe (71 to 90 dB), profound (91 to 110 dB) and total SSNHL (over 110 dB). The definition of a significant hearing improvement was a decrease in pure tone average of 20 dB, regardless of the degree of the initial hearing loss.

A blood sample was obtained to determine the complete blood cell count, the level of glucose, creatinine, electrolytes, cholesterol, triglycerides and thyroid hormones (T_3 , T_4 and thyroid-stimulating hormone). In addition, all the patients both outpatients and inpatients were sent for Magnetic Resonance Imaging (MRI) with gadolinium to detect any pathological finding in cerebellopontine angle such as acoustic neuroma. Concurrent systemic diseases including hypertension and diabetes mellitus were evaluated. The examined parameters included age, time to initial treatment, type of SSNHL (bilateral or unilateral), history of upper respiratory tract infection, history of trauma, family history, severity of hearing loss, previous treatments and presence of associated symptoms with hearing loss such as tinnitus, vertigo and aural fullness.

Patients were assigned into 2 groups. Group U, the study group, included 30 patients who willingly put on bed rest and treated with intravenous urografin 2 mL four times a day (qid) and hydrocortisone 1 mg/kg/day three times a day (tid) on the first day of treatment. The dosage of urografin increased to 5 mL qid by the 2nd day for the maximum of 5 days. Hydrocortisone with the same dosage

continued to be administered for ten days. Group H, the control group, consisted of 30 outpatients who didn't accept to be hospitalized, treated with oral hydrocortisone (1 mg/kg/day tid) for a course of 10 days followed by a slow taper. In addition, oral acyclovir, 1000 mg tid for ten days, was administered to both groups.

Statistical analyses were performed using SPSS version 12. We used various descriptive analytical calculations and both Chi-square and t-test to analyze the data. A two-tailed p-value less than 0.05 was considered statistically significant.

RESULTS

Of the 60 patients, 28 (46.7%) were male and 32 (53.3%) were female. The average age was 36.95 years (range, 18 to 66). No differences were found between groups H and U with regard to the age, gender and severity of hearing loss at the onset of treatment (t-test and Chi-square; $p>0.05$). The right ear was involved in 50% and the left ear in 43.3% and bilateral involvement was in 6.7% of the patients. Gender and laterality of the affected ear were not statistically significant in recovery (Chi-square, $p>0.05$).

According to the pretreatment audiogram, a significant proportion of our sample had mild (20 cases, 32.8%), moderate (16 cases, 26.5%) and severe (13 cases, 21.8%) SSNHL. In contrast, patients with total and profound SSNHL constituted 12.5 and 6.25% of patients, respectively.

Fifty-one (85%) of patients referred to the otological clinics for the appropriate treatment within the first two weeks after the onset of hearing loss, compared to 9 (15%) patients referred after 2 weeks. The duration of onset of hearing loss to the time of treatment varied from one day to 60 days. The average time from onset of symptoms to beginning of therapy was 9 days. A significant association was found between a positive response to the treatment and the early medical consultation (Chi-square, $p<0.05$).

No hearing improvement was observed at the age of 55 and more (Table 1). However, the age group and the response to the treatment were not significantly associated (Chi-square, $p>0.05$).

Table 1: Percentage of patients with hearing improvement according to the age group distributions

Age group	Hearing improvement (%)	No hearing improvement (%)
15-24	15.6	17.8
25-34	21.8	35.7
35-44	43.7	17.8
45-54	15.6	17.8
55-64	0.0	10.7
>65	0.0	3.1

Table 2: Prevalence of the associated pathological conditions in SSNHL at the time of insult

Condition	No. of cases (%)
Hypertension	15.0 (9)
Hypercholesterolemia	5.0 (3)
Diabetes mellitus	3.3 (2)
Depression	3.3 (2)
Collagen vascular diseases	1.7 (1)

SSNHL: Sudden Sensorineural Hearing Loss

Approximately 81.6% of patients declared the presence of the associated symptoms. The most frequent associated symptom was tinnitus, which was present in 90% of patients. Aural fullness and vertigo were far less common and were present in 43 and 42% of patients, respectively. It appeared that patients with vertigo, tinnitus and aural fullness significantly have better possibilities to be improved in hearing (Chi-square, $p < 0.05$).

Hypertension was the most prevalent concurrent pathologic condition (Table 2). Hypertension was associated commonly with SSNHL. Hypercholesterolemia, Diabetes mellitus and depression were also reported in association with SSNHL. The findings revealed no significant association between the associated pathologic conditions and the positive response to the treatment (Chi-square, $p > 0.05$).

Recent upper respiratory infection and smoking were the most common findings of past medical history and social history, respectively (Table 3). Findings revealed that no significant association was found between the trauma to the ear, ototoxic drugs, ear surgery and the positive response to the treatment (Chi-square, $p > 0.05$). On the contrary, the patients having recent upper respiratory tract infection showed better possibilities of hearing improvement rather than the patients having no such history (Chi-square, $p < 0.05$).

The assessment of the routine paraclinical tests demonstrated abnormal findings in nearly 12% of the patients. The analysis of the patients' complete blood cell count revealed an increase in the number of White Blood Cells (WBC) in one-tenth of the patients. According to the findings of MRI, only two patients (3.3%) were diagnosed as having an acoustic neuroma.

In summary, with regard to the improvement of more than 20 dB as a hearing improvement, the overall improvement of both groups was 53.3% (32 of a total of 60 patients). Seventeen (56.6%) of 30 patients treated in the inpatient group who received intravenous urografin and corticosteroid (Group U) had hearing improvement, while half of the outpatient patients received oral corticosteroid (Group H) responded positively to the treatment. The patients of group U did not show significantly positive response to the treatment rather than the patients in group H (Chi-square, $p > 0.05$).

Table 3: Past medical and social history of the patients with SSNHL

Past medical and social history	Yes (%)	No (%)
Trauma	3.3	96.6
Recent upper respiratory tract infection	26.7	73.3
Ototoxic drugs	18.3	81.7
Ear surgery	5.0	95.0
Family history of SSNHL	0.0	100.0
Smoking	20.0	80.0
Alcohol	1.7	98.3

DISCUSSION

The most appropriate therapy for the treatment of SSNHL still remains a matter of controversy due to the unproven origins of sudden sensorineural hearing loss and empirical treatment (Huang *et al.*, 1989). However, most physicians agree that steroid therapy, which is associated with significant complications and side effects, is an accepted treatment choice of SSNHL (Roebuck and Chang, 2006). Hence, a cocktail therapy (combination therapy) aimed at several probable mechanisms of hearing loss has been frequently used including systemic corticosteroids, vasodilators, diuretics, HBO, anticoagulants, carbogen inhalation and vitamins (Kanzaki *et al.*, 2003; Psifidis *et al.*, 2006; Narozny *et al.*, 2004).

In an experimental study by Noi and Makimoto (1998) on the healthy guinea pig inner ear, measurement of cochlear blood flow was performed before and after an infusion of urografin. They found an increased cochlear blood flow following the urografin infusion considering a mechanism of osmolarity gradient (Noi and Makimoto, 1998). This may clarify the mechanism by which urografin leads to the hearing improvement in the patients suffering from SSNHL.

An intravenous administration of urografin leading to hearing improvement was first reported by Morimitsu in 1976 (Yanagihara and Asai, 1993). Nonetheless, the true efficacy of urografin therapy for SSNHL is still unclear. In a study by Strohm (1980), only 16% of patients had a hearing improvement after urografin therapy revealing no particular clinical criteria which indicating a favorable prognosis with urografin-therapy. Unlike this finding, Emmett and Shea (1979) reported 80% of hearing improvement after the administration of urografin. Redleaf *et al.* (1995) reviewed the efficacy of intravenous infusion of the radiopaque contrast for the treatment of SSNHL in the University of Iowa for the last 10 years. It is reported that sixty-four percent of 39 cases showed audiometric improvement in their pure-tone averages after the therapy (Redleaf *et al.*, 1995). Huang *et al.* (1989) analyzed the outcomes of administration of diatrizoate meglumine (urografin), steroids and a vasodilator for the treatment of SSNHL suggesting that none of the above mentioned regimens produced consistently better results than the spontaneous recovery rate of 65%. Likewise,

Wilkins *et al.* (1987) treated 109 SSNHL patients with such a cocktail therapy consisting of dextran, histamine, Hypaque meglumine (urografin), diuretics, steroids, vasodilators and carbogen inhalation. They concluded that there was no difference between the cocktail therapy and spontaneous recovery. The overall hearing improvement rate in the current study was found to be 53.3%. This improvement rate seems to be similar to the high spontaneous recovery rate of 30% to 60% known in the literature (Uri *et al.*, 2003). In the current trial, there was no significant difference in hearing improvement between the hospitalized patients who received intravenous urografin and corticosteroid and the patients managed on outpatient who received oral corticosteroid.

Present findings demonstrated that right ear involved slightly more than the left ear which was incomparable with the prior reports in which left ear was more affected than the right ear (Zadeh *et al.*, 2003; Psifidis *et al.*, 2006; Tiong, 2007). Although the bilateral occurrence is reported rare in SSNHL, bilateral hearing loss was detected in more than one-twentieth of the patients in this study (Oh *et al.*, 2007).

The presence of associated symptoms, such as tinnitus and vertigo, was related with worse prognosis by many authors (Psifidis *et al.*, 2006; Roebuck and Chang, 2006; Stokroos *et al.*, 1998). On the contrary, Uri *et al.* (2003) mentioned tinnitus as an indicator of better prognosis, while no association was found between the incidence of accompanying symptoms and the prognosis in other studies (Zadeh *et al.*, 2003; Penido Nde *et al.*, 2005; Oh *et al.*, 2007). Likewise the prior reports (Uri *et al.*, 2003; Roebuck and Chang, 2006), tinnitus and vertigo were the commonest accompanying symptoms in present study. In addition, all the three associated symptoms (tinnitus, vertigo and aural fullness) presented significant association with better prognosis in present study.

In this study, it is found that acoustic neuroma in 3.3% of the cases which is much less compared with the 13.9% reported by Pensak *et al.* (1985) and the 19% by others (Berg *et al.*, 1986; Yanagihara and Asai, 1993). Furthermore, Chaimoff *et al.* (1999) declared the high rate of acoustic neuroma (47.5%) among the Israeli patients suffering from SSNHL. However, present finding is well compared to the acoustic neuroma prevalence of 0.8-3% among the general population (Art, 2005).

Present data suggest that the sooner treatment is started; the better is the chance for recovery. The overall hearing improvement in pure tone is higher when treatment was started within the first two weeks after the onset of hearing loss compared with the patients referred after 2 weeks from onset of hearing loss. Similar finding has been reported in other studies (Penido Nde *et al.*, 2005; Redleaf *et al.*, 1995; Tiong, 2007).

Severity of hearing loss is one of the main prognostic indicators of hearing improvement in SSNHL (Stokroos *et al.*, 1998). Better prognosis has been found in patients with mild and moderate SSNHL by Psifidis *et al.* (2006), Tiong (2007) and Kanzaki *et al.* (1988). The same observations were found in the results of this study.

Numerous factors such as hypertension, hypercholesterolemia and diabetes mellitus have been considered to be implicated in the pathogenesis of SSNHL (Psifidis *et al.*, 2006). Approximately a quarter of the patients, 14 of 60 patients, had these risk factors in this trial, compared well with 17 to 28% in the report by Hirano *et al.* (1999). However, these were not statistically significant prognostic factors in the current study.

The true efficacy of intravenous urografin therapy for SSNHL is still unclear. This study was a cohort study and was not randomized, so there is a significant possibility of bias. However, the patients in this study were evenly matched in reference to age, sex and pretreatment severity of hearing loss. Furthermore, large sample sizes seem to be needed to achieve statistically significant results in rigorous clinical trials. On the other hand, the efficacy of urografin therapy was assessed in combination with the steroid therapy which is declared to be the first treatment choice. It is obvious that if the intravenous urografin therapy was performed without combination of any other treatments, the findings would be more valuable. However, due to the proven efficacy of steroid therapy as well as research ethics the urografin therapy was not performed solely in present study.

Based on this study, despite the probable ineffectiveness of intravenous urografin injection in the treatment of SSNHL, the urografin administration would be beneficial in patients who have already failed other common and proven therapies such as steroid therapy. Practitioners who use this treatment modality will need to counsel patients of the limited benefit of any treatment available today when initial steroid treatment fails.

CONCLUSION

This study showed no significant indication that intravenous urografin infusion likely provides more benefit compared with oral steroids. We, therefore, can not support a possible role of the intravenous urografin injection as a therapeutic advantage in the treatment of SSNHL.

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