

The Effect of Rivaroxaban in the Complementary Therapy of Sudden Sensorineural Hearing Loss

Mehrdad Rogha¹, Ehsan Moshtaghi²

¹Department of Otorhinolaryngology, Head and Neck Surgery, Isfahan University of Medical Sciences, Isfahan, Iran, ²Department of Otolaryngology, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Due to the importance of sudden sensorineural hearing loss (SSNHL) and the possible role of blood coagulation in its mechanism and the likely therapeutic effect of anticoagulants and also the lack of studies in this field, this study aimed to evaluate the effect of rivaroxaban (RXA) in the treatment of this disease.

Materials and Methods: The present double-blind randomized clinical trial study was performed on 34 patients with SSNHL. Patients were randomly divided into two groups. In the first group, in addition to corticosteroid therapy (CST), RXA 10 mg tablets were used daily for 10 days (RXA group), and in the second group, only CST (CST group) treatment was prescribed. Hearing recovery was then assessed and recorded according to the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) criteria.

Results: This study showed that the grade of hearing recovery in the RXA group (58.8%) was higher than the CST group (47.1%), but this difference was not significant (P value >0.05). Also, RXA treatment increased the odds of hearing recovery, and this difference was not statistically significant (odds ratio (95% confidence interval)(OR (95% CI): 2.327 (0.180–18.082); P value = 0.518). In contrast, delay to treatment, more increased PTA (pure tone average (PTA)), and having vertigo reduced the odds of hearing recovery by 0.138-, 0.019-, and 0.069-fold, respectively (P value <0.05).

Conclusion: According to the results of this study, although the percentage of hearing recovery was higher in the RXA group, in general, the results of the two treatments were not significantly different.

Keywords: Anticoagulants, corticosteroids, hearing loss, rivaroxaban, sensorineural

Address for correspondence: Dr. Ehsan Moshtaghi, Department of Otolaryngology, Isfahan University of Medical Sciences, Isfahan, Iran.

E-mail: ehsan_moshtaghi1989@yahoo.com

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INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) is a rare disease that, although often idiopathic, requires comprehensive clinical and extra-clinical examinations to determine the cause.^[1,2] Despite many advances in otolaryngology techniques, there are still some questions about the definition of the disease, its etiology, incidence, short-term and long-term prognosis, and treatments. The etiology of SSNHL includes circulatory disorders, viral and bacterial infections, immune disorders, ruptured eardrum, vascular disorders, metabolic disorders,

toxins and drugs, tumor lesions, comorbid trauma fistulas, immunological disorders, and neurological problems.^[3-6]

Various protocols such as intravenous and oral steroids, meglumine, antiviral drugs, anticoagulants, vasodilators such as papaverine and nicotinic acid, and anti-inflammatory drugs have been reported to treat SSNHL. Most of these therapies have limited benefits, and the best and most widely accepted treatment protocol is systemic corticosteroids and intratympanic injection; which can reduce cochlear inflammation.^[7-9] However, some patients do not respond to

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corticosteroid therapy (CST), which may be due to the different multifactorial etiologies of disease,^[10] and led to seeking for therapeutic approaches to improve the treatment of this disease.

In this regard, much attention has recently been paid to the theory of impaired blood flow, because the blood supply within the inner ear is its termination and intraosseous position and symptoms of SSNHL develop abruptly.^[11] Disorders of the inner ear microcirculation may also be involved in the pathophysiology of circulatory disorders and the development of SSNHL.

Regarding the condition as a thromboembolic, vasospasm or hemorrhagic event suggests that plasma expanders, anticoagulants, and vasodilators are used as common medical treatment.^[12-14]

The use of anticoagulants due to the possible etiology and role of blood coagulation in this disease has been associated with good therapeutic effects. Some studies have considered the use of heparin or unfractionated heparins (UFHs) as complementary drugs in addition to corticosteroids for hearing recovery, while others have found no significant benefit.^[10,15-17] Rivaroxaban (RXA) is one of the newest anticoagulants that works by binding selectively and reversibly to the clotting factor Xa. It has many advantages over conventional anticoagulants including the lack of need for careful monitoring of the patient by laboratory tests as one of the most important of it is now used as an alternative to warfarin in blood coagulation-induced diseases and also to prevent blood clot formation.^[18,19]

The use of anticoagulants with a selective inhibitory mechanism of factor Xa has revealed beneficial effects in the treatment of SSNHL. In their study, Mora *et al.* showed the effects of enoxaparin on SSNHL recovery.^[20]

Therefore, considering the importance of SSNHL disease and the possible role of blood coagulation in its mechanism and regarding the effectiveness of anticoagulants in previous studies and the lack of studies in this field, this is the first study aimed to evaluate the effect of RXA in treatment of this disease.

MATERIALS AND METHODS

This study is a double-blind randomized clinical trial. The study population includes all patients with SSNHL referred to Isfahan Kashani Hospital from May 2020 to April 2021.

The sample size at a confidence level of 95%, the test power of 80%, and considering the results of previous studies^[16] of the percentage of recovery of patients with SSNHL in two groups with and without receiving anticoagulants equal to 60.9% and 38.9%, respectively, and the error level of 0.46; 34 people were determined (17 people in each group).

SSNHL was defined as a hearing loss of at least 30 dB in three contiguous frequencies, for 72 hours or less. Inclusion criteria included the diagnosis of SSNHL by an otorhinolaryngologist, age over 18 years, body mass index (BMI) between 18 and 30 kg/m², no pregnancy, no underlying diseases such as

coagulation disorders (including the history of thrombosis), kidney diseases, bleeding disorders such as intracranial hemorrhage, mental illness, active gastric ulcer, uncontrolled diabetes, and do not use opioid drugs (such as methadone). In the case of having a systolic and diastolic blood pressure higher than 110 and 180 mmHg, respectively, sensitivity to corticosteroids, history of any previous ear-related disease or surgery, any symptoms of ear inflammation or infection, history of previous hearing loss, Meniere's disease, recent acoustic or pressure trauma, and having an underlying disease that may be the cause of SSNHL (such as trauma, ototoxic medications, and infection), the patients were not included in the study. It should be noted that during the study, if patients had drug side effects (corticosteroids and RXA) or did not continue the treatment completely and were not participated in follow-up were excluded from the study and replaced with another sample [Figure 1].

After approval of the ethics committee of Isfahan University of Medical and obtaining the clinical trial code and filling the written consent by eligible patients, demographic and clinical information including age, sex, SSNHL-affected ear, presence of vertigo, and interval from symptom onset to treatment were recorded. Then, the patients were divided into two groups using random allocation software.

Then, the patients underwent ears' examination and complete blood test (CBC) and kidney function were performed for all of them to ensure their health.

If patients' glomerular filtration rate (GFR) was above 30 ml/min and platelet levels, prothrombin time (PT), and activated partial thromboplastin time (APTT) were normal, they were eligible for RXA treatment.^[19,21]

All patients in both groups were treated with daily prednisolone 1 mg/kg tablet for the first 10 days of the disease and every other day intratympanic injection of dexamethasone (5 mg/mL up to five doses).^[22,23] If patients had a partial response to corticosteroids after 10 days (based on audiometric tests), treatment with prednisolone tablets was continued for another 10 days until more recovery based on audiometric tests.^[24]

In the first group, in addition to CST, patients received 10 mg RXA tablets daily for 10 days (RXA group). In the second group, patients were treated only with CST and received placebo tablets with the same protocol (CST group) to match it in the two groups.

To observe the blinding conditions, a placebo was previously prepared by a pharmacist similar to RXA tablets in terms of shape, size, and color. He also prescribed them without knowing the type of medicine. The patients' assessor was not aware of the intervention in each group until the end of the study. Also, the statistician had no knowledge about the intervention in each group until the end of the data analysis.

At the end of the treatment period, all patients underwent SSNHL recovery measurement using a scale developed by

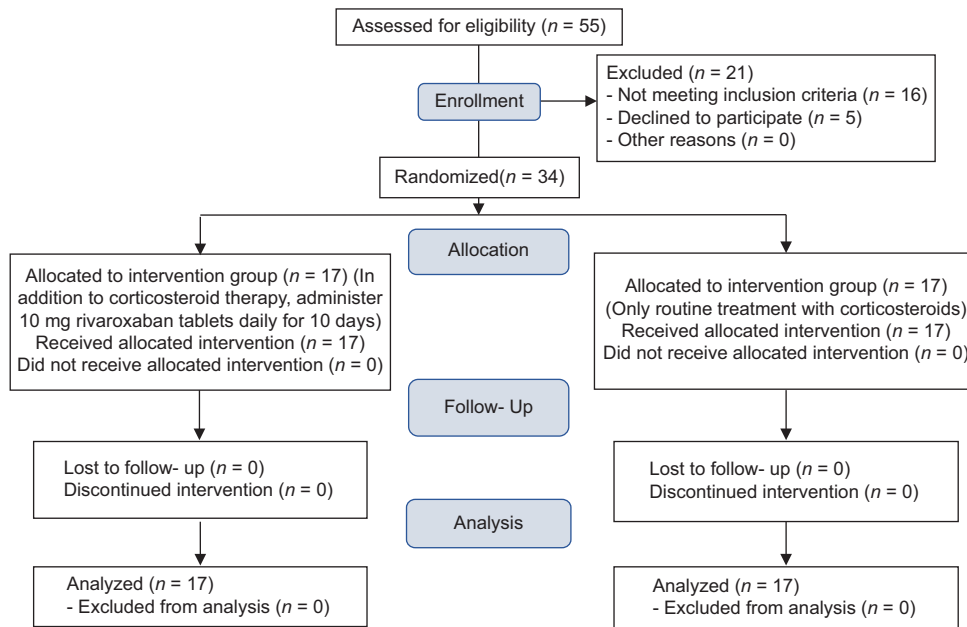


Figure 1: Consort flowchart of patients

the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS), more increased pure tone average (PTA), and word recognition score (WRS)^[25] [Table 1].

Statistical analysis

Finally, the collected information was entered into Statistical Package for the Social Sciences (SPSS) software (ver. 25) and the data were reported as mean ± standard deviation (SD) or frequency (percentage).

Fisher’s exact and Chi-square tests were used to compare the frequency distribution of qualitative data between the two groups, and independent-samples *t*-test was used to compare the mean of quantitative data. Logistic regression analysis was also used to assess the factors associated with the percentage of hearing recovery immediately after completion of treatment (grades I and II compared with grades III and IV) in patients. In this regard, odd ratio (OR) and confidence interval (CI) were reported. In all analyses, a significance level of less than 0.05 was considered.

RESULTS

In this study, the CST group consisted of seven (41.2%) males and 10 (58.8%) females with a mean age of 47.88 ± 15.58 years, and the RXA group consisted of five (29.4%) males and 12 (70.6%) females with a mean age of 48.18 ± 13.95 years (*P*-value > 0.05) [Table 2].

The frequency distribution of grade of hearing recovery (according to AAO-HNS criteria) was not significantly different between the two groups (*P*-value >0.05) [Table 3 and Figure 2].

According to the results of logistic regression analysis, although RXA treatment increased the odds of hearing recovery, this difference was not statistically significant (OR (95% (CI):

Table 1: American Academy of Otolaryngology–Head and Neck Surgery criteria for hearing recovery in idiopathic sudden sensorineural hearing loss

Grade	Type	Hearing recovery
I	Complete recovery	PTA within 10 dB of the unaffected ear and WRS within 5%–10% of the unaffected ear
II	Partial recovery, serviceable hearing	≥10 dB improvement in PTA, PTA ≤50 dB, and WRS ≥50%
III	Partial recovery, non-serviceable hearing	≥10 dB improvement in PTA, PTA >50 dB, or WRS <50%
IV	No recovery	<10 dB improvement in PTA

2.327 (0.180–18.082); *P*-value = 0.518). It has also been shown that the relationship between age and sex with hearing recovery was not significant (*P*-value > 0.05), but delay to treatment, PTA (high severity of preliminary hearing loss), and having vertigo significantly reduced the odds of hearing recovery by 0.138-, 0.019-, and 0.069-fold, respectively (*P*-value <0.05) [Table 4].

DISCUSSION

In the present study, more than 50% of patients with SSNHL were female with a mean age of above 45 years. Mattox reported the age peak of patients in the sixth decade and reported an equal proportion of involvement between the sexes.^[26] They also reported the onset of symptoms in the early morning and balance disorders and vertigo as the most common symptoms.^[27]

Our study on the therapeutic effects of SSNHL recovery showed that both CST alone and CST with RXA were associated with significant improvement. In the CST and RXA groups, they

Table 2: Demographic and clinical characteristics of patients in the two groups

Characteristics	CST group (n=17)	RXA group (n=17)	P
Sex			
Male	7 (41.2%)	5 (29.4%)	0.473*
Female	10 (58.8%)	12 (70.6%)	
Age, year	47.88±15.58	48.18±13.95	0.954**
Vertigo	6 (35.3%)	7 (41.2%)	0.724*
Delay to treatment, day	2.50±1.19	2.84±1.05	0.376**
PTA (mean threshold), dB	57.41±19.16	48.41±22.42	0.217**

CST=corticosteroid therapy, RXA=rivaroxaban, PTA=pure tone average. *Chi-square test; ** independent-sample t-test

Table 3: Comparison of the grade of hearing recovery between the two groups

Grade	CST group (n=17)	RXA group (n=17)	P
I	8 (47.1%)	10 (58.8%)	0.732*
II	1 (5.9%)	2 (11.8%)	0.545**
III	3 (17.6%)	1 (5.9%)	0.287**
IV	5 (29.4%)	4 (23.5%)	0.697**
Improvement†	12 (70.6%)	13 (76.5%)	0.697*

CST=corticosteroid therapy, RXA=rivaroxaban. †Grades I, II, III; *Chi-Square test; **Fisher's exact test

Table 4: The results of logistic regression for evaluation of factors related to hearing recovery

Variables	OR	95% CI	P
Intervention (RXA)	2.327	0.180-18.082	0.518
Sex (female)	1.157	0.072-8.601	0.918
Age (>40 years)	0.619	0.022-7.072	0.777
Delay to treatment	0.138	0.025-0.745	0.021
PTA (<70 dB)	0.019	0.001-0.254	0.002
Vertigo	0.069	0.005-0.943	0.045

RXA=rivaroxaban, PTA=pure tone audiogram, OR=odds ratio

recovered by 70.6% and 76.5%, respectively. Although the recovery rate was slightly higher in the group of combined treatment with RXA (as a family of anticoagulants), the logistic regression results confirmed that hearing recovery in the RXA group was 2.327-fold higher than in the CST group. However, this relation was not considered as significant.

In this regard, it can be said that steroids have effects such as ionic homeostasis, inhibition of apoptosis, reduction in local pro-inflammatory cytokines, antioxidant activity, and increase in cochlear blood flow (promotion of cochlear blood flow) in the inner ear.^[28] In addition, SSHL may be viral and the related damage to the ear is rather completed quickly, and these inflammatory effects and other effects of the virus are successfully treated with steroids. Therefore, significant improvement in the CST group was normal.

However, the use of heparin and stellate ganglion block is based on the suggestion that impairments in the inner ear

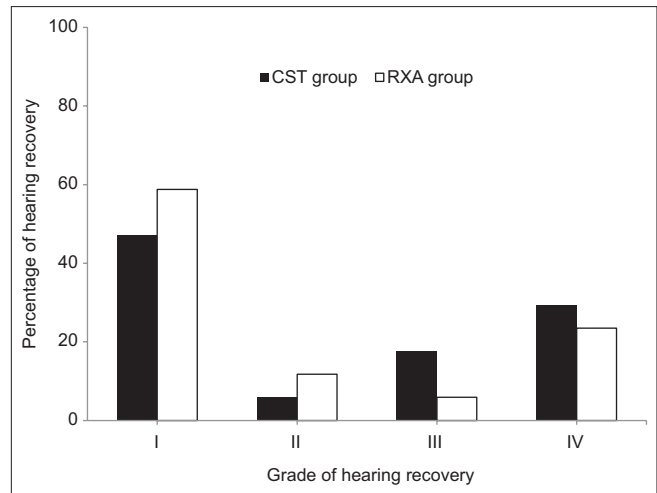


Figure 2: Frequency distribution of grade of hearing recovery between the two groups

microcirculation may be involved in the pathophysiology of SSNHL.^[15,29] Thromboembolism or vasospasm has been suggested as cause of blood flow disturbance based on the etiology of SSNHL, because the blood supply within the inner ear is its termination and intrasosseous position and symptoms of SSNHL develop suddenly.^[11,30]

In the study, Kim *et al.* also used heparin as an adjunct to corticosteroids and showed that this treatment was associated with further improvement.^[10] They also suggested that anticoagulants could have beneficial effects on patients with SSNHL. Mora *et al.* in Italy also evaluated the effectiveness of enoxaparin treatment in patients with SSNHL and reported acceptable therapeutic effects.^[20]

Although these results are inconsistent with the present study and the use of RXA as a complementary treatment did not differentiate in recovery, the percentage of improvement in SSNHL was higher in this group. Perhaps the reason for the lack of significant differences was the small sample size or short-term follow-up.

According to previous studies, low molecular weight heparin can prevent venous thrombosis and reduce complications compared with general heparin.^[31]

RXA is one of the anticoagulants with a selective inhibitory mechanism of factor Xa with renal excretion (about 33%). Optimal pharmacokinetics (rapid onset of action), very few drug interactions, and no need for anticoagulant monitoring are some of the advantages of this drug. In addition, many meta-analytic studies have identified RXA as an effective anticoagulant like enoxaparin.^[32,33] Yue *et al.* used liveracine as low molecular weight heparin and routine steroid therapy. They reported that hearing improvement in heparin-treated patients was significantly more than in conventionally treated patients.^[15]

Therefore, perhaps the rationality of this study can be considered the use of a less dangerous drug with a similar

effect to heparin. However, further studies are needed to confirm its therapeutic effect and generalize its results to the larger community.

Finally, a review of other factors related to hearing recovery found that although women were more likely to recover than men and it was less likely to be higher age (over 40), these factors were not significant. The only factors of late treatment, severity of hearing loss, and vertigo were significantly associated with hearing recovery. So that in the case of vertigo and more severe hearing loss or longer interval from onset to treatment, there are less odds of recovery.

Consistent with the present study, Zadeh *et al.* reported that there was more recovery in the hearing of patients who were referred within the first three days of symptom onset than those who refer later.^[34] Another study showed that 100% of patients treated with steroids recovered within seven days.^[35] The time of starting treatment is essential in terms of response rate. The earlier treatment is started, the greater the response rate to treatment.

In addition, the results of the study by Hashemi *et al.* showed that patients with no vertigo had an equal improvement with the presence of vertigo. In addition, they showed that patients with hearing loss of more than 90 dB had a recovery of 60%, and it was 75% in the patients with hearing loss of less than 90 dB. As a result, they stated that the severity of hearing loss is one of the prognostic factors, and the more the severity of hearing loss, the less the prognosis.^[36]

Park *et al.* showed that although combination therapy with systemic steroids, an antiviral agent, anticoagulants, and stellate ganglion block increased the odds of hearing recovery, this effect was not significant. In addition, they reported that age (less than 40 years) and shorter onset time (less than one week) increased the odds of recovery. The severity of hearing loss at the time of enrollment would decrease the odds of recovery.^[16]

Therefore, it is worth mentioning that in addition to the treatment protocol, the patient's condition can also be effective in the success of the selected treatment. For the first time in our study, RXA was used as a complementary treatment of SSNHL; it is suggested that more studies with larger sample sizes be performed to achieve more definitive and increase the generalizability of a study's results.

CONCLUSION

According to the present study results, treatment with corticosteroids alone and corticosteroids with RXA had a significant effect on hearing recovery. Although the percentage of complete hearing recovery in the RXA group was higher than in the corticosteroid group alone, and the odds of recovery increased, this difference was not significant. In addition, delay in treatment, high severity of preliminary hearing loss, and having vertigo were among the factors that impaired SSNHL recovery and response to treatment.

Ethics approval and consent to participate

This study has been approved by ethics committee of Isfahan University of Medical Sciences (approval code: IR.MUI.MED.REC.1399.631) and obtained the clinical trial code (code: IRCT20110603006699N5). The written consent has been filled by eligible patients and they were informed about the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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