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Sodium Enoxaparin and Venovenous Hemofiltration in Treating Sudden Sensorineural Hearing Loss and Tinnitus

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Abstract: Sudden sensorineural hearing loss (SSNHL) constitutes a considerable diagnostic challenge because it may be caused by many diverse conditions that may be difficult to recognize. No definitive treatment for SSNHL is universally accepted; the goal of this study was to evaluate the efficacy of sodium enoxaparin associated with venovenous hemofiltration in a therapeutic regimen. We treated 20 patients divided randomly into two numerically equal groups (A and B). Group A patients underwent this therapeutic protocol: Hemofiltration was performed at the first and last day of the protocol while, beginning on the second day of the protocol, sodium enoxaparin was administered subcutaneously at a dose of 4,000 IU once a day for 10 days. After the first hemofiltration, all the patients with complete auditory recovery were discharged without receiving the treatment with sodium enoxaparin. Group B patients received conventional therapy (cortisone, vasoactive agents, and vitamin complexes) administered in physiological solution intravenously twice daily for 10 days. In our randomized, controlled trial, treated patients in group A showed more improvement than did those in group B.

Key Words: sodium enoxaparin; sudden sensorineural hearing loss; tinnitus; venovenous hemofiltration

Sudden sensorineural hearing loss (SSNHL) is a symptom of cochlear injury. It is characterized by sudden onset, and it may be accompanied by vertigo and tinnitus. Many potential causes can trigger SSNHL but, despite extensive evaluation, the majority of cases elude definitive diagnosis and therefore remain idiopathic.

Disturbances of microcirculation, autoimmune pathology, and viral infection are among the most likely causes of SSNHL. Hypercholesterolemia, hyperfibrinogenemia, and increased platelet aggregation are frequently observed in patients with SSNHL. Several authors highlighted the acute reduction of plasma fibrinogen and serum low-density lipoproteins as positively influencing hemorheology and endothelial function, and this finding might thus lead to an effective therapy for SSNHL [1–5].

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The therapeutic approaches normally used for this pathological condition include the systemic and local administration of cortisone, vasoactive agents, anticoagulants, vitamin complexes, and plasmapheresis. These drugs can be effective in reversing such hearing loss, although at the cost of occasionally severe side effects [6,7]. This study aimed to assess the effect of sodium enoxaparin associated with an extracorporeal procedure of venovenous hemofiltration (VVHF) on the recovery of hearing in patients affected by SSNHL.

PATIENTS AND METHODS

We analyzed patients who had suffered from SSNHL and tinnitus. Patients were selected on the basis of the following inclusion criteria: They were between 18 and 65 years of age; presented with an SSNHL of at least 30 dB of audibility threshold involving at least three contiguous audiometric frequencies occurring within 3 days or fewer; and provided informed consent.

We did not accept for treatment patients with (1) a history of thrombocytopenia after heparin treatment;

(2) hemorrhagic manifestations or tendencies due to hemostasis disorders that are not heparin-dependent or related to consumption coagulopathy; (3) organic injuries at risk of bleeding, renal failure, or acute infectious endocarditis; (4) hemorrhagic cerebrovascular events; (5) allergy to enoxaparin; (6) concurrent use of ticlopidine, salicylate, or nonsteroidal antiinflammatory drugs with sodium enoxaparin; (7) association with platelet anticoagulants (dipyridamole, sulfinpyrazone, etc.); or infectious diseases (hepatitis, HIV, and syphilis). All patients were hospitalized during the protocol.

We analyzed 20 patients divided randomly into two numerically equal groups (A and B). Group A patients underwent a therapeutic protocol of hemofiltration performed on the first and last days of the protocol and, beginning on the second day of the protocol, sodium enoxaparin administered subcutaneously at a dose of 4,000 IU once a day for 10 days. After the first hemofiltration, all the patients with complete auditory recovery were discharged without receiving the treatment with sodium enoxaparin [8,9].

Group B patients received conventional therapy (cortisone, vasoactive agents, and vitamin complexes) administered intravenously in a physiological solution (100 ml) twice daily for 10 days. At the beginning and at the end of the therapy and after 1 month after discharge, all patients underwent the following instrumental examinations: electrocardiography, laboratory tests, and liminal tonal audiometry; tympanometry; otoacoustic emissions; otoacoustic products of distortion; and subjective assessment of symptoms on a scale from 0 to 7 (with 0 indicating absence of tinnitus and 7 denoting incapacitating tinnitus).

The laboratory screening tests included erythrocyte sedimentation rate (ERS); C-reactive protein (CRP); prothrombin and fibrinogen levels; lipoprotein α; rheumatoid factors; antinuclear and antithyroglobulin antibodies; anti-double-stranded DNA antibodies; levels of antinuclear antibodies (ANA); circulating immunoglobulins, classes G, M, and A (IgG, IgM, IgA); and complement levels (CH50, C3, C4), as shown in Table 1.

Daily during the treatment, all patients underwent the following instrumental examinations: liminal tonal audiometry; otoacoustic emissions; and otoacoustic products of distortion. We performed blood tests and instrumental examinations preceding the first treatment, after the first day of the protocol, on the day of discharge, and 1 month after the end of treatment.

RESULTS

At discharge, seven patients (70%) treated with sodium enoxaparin and VVHF (group A) presented with a subjective abatement of tinnitus. The mean value of scores on the subjective symptom scale fell from 4.8 (before the therapy) to 3.4 (at the end of the protocol); in the patients with hearing improvement (n = 9), the scores fell from 4.7 (before the therapy) to 3.2 (at the end of the therapy). In group B, eight patients (80%) treated with conventional therapy presented a subjective abatement of tinnitus scores: The mean value of the subjective symptom scale fell from 4.9 (before the therapy) to 3.5 (at the end of the protocol); in the patients with hearing improvement (n = 8), the scores fell from 4.7 (before the therapy) to 3.3 (at the end of the therapy). The last checkup confirmed these data in the two groups.

In group A, four patients (40%) showed a complete auditory recovery after the first VVHF, and these patients had no particular characteristic that would segregate them as a subgroup. Five patients (50%) had hear-

Table 1. Laboratory Screening Test Results of Both Groups

	Group A (n = 5)		Group B (n = 6)	
Test	**t = 1**	**t = 2**	**t = 1**	**t = 2**
ESR (mm/hr)	68.1 ± 2.44	8.4 ± 2.34	70.7 ± 2.13	15.6 ± 2.64
CRP (mg/liter)	9.2	<3.2	10.4	<3.2
Prothrombin (sec)	98.6 ± 0.77	98.8 ± 0.69	98.4 ± 0.75	98.7 ± 0.69
Fibrinogen (mg/dl)	310.3 ± 3.44	288.5 ± 3.78	319.5 ± 4.12	307.6 ± 2.44
Lipoprotein α (mg/dl)	221.3 ± 2.40	174.3 ± 2.17	218.2 ± 3.28	211.3 ± 2.04
Rheumatoid factors (IU)	193.6 ± 1.74	25.3 ± 2.09	201.2 ± 2.77	34.6 ± 1.88
Antithyroglobulin antibodies (IU/ml)	178.2 ± 1.23	50.8 ± 1.04	183.1 ± 1.44	124.4 ± 1.29
IgG (mg/dl)	1477.4 ± 5.36	1048.6 ± 5.59	1493.7 ± 5.49	1150.4 ± 5.66
IgM (mg/dl)	272.4 ± 2.48	105.0 ± 2.51	271.3 ± 2.44	201.3 ± 2.34
IgA (mg/dl)	349.4 ± 1.49	174.3 ± 1.23	357.5 ± 2.26	277.7 ± 2.04
CH50 (units)	165.4 ± 0.77	159.2 ± 0.83	162.7 ± 0.91	163.5 ± 0.87
C3 (mg/dl)	188.7 ± 1.88	159.9 ± 1.44	188.1 ± 1.63	174.8 ± 1.33
C4 (mg/dl)	49.2 ± 0.74	24.3 ± 0.84	50.7 ± 0.94	43.9 ± 0.93

CH50, C3, C4 = complement components; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IgG, IgM, IgA = immunoglobulins G, M, A, respectively; t = 1 = mean levels before the protocol ± standard error of the mean; t = 2 = mean levels at the end of the protocol ± standard error of the mean.

ing improvement at the end of therapy; these patients presented with blood immune parameter alterations at the beginning of the treatment. Hearing was unchanged in only one patient, this patient having no particular blood tests results that warranted consideration as a subgroup. Mean hearing improvement for these patients ranged from 22.2 to 24.9 dB across the 500- to 4,000-Hz range examined. These data were confirmed 1 month after discharge. The characteristics of these patients' blood tests are summarized in Table 1.

In group B, hearing improved in eight patients (80%); six of these presented blood immune parameter alterations at the beginning of the protocol. Hearing was unchanged in two patients (20%), and these patients had no particular blood tests results that would qualify them as a subgroup. Mean hearing improvement for these patients ranged from 20.4 to 24.2 dB across the 500- to 4,000-Hz range examined. These data were confirmed at the last control (1 month after discharge). The characteristics of these patients' blood tests are summarized in Table 1.

In all the patients (group A and group B) with hearing improvement, the evoked otoacoustic emissions revealed an improvement from "fail" to "pass," and otoacoustic distortion products, which were previously absent, were evoked at frequencies of the tonal field normally examined.

Comparison of groups was made by the unpaired *t*-test, and correlations were analyzed by regression analysis; probability values at less than .05 were regarded as significant. Comparisons of groups also were made for repeated measures by analysis of variance. No patient experienced side effects from this treatment.

DISCUSSION

SSNHL is still a diagnostic and therapeutic dilemma, and predicting recovery from it is very difficult. Different factors may influence a prognosis (e.g., severity of hearing loss, duration of symptoms before treatment, presence of vertigo, type of audiogram, and age of patients) [10]. This study aimed to evaluate possible hearing benefits of sodium enoxaparin and VVHF in the treatment of SSNHL. Sodium enoxaparin is a particular kind of heparin with a low molecular weight (LMWH) and is endowed with a high antithrombotic activity. The drug exerts its effects essentially on capillary blood viscosity, erythrocyte deformability, thrombocyte aggregation, and antiphospholipid antibody activity and shows an antiinflammatory action in subcutaneous administration [11].

The various modalities of extracorporeal plasma therapy have found widespread use and acceptance over the last decade; VVHF selectively eliminates fibrinogen, low-density lipoprotein, cholesterol, triglycerides, and complement from the blood plasma by means of extracorporeal circulation. The reduction of these macromolecules immediately improves the hemorheologic situation and leads to a significant decrease of plasma viscosity and red cell transmission time, which correlates to the deformation of red blood cells. Reestablishment of vascular endothelial function and improved blood rheology may be the underlying cause of better results in patients treated with VVHF (see Table 1) [12,13].

The pathogenesis of SSNHL is probably multifactorial: Immune mechanisms may be the primary and triggering stimuli, whereas such risk factors as hyperlipoproteinemia or lipoprotein elevation may accelerate the progression of the disease. In immune-mediated hearing loss, the hyperviscosity is determined by the development of immune complexes; such complexes are usually caused by binding of polyclonal IgG to monoclonal IgM. The significant reduction of C3, C4, IgG, and IgM blood levels leads to a significant improvement of capillary blood flow and to a drop in the rheumatoid factors. In agreement with those from other authors, our results suggest that the removal of immune complexes may be remarkably enhanced using VVHF with an appropriate filter and show that VVHF may be beneficial as adjunctive therapy for maintaining hearing in some patients with immune-mediated hearing loss (see Table 1) [14].

The possibility that viral infections may be associated with viral cochleitis and SSNHL should be recognized. This association may even account for some "idiopathic" cases of SSNHL. In group A patients, the final lower complement, immunoglobulin, CRP, and ERS levels highlight the effectiveness of the association between sodium enoxaparin and VVHF. Because many cytokines, growth factors, and complements are known to interact with LMWH, the reduction of inflammatory responses by sodium enoxaparin is likely to depend on this heparin-binding nature of the inflammatory cytokines [12,14,15].

Heparin-induced extracorporeal LDL precipitation (HELP) apheresis is among the most widely used LDL apheresis methods. In this apheresis, the low-density lipoprotein precipitation works on the principle of specific precipitation of LDL cholesterol, lipoprotein α, and fibrinogen at an acidic pH in the presence of heparin (heparin-induced extracorporeal LDL precipitation = HELP procedure). Double filtration is necessary to avoid possible rebound effects of the blood parameters in the case of immune-mediated hearing loss [7,12].

The contemporary use of LMWH considerably improves the rate of hearing improvement in SSNHL patients without such potential risk as unfractionated hep-

arins (see Table 1). The incidence of adverse effects (catheter dysfunction, local or systemic infection, and thrombosis) directly attributable to VVHF does not exceed 1–2%: the use of sodium enoxaparin appears useful in reducing these risks. The only possible side effects are slight hemorrhaging, usually due to preexisting risk factors; thrombocytopenia; sometimes serious cutaneous necrosis near the injection site; cutaneous or systemic allergy; and increased transaminase levels [7,9,11].

CONCLUSIONS

VVHF may be beneficial as an adjunctive therapy for maintaining hearing in patients with SSNHL, and our data highlight the possibility of long-term hearing benefits from VVHF in presumed immune-mediated inner-ear disease. Cost and reimbursement factors are major obstacles to the use of this therapy. Nonetheless, the overall success rate and individual patient results warrant further study of VVHF in the treatment of SSNHL.

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