Fibrinogen and LDL apheresis in treatment of sudden hearing loss: a randomised multicentre trial

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Summary

Background Sudden sensorineural hearing loss (SSHL) is thought to have many different origins, including disturbances of microcirculation, autoimmune pathology, and viral infection. We aimed to determine whether acute reduction of plasma fibrinogen and serum LDL is effective for treatment of SSHL of suspected vascular origin.

Methods Between January, 2000, and June, 2001, we recruited 201 patients with sudden hearing loss from four otorhinolaryngology clinics in Germany. Patients were randomly allocated to single fibrinogen/LDL apheresis or standard treatment (250 mg prednisolone reduced by 25 mg per day, 500 mL 6% hydroxyethyl starch, 400 mg pentoxifylline per day). The primary outcome was recovery of hearing as measured by pure-tone audiometry 48 h after the start of treatment. Secondary outcomes were recovery of hearing 6 weeks after treatment, improvement of speech audiometry, tinnitus, and frequency of side-effects. Analysis was done per protocol.

Findings Overall improvement of pure-tone thresholds was slightly but not significantly better in patients given apheresis than in those given standard treatment (difference 7·7, 95% CI –8·2 to 23·6). However, the mean sound level at which 50% of recorded digits were recognised was significantly lower after 48 h in the apheresis group (21·6 dB, SD 20·8) than in the standard group (29·3 dB, 29·4; p=0·034). After 6 weeks, the mean 50% speech perception was at 13·6 dB (SD 14·3) in the apheresis group and at 20·8 dB (25·4) in those on standard treatment (p=0·059). At 48 h, in patients with plasma fibrinogen concentrations of more than 295 mg/dL, speech perception was improved much more in those on apheresis (15·3 dB, 17·3) than in those on standard treatment (6·1 dB, 10·4; p=0·005).

Interpretation A single fibrinogen/LDL apheresis lasting for 2 h could be used as an alternative to conventional infusion treatment and prednisolone for 10 days. Patients with a plasma fibrinogen of more than 8·68 μmol/L improve much better when treated with apheresis, especially if serum LDL concentrations are also raised.

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Introduction

Incidence of sudden sensorineural hearing loss (SSHL) in developed countries is estimated to be about 20 cases per 100 000 inhabitants per year,[1] but could be much higher (W Elies, HNO Nachrichten, personal communication). Single-sided hearing impairment can severely impair the speech perception of an individual in a noisy surrounding. Although at least part remission is frequent, hearing loss and tinnitus are common sequelae. In Germany, 8% of the population are thought to have chronic tinnitus, 15% of whom have severe impairment from permanent loss of silence. Yet, few clinical studies have been done on SSHL, and the evidence derived from these studies is limited by the small number of participants. Reasons for this are that most centres do not see enough early cases because they are not treated at all, or because they are mainly treated on an outpatient basis by private practitioners. Furthermore, SSHL is unlikely to result from a single cause. The disease has been attributed to disturbance of cochlear microcirculation, viral infection, an immunopathological process, or an overlap of such mechanisms.[1] Up to now, there is no scientific basis for formation of subgroups with different causes and requirements for adequate SSHL treatment strategies.

SSHL is characterised by sudden-onset hearing loss that can resolve within hours or days, and unilateral symptoms indicate vascular disturbance. Cochlear microcirculation is sensitive to changes in animals, and even limited impairment of perfusion leads to immediate loss of function of the organ of Corti.[2] Blood supply of the inner ear is provided by the labyrinthic artery which is a functional end artery, and thus, shunting from the periphery cannot compensate for disturbances of regional blood flow. Furthermore, the labyrinthic artery supplies the vestibulocochlearic artery and the spiralis modiolic artery, which supply the cochlea and the vestibular organ. Therefore, that 30% of patients also have vestibular symptoms lends support to the hypothesis that SSHL has a vascular pathogenesis. SSHL is usually treated with plasma expanders such as hydroxyethyl starch or dextrane, although Probst and colleagues[3] showed that dextranes were no more effective than saline infusions in treatment of this disease. In a pilot study[4] of patients with SSHL and hyperfibrinogenaemia or hypercholesterolaemia, hearing was regained in more patients given LDL-apheresis than in those given prednisolone, dextrane, and pentoxifylline. Fibrinogen/LDL apheresis greatly reduces the concentration of plasma fibrinogen thus leading to substantially improved blood flow without haemodilution.[5] Furthermore, the reduction of serum cholesterol increases release of nitric oxide, the main mediator of the diameter of the blood vessels in the cochlea, and could therefore re-establish autoregulation of cochlear blood flow.

In developed countries, steroids are a popular treatment for SSHL, even though the mechanism of action of these drugs is not clearly understood.[6] Histopathological analysis of temporal bones in patients

who died shortly after sudden hearing loss suggests that the hearing loss was caused by a virus, and corticosteroids could be effective because of their anti-inflammatory action. Use of steroids greatly improved recovery of hearing in patients with SSHL.[7–9] In patients with chronic sensorineural hearing loss, circulating antibodies to a 68-kDa constituent of bovine inner ear extract have been detected, which are strongly correlated with responses to corticosteroid treatment.[10] Thus, the beneficial effect of steroids in SSHL could be due to immunosuppression.

We aimed to assess whether the therapeutic effect of a single fibrinogen/LDL apheresis, an exclusively vascular treatment strategy (acute and drastic reduction of plasma fibrinogen, lipoprotein, and LDL cholesterol), is as effective or more effective than an anti-inflammatory immunosuppressant therapy. We also aimed to see whether patients who benefit from fibrinogen/LDL apheresis have different characteristics to those who benefit from prednisolone and hydroxyethyl starch.

Methods

Participants

We included patients if they were aged 18–80 years and had sudden-onset sensorineural hearing loss in one ear only that started 7 days or less before the start of treatment. Hearing loss had to extend to more than 15 dB in three frequencies (range 0·125–8·000 kHz) compared with the healthy ear or, if available, compared with a pre-existing audiogram. We excluded patients if they had previously been treated for their hearing loss or had subacute hearing loss, conductive hearing loss, Menière's disease, other disorders of the inner ear with a known cause, retrocochlear or middle-ear disease, or psychogenic hearing loss. We also excluded patients if they had a clotting disorder, malignant disease, heart failure (NYHA III or IV), arrythmia, haemodialysis, hepatitis B or C, HIV-1, HIV-2, or dementia. Diagnosis was made from a general otolaryngological examination, determination of laboratory values, and audiometric testing.

Settings and locations

Patients were attending a university clinic of otorhinolaryngology at Munich, Berlin, Hamburg, or Bochum. We recruited patients between January, 2000, and July, 2001. The study was done in accordance with the Declaration of Helsinki, and the study protocol was approved by the local ethics committee of all participating hospitals. All patients provided written informed consent. An independent office (MWI, Munich, FRG) monitored and analysed the data. A safety board of four experts was formed to assess serious adverse events.

	Fibrinogen/LDL apheresis (n=134)	Standard treatment (n=67)
Characteristics		
Age (years)	49·7 (13·5)	52·2 (13·9)
Body-mass index (kg/m²)	25·7 (3·8)	26·0 (4·1)
Blood pressure (mm Hg)		
Systolic	129·0 (14·0)	134·0 (18·4)
Diastolic	79·8 (8·4)	80·6 (9·1)
Smokers	28 (21%)	15 (22%)
History of coexisting disease		
Hyperlipidaemia	14 (10%)	4 (6%)
Diabetes	6 (5%)	3 (5%)
Coronary artery disease	2 (2%)	0

Values are mean (SD) or number of patients (%).

Table 1: **Patients' baseline characteristics**

We randomly assigned patients in a two to one ratio to single fibrinogen/LDL apheresis (B Braun, Melsungen, Germany) or 10 days of standard therapy, which was based on prednisolone and infusions with plasma expander. Centres were provided with sealed cards with the randomisation codes to assign the patients to one of the two treatment protocols. The randomisation code was developed with a computerised random number generator to select random permuted blocks of nine. Three patients were assigned to standard therapy for every six assigned to fibrinogen/LDL apheresis. An independent medical doctor from the ear, nose, and throat clinic obtained informed consent from and enrolled the patients, and ascertained the individual treatment.

Because of the substantial difference of the two treatment groups, we could not blind the patients or investigators. However, the audiologists who did the hearing tests were unaware of the randomisation status of the participants.

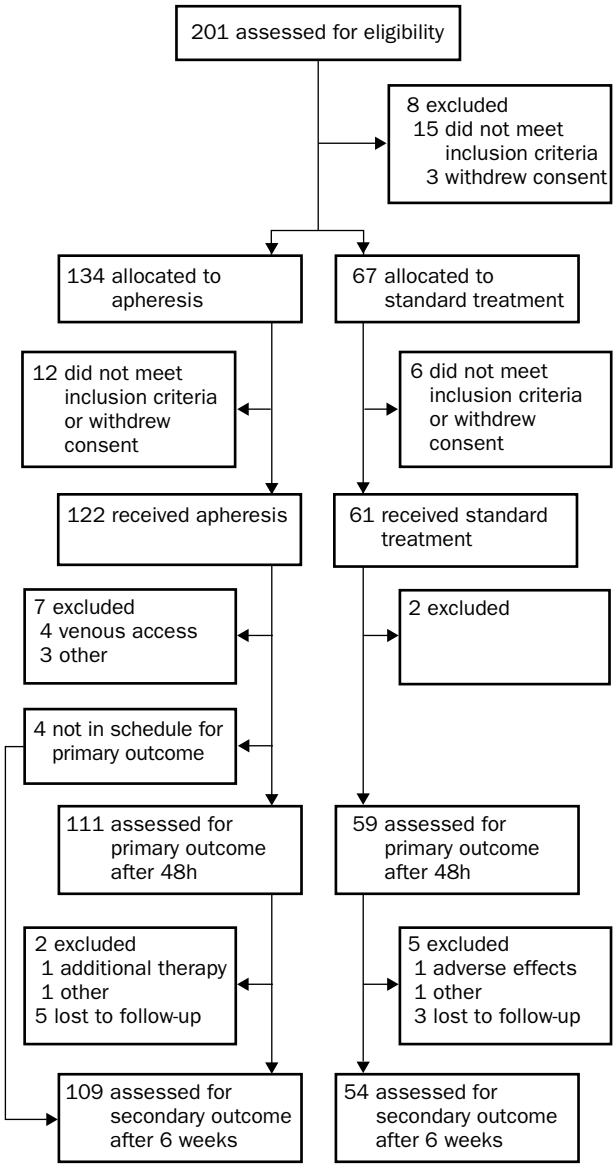

Figure 1: **Trial profile**

	Before treatment		After 48 h		After 6 weeks	
	Apheresis	Standard	Apheresis	Standard	Apheresis	Standard
Sodium (mmol/L)	140 (3)	140 (3·4)	141 (3)	142 (3·4)	140 (2·4)	141 (2·4)
Potassium (mmol/L)	4·2 (0·4)	4·2 (0·4)	4·3 (0·6)	3·8 (0·4)	4·3 (0·4)	4·3 (0·3)
Calcium (mmol/L)	2·4 (0·1)	2·4 (0·1)	2·4 (0·1)	2·3 (0·1)	2·4 (0·2)	2·4 (0·1)
Uric acid (μmol/L)	321 (83)	333 (89)	315 (77)	286 (83)	333 (77·3)	345 (89)
Glucose (mmol/L)	5·94 (2·22)	5·78 (1·24)	5·67 (2·49)	6·34 (2·88)	5·56 (2·00)	6·22 (2·15)
Creatinine (μmol/L)	79·56 (17·68)	79·56 (17·68)	79·56 (17·68)	79·56 (17·68)	79·56 (17·70)	77·79 (17·70)
Total protein (g/L)	75 (5)	74 (6)	71 (4)	68 (6)	73 (5)	70 (5)
Urea (mmol/L)	9·78 (0·33)	10·46 (0·43)	9·28 (0·32)	12·32 (0·51)	10·21 (0·33)	10·35 (0·36)
Total bilirubin (μmol/L)	9·92 (6·84)	9·75 (5·13)	9·41 (6·84)	8·89 (3·42)	9·9 (6·84)	8·34 (5·13)
Total cholesterol (mmol/L)*	5·66 (1·13)	5·74 (1·30)	4·22 (0·73)	5·48 (1·25)	5·46 (0·89)	5·35 (1·1)
HDL cholesterol (mmol/L)	1·49 (0·38)	1·40 (0·44)	1·35 (0·34)	1·43 (0·44)	1·43 (0·40)	1·38 (0·42)
LDL cholesterol (mmol/L)*	3·57 (1·00)	3·64 (1·09)	2·22 (0·60)	3·36 (0·99)	3·3 (0·82)	3·21 (0·97)
Triglycerides (mmol/L)	1·48 (0·76)	1·75 (1·03)	1·64 (0·82)	1·77 (1·03)	1·81 (1·2)	2·05 (1·27)
Lipoprotein A (mg/L)	249 (307)	207 (287)	153 (206)	167 (270)	256 (352)	162 (246)
C-reactive protein (mg/L)	4·2 (6)	4·6 (4)	4·6 (12)	3·2 (2)	3·4 (3)	4·0 (3)
Alanine transaminase (IU/L)	13·7 (7·9)	16·3 (9·2)	14·6 (11·4)	18·7 (13·6)	13·5 (8·2)	14·0 (7·2)
Aspartate transaminase (IU/L)	11·2 (3·5)	12·0 (4·0)	10·8 (3·5)	11·7 (6·6)	10·7 (3·4)	10·1 (2·5)
Alkaline phosphatase (IU/L)	105 (34)	114 (37)	99 (31)	98 (34)	103 (34)	111 (38·6)
Leucocytes (g/L)†	7·13 (2·0)	7·33 (2·6)	6·53 (1·7)	10·9 (2·9)	6·44 (1·70)	6·24 (1·6)
Erythrocytes (number/L)	4·84 (0·4)	4·82 (0·5)	4·77 (0·4)	4·49 (0·5)	4·76 (0·4)	4·70 (0·50)
Thrombocytes (g/L)	248 (60)	255 (47)	232 (62)	249 (46)	248 (56)	258 (58·9)
Haemoglobin (g/L)	148 (12)	146 (15)	146 (12)	137 (15)	146 (12)	143 (11)
Packed-cell volume†	0·43 (0·03)	0·43 (0·04)	0·43 (0·03)	0·40 (0·04)	0·43 (0·03)	0·42 (0·03)
Mean corpuscular volume (fL)	90·0 (4·1)	89·4 (6·6)	90·4 (4·0)	90·3 (6·8)	89·6 (6)	89·3 (6·6)
Mean corpuscular haemoglobin (pg)	30·6 (1·4)	30·6 (2·5)	30·6 (1·5)	30·9 (2·6)	30·7 (1·6)	30·6 (2·5)
Mean corpuscular haemoglobin concentration (g/L)	339 (14)	342 (11)	338 (12)	342 (13)	340 (12)	343 (11)
Fibrinogen (μmol/L)*	89·99 (22·32)	94·40 (23·26)	61·76 (17·18)	78·23 (18·59)	87·05 (19·6)	93·81 (19·9)
Thrombin time (%)	99·9 (11·6)	97·6 (8·0)	94·8 (11·1)	95·8 (9·9)	98·9 (13·5)	97·4 (9·3)
Part thrombin time (s)	31·5 (3·4)	31·9 (4·0)	31·8 (3·2)	29·8 (4·2)	31·5 (3·1)	31·6 (3·4)
Plasma viscosity (mPa/s)‡	1·23 (0·07)	1·25 (0·1)	1·15 (0·1)	1·20† (0·1)	1·21 (0·1)	1·20 (0·1)

Values are mean (SD). *p<0·0001 for comparison of patients on apheresis before and 48 h after treatment. †p<0·0001 for comparison of patients on standard treatment before and 48 h after treatment. ‡p=0·0002 for comparison of patients on apheresis before and 48 h after treatment.

Table 2: **Laboratory measurements before, 48 h after, and 6 weeks after treatment**

Procedures

The procedure of the fibrinogen/LDL apheresis has been described previously.[5] Briefly, plasma is obtained by filtration of whole blood through a 0·55 μm filter and then mixed continuously with an equal volume of a 0·2 M sodium acetate buffer (pH 4·85) containing 100 IU/mL heparin. The solution precipitates at a final pH of around 5·12. The suspension is continuously recirculated through a 0·4 μm polycarbonate filter from which plasma free from LDL cholesterol and fibrinogens is obtained and then passed through an anion exchange filter to adsorb excess heparin. Finally, we restored the physiological pH by bicarbonate dialysis and removed excess fluid by ultrafiltration before mixing the plasma with the blood cells and returning the solution to the patient. We treated 3 L plasma within 2 h with a machine that monitors and controls LDL apheresis (Plasmat Secura, B Braun, Melsungen, Germany) on an outpatient basis. This procedure reduced plasma cholesterol, fibrinogen, LDL, and lipoprotein A by more than 50% in a very short time.

Standard treatment consisted of 250 mg prednisolone (Soludecortin H, Merck, Germany), which was reduced by 25 mg per day, 500 mL hydroxyethyl starch (HES sterile 6%, Fresenius, USA) and 400 mg pentoxifylline (Trental 400, Aventis, Germany). The infusions were given once a day for 10 days.

Audiometric testing included pure-tone audiometry (frequencies 125, 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz) in accordance with ISO 7029, tympanometry, stapedius reflex measurements, and the German speech intelligibility test (Freiburger Sprachtest). The sound level in dB at which 50% of the recorded digits were recognised corresponds to perception of speech. We used brainstem audiometry and otoacoustic emissions to confirm the diagnosis.

For patients with symmetrical hearing before sudden hearing loss started, we defined the absolute hearing loss in each frequency as the difference between the affected and the healthy ear in dB. If patients did not have symmetrical hearing before sudden hearing loss started, they had to have pre-existing audiograms available, in which case, absolute hearing loss was the difference between the pure-tone threshold in the affected ear and in the pre-existing audiogram of the same ear. Absolute improvement of hearing was compared before and 48 h after treatment, and before and 6 weeks after therapy. Relative improvement of hearing was calculated as the ratio of absolute hearing loss and absolute hearing improvement.

Laboratory tests were done at the departments of clinical chemistry of the four participating university clinics with standard methods. Blood tests were done before treatment, and 48 h and 6 weeks after the start of therapy. We measured concentrations of sodium, potassium, calcium, urea, glucose, creatinine, total protein, bilirubin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, lipoprotein A, C-reactive protein, alanine transaminase, and aspartate transaminase. We also assessed leucocytes, erythrocytes, thrombocytes, haemoglobin, packed-cell volume, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration; the concentration of fibrinogens, the international normalisation ratio, and the partial thrombin time; and plasma viscosity, and erythrocyte aggregation. We measured plasma viscosity with a Plasmaviskosimeter (Fresenius, Bad Homburg, Germany) and erythrocyte aggregation with the Myrenne Erythrocyte Aggregometer (Myrenne, Roettgen, Germany).

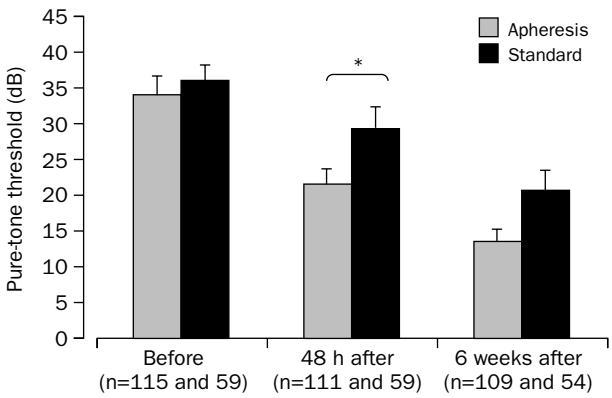

Figure 2: **Pure-tone thresholds of patients before, 48 h after, and 6 weeks after treatment**
Values are mean. Bars are SD. *p<0·034.

Statistical analysis

We aimed to test the hypothesis that single fibrinogen/LDL apheresis is equally or more effective than treatment with prednisolone, hydroxyethyl starch, and pentoxifylline. The primary outcome was recovery of hearing measured by pure-tone audiometry 48 h after the start of treatment. Secondary outcomes were recovery of hearing 6 weeks after the start of treatment, improvement of speech audiometry, tinnitus, and the frequency of side-effects. Analysis of data was restricted to those participants who adhered fully to the protocol in relation to eligibility, interventions, and outcome assessment (per protocol analysis). An additional intention-to-treat analysis was done.

We used results from a pilot study[4] of improvement in pure-tone audiometry within 24 h to calculate the number of patients needed. Based on a randomisation ratio of two to one and a drop-out rate of 20%, we needed 134 patients in the fibrinogen/LDL apheresis group and 67 in the standard group to have 80% power to detect a difference of 4·7% between treatment groups in the change in hearing loss from baseline to 48 h.

The descriptive and confirmatory analyses were done with the SAS System for Windows, version 6.12. A p value of 0·05 or less was judged significant (two tailed). We compared all quantitative variables and the changes between groups in the audiometric and laboratory measurements with Student's *t* test. Qualitative variables were assessed with the χ^2 test.

Role of the funding source

MWI, Munich, Germany did the monitoring and statistical analysis.

Results

Table 1 shows the participants' baseline characteristics. Significantly more patients in the standard group (n=18, 30%) than in the apheresis group (n=16, 14%) had anamnestic incidence of hypertension (p=0·006), but neither systolic nor diastolic blood pressure differed between groups.

We randomly allocated 134 patients to the apheresis group and 67 to standard treatment (figure 1). We were able to assess the primary outcome in 111 (83%) of 134 patients in the apheresis group and in 59 (88%) of 67 in the standard group. 15 patients did not meet the inclusion criteria and were excluded. Four patients in the apheresis group were not in time schedule (within 6 h) for the primary outcome analysis after 48 h and had to be excluded. However, these four patients could be included

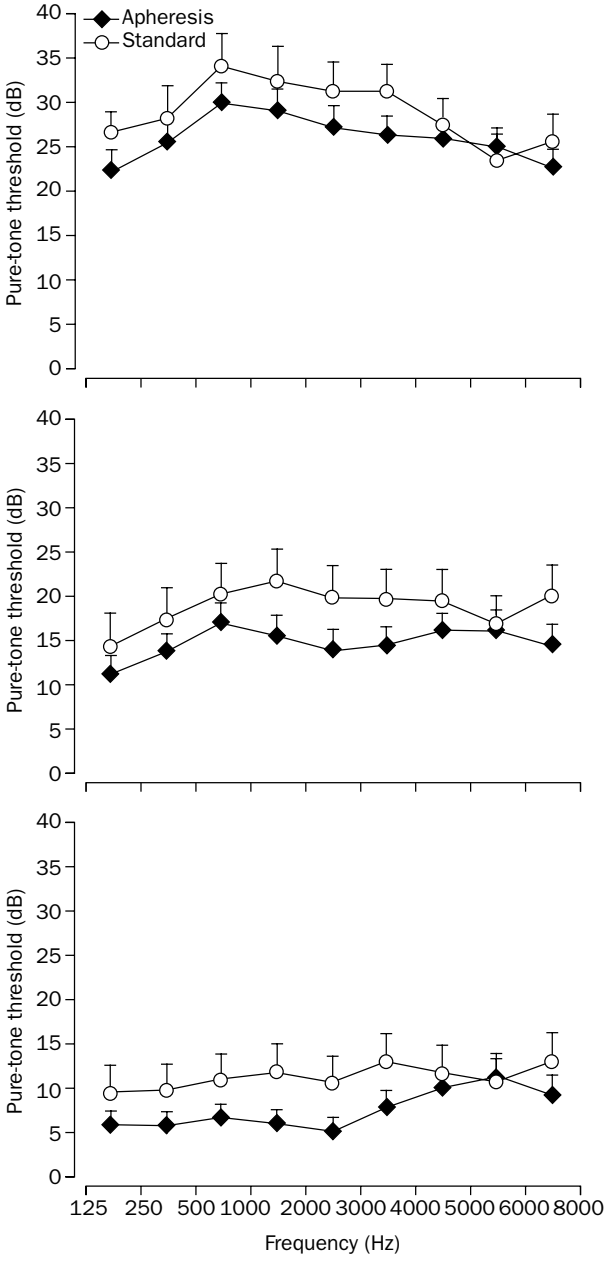

Figure 3: **Speech perception of test words before (upper), 48 h after (middle), and 6 weeks after (lower) treatment**
Values are means. Bars are SDs.

in the secondary outcome analysis after 6 weeks. Since all patients in the standard treatment group were treated on an inpatient basis none of those missed the investigation after 48 h. We could assess secondary outcomes in 109 patients in the apheresis group and in 54 in the standard group. One patient in the apheresis group requested additional prednisolone 4 days after apheresis, and standard infusion treatment was stopped in one patient on day 5 after an epileptic fit. Figure 1 shows the trial profile. Audiological and laboratory data were almost identical. Thus, bias from non-random loss of participants is unlikely.

Table 2 shows the laboratory data before, 48 h after, and 6 weeks after treatment. Patients receiving apheresis had acute, substantial reductions of total cholesterol, LDL cholesterol, lipoprotein A, fibrinogen, blood, and plasma viscosity. For the following 48 h, plasma

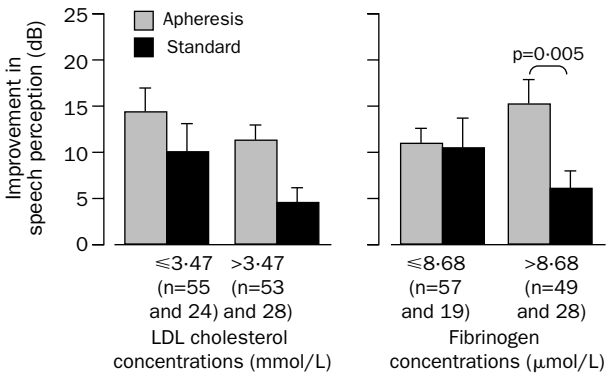

Figure 4: **Improvement of speech perception after 48 h on the basis of serum LDL concentration (left) and fibrinogen concentration (right)**
Values are mean. Bars are SD.

concentrations of these compounds remained 20–35% lower than these concentrations before apheresis. Haemodilution in the standard group reduced fibrinogen concentrations significantly, but less so than in the apheresis group. Haemoglobin, packed-cell volume, and plasma viscosity were reduced but not significantly so by standard treatment and urea and leucocytes were increased (table 2). Thus, 48 h after treatment, total cholesterol, LDL cholesterol, and fibrinogen all remained significantly lower in the apheresis group than in the standard group. 6 weeks after treatment, all patients returned back to their baseline values in all blood chemical tests done (table 2).

Figure 2 shows the average audiogram of patients. Before treatment, hearing loss did not differ between groups. 48 h after treatment, hearing had improved in both groups. The mean improvement was 50·3% (50·0) in the apheresis group and 42·6% (50·4) in the standard group (difference 7·7, 95% CI –8·2 to 23·6, p=0·34). After 6 weeks, hearing had improved further in both groups (apheresis group 67·4% [57], standard group 61·8% [52]; p=0·53). Mean speech perception measured by the sound level at which patients could recognise 50% of the presented test words (digits) after 48 h was 21·6 dB (20·8) in the apheresis group and 29·3 dB (29·4) in the standard group (p=0·034). 6 weeks after treatment, mean speech perception was better, but not significantly so, in patients given apheresis (13·7 dB, 14·3) compared with those on standard treatment (20·8 [25·4], p=0·059; figure 3).

We also did a subgroup analysis on the basis of baseline plasma concentrations for LDL cholesterol and fibrinogen. We used the median for LDL cholesterol (3·47 mmol/L) and fibrinogen (8·68 μmol/L) to divide participants in groups with low values and those with high values. In patients with low serum LDL cholesterol, speech perception improved with apheresis (14·4 dB, SD 2·3) compared with standard treatment (10·1 dB, 3·0), but not significantly so. In patients with baseline concentrations of LDL cholesterol of greater than 3·47 mmol/L, apheresis treatment resulted in a significantly greater improvement in speech perception (11·2 dB, 1·7) than did standard treatment (4·6 dB, 1·6; figure 4). In patients with plasma fibrinogen below 8·68 μmol/L, the improvement in speech perception did not differ between groups. However, patients with plasma concentration of fibrinogen of more than 8·68 μmol/L showed significantly improved speech perception with apheresis (15·3 dB, SD 2·5) than with standard treatment (6·1 dB, 2·0; p=0·005).

Discussion

Our results showed that pure-tone thresholds in patients with sudden hearing loss improved more, but not significantly so, with apheresis treatment compared with plasmaexpander and prednisolone treatment (standard therapy in Germany). However, the remission rate of speech perception in the patients given apheresis was significantly higher than in those given standard treatment. Restriction of the analysis to patients with median plasma concentrations of fibrinogen above 8·68 μmol/L and of LDL cholesterol above 3·47 mmol/L, showed a much better improvement in speech perception in patients on apheresis than in those on plasma expanders and prednisolone.

Little is known about the pathogenesis of SSHL, but vascular insults, immunopathological processes, and viral infections are the most frequently discussed causes. There is general consent that SSHL is a symptom, rather than a distinct disease with different causes. In many patients, the clinical picture of SSHL is similar to that of other vascular diseases such as cerebral insult, myocardial infarction, or retinal ischaemia. In animals, the function of the cochlea is very sensitive to even moderate changes in regional blood flow.[2] Whether vascular risk factors play a part in SSHL is unclear.[11,12] Chronic sensorineural hearing loss has been associated with haemorheological characteristics,[13] and serum cholesterol has been associated with development of noise-induced hearing loss.[14] However, only a few studies, with only a few patients have been done on SSHL. Increased plasma viscosity and erythrocyte filterability is thought to be a cause of SSHL in human beings.[15,16] Since fibrinogen is a large glycoprotein (340 kDa) that defines rheological properties of whole blood by increasing plasma viscosity and inducing aggregation of erythrocytes, thrombocytes, and leucocytes, it is also thought to be a cause of SSHL.[17] In vascular disease, such as cerebral stroke or infarction or myocardial infarction, fibrinogen is a well established risk factor.[18]

Treatment to lower fibrinogen increases cochlear blood flow in animals[19] and has also been used in patients with SSHL. In a prospective study of 169 patients,[20] Kubo and colleagues showed that hearing recovery was much better in patients on the thrombin-like venom enzyme batroxobin than in those on steroids. The larger absolute recovery of hearing (average gain 30 dB) compared with our results (14 dB) could have been because Kubo and colleagues included patients with more severe SSHL. The criteria for overall improvement are very strict, and thus, recovery rates were only 57% and 39%, despite the large absolute average hearing gain.[20] In our study, the results of the speech audiometry are clearly better with apheresis than with standard treatment, which is in keeping with the fact that Kubo and colleagues tested fewer frequencies than we did, but those are almost all in the area of speech perception. The very definite result in favour of treatment to lower fibrinogen recorded by Kubo and co-workers could also have been because the dose of betamethasone given in the control group was low and not the same as the high dose of prednisolone that we gave to our control group. Thus, the difference between Kubo and colleagues' findings and ours, could be accounted for by differences in the study design.

The nitric oxide system is a major regulatory system in cell physiology and tissue haemostasis. In the cochlea,

production of nitric oxide by the cochlear vessels actively regulates regional blood flow.[21] Release of nitric oxide is dependent on the integrity of endothelial function. Patients with raised concentrations of LDL cholesterol and lipoprotein A can have impaired endothelial function in coronary and peripheral arteries.[22] Increased lipidperoxidation in the vessel wall and consecutive reduced synthesis of nitric oxide seems to be the underlying cause. Treatment for 6 months with cholesterol-lowering drugs improves restoration of impaired endothelial function in patients with coronary artery disease and raised LDL cholesterol.[23]

Fibrinogen/LDL apheresis is an established procedure for secondary prophylaxis in patients with coronary artery disease whose LDL concentrations, despite exhaustive dietetic and drug treatment, are still much higher than the recommended concentrations. Reduction of serum LDL and lipoprotein A to 60%, and of fibrinogen to 65% of the original values, can be achieved by a single apheresis within 2 h. Reduction of plasma fibrinogen improves the blood's rheological properties and improvement in blood rheology has been attributed to a significant reduction of plasma viscosity of almost 20%. This effect of apheresis is well known and can be measured for example by an increase in tissue oxygenation measured by a polarographic needle method in the skeletal muscle of patients.[5,24] Furthermore, a very large and quick reduction of plasma LDL cholesterol by single apheresis greatly improved endothelial function in coronary and peripheral arteries,[25] as shown by positron emission tomography.[26] Thus, single LDL-apheresis results in substantial improval of haemorheology and endothelial function.

In addition to the vascular and haemorheological effects of apheresis, the direct effect on plasma cholesterol concentrations by such treatment could also affect the perilymph compartment and the composition of outer hair cell membranes, in particular the ratio of phospholipids to cholesterol, thus affecting basic mechanisms of SSHL. Nguyen and colleagues[27] showed that cochlear outer hair cells incubated in a cholesterol rich medium have a significantly higher lateral wall stiffness than do cells incubated in a cholesterol-free medium. Electromotility of the outer hair cells depends on very fast (more than 10 kHz) changes in the length of the cells and is a vulnerable key process in the mechano-electrical transduction process. Thus, depletion of cholesterol could affect the ability of the outer hair cells to change length and thus result in improved fine-tuning of the cochlear membrane and, thereby, cochlear function. Such a process has been investigated in patients by otoacoustic emissions generated by the outer hair cells. Preyer and colleagues[28] suggested that non-linear mechanical processes in the cochlea are compromised in patients with hypercholesterolaemia, and the effect of apheresis on the vascular system and on acute reduction of serum cholesterol could directly improve the cochlear amplifier and thus recovery of hearing in SSHL compared with standard treatment.

Spontaneous remission of hearing is estimated at about 65%.[29] In our study, the remission rate was 78% in the standard group and 84% in the apheresis group, suggesting that the improvement in hearing was more likely to be a result of treatment than of spontaneous remission. However, since remission of hearing does not have well defined criteria, comparison of remission between studies is difficult.

The high rate of mostly part remissions usually takes place within the first 2 weeks, thereby superimposing the effects of any treatment for sudden hearing loss. Since prednisolone and apheresis are effective within minutes to 2 h, we expected a prompt recovery of hearing in both groups. This effect and the fact that spontaneous remission is low in a short observation period prompted us to do hearing tests as early as 48 h after the start of treatment.

Mean pure-tone thresholds in our patients seem to be low but they can not be directly compared with audiograms of individual patients because SSHL does not usually affect all frequencies and the mean values of hearing loss in every single frequency consist of 30–50% values of pure-tone thresholds in healthy individuals. Most patients in our study had more than moderate hearing loss. The results of two small double-blind controlled studies[7,8] showed that patients with SSHL on prednisolone had better recovery than did those on placebo. In two larger retrospective studies,[9,30] the beneficial effect of glucocorticoids was confirmed.

Our finding that patients with LDL concentrations above 3·49 mmol/L or fibrinogen concentrations above 8·68 μmol/L, or both benefit significantly more from apheresis treatment than do than those with lower concentrations lends support to the notion that SSHL has several causes and is not caused just by vascular disturbances. We assume that, in patients with high plasma fibrinogen or LDL cholesterol, vascular events are the main reason for SSHL and therefore apheresis treatment is especially effective. This assumption is lent support by the clinical observation that in several patients, SSHL could be reversed within hours after reduction of plasma fibrinogen and LDL cholesterol.

Strategies to individualise treatment of ischaemic SSHL might have to focus on new diagnostic criteria such as LDL cholesterol, fibrinogen, C-reactive protein, haemostaseology, etc, to start a more specific treatment for different forms of SSHL. Our results suggest that both fibrinogen and LDL cholesterol should be considered important compounds for diagnosis and treatment of SSHL and show that apheresis could be an effective therapeutic option in treatment of SSHL.

Contributors

M Suckfüll designed the study, wrote the study protocol, supervised data collection, monitoring, and analysis, and prepared the report. D Seidel and J Thiery contributed to the initiation of the study, the design, the analysis, and the editing of the report. B Mazurek, M Jaehne, J Gronemeyer, O Reichel, J Sasama, S K Kichigina, and M Möller recruited and treated patients and gathered data. A Schrameyer-Wernecke, F Biel, U Kassner, M Koch, and B Jaeger supervised the apheresis. K Osterkorn did the statistical analysis, monitoring was done by D Osterkorn.

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Conflict of interest statement

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