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Batroxobin can improve the efficacy of combination therapy for profound sudden sensorineural hearing loss greater than but not less than 100 dB HL

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Main Article

Li Zhu Jiang takes responsibility for the integrity of the content of the paper

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Abstract

Objective. To investigate the effects of combination therapy with and without batroxobin, and the frequency of batroxobin use on the prognosis of profound sudden sensorineural hearing loss.

Methods. Hearing recovery in the batroxobin group (231 patients) and non-batroxobin group (56 patients) was compared. The correlation between the number of times batroxobin was used and hearing recovery was analysed.

Results. The decrease in hearing threshold and overall improvement rate in the batroxobin group with hearing loss exceeding 100 dB HL was significantly higher than that in the non-batroxobin group. There was no linear correlation between the number of times batroxobin was used and the overall improvement rate. Using batroxobin two to three times achieved a therapeutic effectiveness plateau.

Conclusion. Batroxobin can improve the efficacy of combination therapy for profound sudden sensorineural hearing loss exceeding 100 dB HL, and using batroxobin two to three times yields the maximum overall improvement rate.

Introduction

Sudden sensorineural hearing loss (SNHL) is a medical emergency defined as an acute loss of 30 dB or more in at least three contiguous audiometric frequencies over a period of less than 3 days.[1] In China, sudden SNHL can be classified into different types based on the frequency and degree of hearing loss: high or low frequency, and flat or profound.[2] Profound sudden SNHL, characterised by decreased hearing thresholds in all frequencies from 250 to 8000 Hz and an average threshold of greater than or equal to 81 dB HL, is the most severe type of sudden SNHL. It accounts for 26.95 per cent of all cases and has the lowest cure rate of the four types of sudden SNHL.[3]

One-third of patients with profound sudden SNHL do not experience any improvement in hearing after treatment,[3,4] and so there is considerable difficulty in improving the therapeutic effects in profound sudden SNHL patients. The pathogenesis of profound sudden SNHL is mainly related to the development of inner-ear vascular embolism or thrombosis;[5–7] therefore, guidelines in China recommend the use of thrombolytics or vasodilators for this condition (no aggregate evidence quality).[2] However, American Academy of Otolaryngology–Head and Neck Surgery guidelines advise against (aggregate evidence quality: grade B) routine prescription of these medications to patients with sudden SNHL because of the unclear pathogenesis of the condition and the lack of research on the efficacy of thrombolytics in its treatment.[1] Thus, there is controversy over whether to use thrombolytics or vasodilators for profound sudden SNHL.

Batroxobin, a serine protease isolated from the common lancehead or fer-de-lance (*Bothrops atrox moojeni*) venom, has been studied for the treatment of deep vein thrombosis and cerebral infarction because of its ability to promote thrombolysis, prevent thrombus recurrence and provide neuroprotection.[8–10] Previous studies have shown that the use of batroxobin alone resulted in significantly better hearing recovery than corticosteroid therapy in patients with sudden SNHL.[11–14] Combination therapy is the first-line option for profound sudden SNHL in China. However, there are few studies on the differences in the efficacy of combination therapy with and without batroxobin for this condition.

This study investigated the effects of combination therapy with and without batroxobin on the prognosis of profound sudden SNHL. Additionally, we explored the correlation between the number of times batroxobin was used and hearing recovery in profound sudden SNHL.

Materials and methods

Ethical declaration and subject selection

This retrospective case–control study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee. From January 2015 to December 2022, a total of 287 patients with profound sudden SNHL were included. The inclusion criteria were: a reduction of all frequencies, from 250 to 8000 Hz, with an average hearing threshold greater than or equal to 81 dB HL, occurring within 3 days or less; a time prior to treatment of no more than two weeks; and first treatment administered at the First Affiliated Hospital of Chongqing Medical University. Patients with profound sudden SNHL caused by a stroke, nasopharyngeal carcinoma, acoustic neuroma, Ménière's disease, various types of otitis media and virus infections, for example mumps and herpes zoster (Hunter's syndrome), were excluded from this study.

Group division and treatment plan

A total of 231 patients with profound sudden SNHL were assigned to the combined batroxobin therapy group (batroxobin group) and received a combination therapy that included batroxobin, while 56 patients were allocated to the combined non-batroxobin therapy group (non-batroxobin group) because of a shortage of batroxobin during their hospitalisation. In the batroxobin group, 70 mg of ginkgo biloba extract was administered intravenously once a day, and oral prednisone was administered at a dosage of 1 mg/kg/day for the first 5 days. After the initial 5 days, 40 mg of methylprednisolone and 0.2 ml of lidocaine were injected into the tympanic cavity every other day. From the first day of treatment, if the patient's fibrinogen level was higher than 1 g/l, batroxobin was administered intravenously every other day, but if the fibrinogen level was lower than 1 g/l, batroxobin was stopped and the patient was suspended for re-examination after 1 day. Batroxobin was continued only when the fibrinogen level was higher than 1 g/l. In the non-batroxobin group, all treatment options except batroxobin were the same as those in the batroxobin group. The entire treatment lasted for two weeks.

Pure tone audiogram

Hearing tests were performed using air- and bone-conduction pure tone audiometry during screening and after one and two weeks of treatment. Efficacy evaluation calculated the average of all frequencies from 0.25 to 8 kHz, including 0.25, 0.5, 1, 2, 4 and 8 kHz. The degree of hearing recovery was classified into four categories: no improvement, improvement, notable improvement and complete recovery. No improvement was defined as an improvement in hearing levels of less than 15 dB HL, while improvement was defined as an improvement in hearing levels of 15–30 dB HL. Notable improvement was defined as an improvement in hearing levels of more than 30 dB HL, and complete recovery was defined as a restoration of hearing levels to those of the unaffected ear or to normal levels.

Statistical analysis

Statistical analysis was performed using statistical software SPSS version 22.0 (SPSS, Chicago, Illinois, USA). A p-value of less than 0.05 was considered statistically significant. The chi-square, Mann–Whitney and Kruskal–Wallis tests were used for comparing the groups, and Spearman correlation analysis was used to analyse the correlation between the number of times batroxobin was used and the overall improvement rate.

Results

The demographic and clinical characteristics of the patients in the batroxobin group and the non-batroxobin group are presented in Table 1. No statistically significant differences among the potentially confounding factors known to impact the prognosis of sudden SNHL were observed between the two groups.

After a two-week treatment period, the hearing threshold of patients in the batroxobin group decreased by 22.53 ± 21.25 dB, while that in the non-batroxobin group decreased by 18.20 ± 22.21 dB, with no significant difference between groups ($p = 0.062$). The improvement in hearing thresholds between the two groups of patients with different initial hearing loss levels was also compared. The results showed that in patients with initial hearing loss of less than or equal to 90 dB HL in the batroxobin group, the hearing threshold decreased by 28.26 ± 25.31 dB, while in patients in the non-batroxobin group, it decreased by 28.50 ± 31.31 dB, with no significant difference ($p = 0.975$). In patients with initial hearing loss exceeding 90 dB HL in the batroxobin group, the hearing threshold decreased by 20.29 ± 19.05 dB, while in patients in the non-batroxobin group, it decreased by 15.96 ± 19.45 dB, with no significant difference ($p = 0.075$). In patients with initial hearing loss of less than or equal to 100 dB HL in the batroxobin group, the hearing threshold decreased by 28.36 ± 22.36 dB, while in patients in the non-batroxobin group, it decreased by 31.83 ± 24.11 dB, with no significant difference ($p = 0.624$). In patients with initial hearing loss exceeding 100 dB HL in the batroxobin group, the hearing threshold decreased by 15.65 ± 17.63 dB, while in patients in the non-batroxobin group, it decreased by 6.39 ± 11.12 dB, with a significant difference ($p = 0.002$).

We also compared the hearing recovery rates between the two groups of patients. The overall improvement rate was significantly higher in the batroxobin group (58.0 per cent) compared with the non-batroxobin group (42.9 per cent) ($p =$

Table 1. Demographic data and clinical characteristics of batroxobin and non-batroxobin groups

Variable	Batroxobin group*	Non-batroxobin group†	p
Age (mean ± SD); years)	46.2 ± 16.1	49.2 ± 14.0	0.302
Sex (male/female (n))	113/118	28/28	0.884
Affected ear (right/left) (n)	112/119	25/31	0.606
Delay to treatment (mean ± SD); days)	5.8 ± 4.0	5.4 ± 4.5	0.127
Hypertension (n (%))	54 (23.4)	17 (30.4)	0.277
Diabetes (n (%))	14 (6.1)	6 (14.3)	0.220
Vertigo (n (%))	98 (42.4)	30 (53.6)	0.132
Initial PTA (mean ± SD); dB HL)	98.8 ± 12.5	100.4 ± 11.1	0.570

*$n = 231$; †$n = 56$. SD = standard deviation; PTA = pure tone average

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Table 2. Comparison of degree of hearing recovery between batroxobin and non-batroxobin groups

Degree of hearing recovery	Batroxobin group* (*n* (%))	Non-batroxobin group† (*n* (%))	*p*
Complete recovery	7 (3.0)	4 (7.1)	0.294
Notable improvement	68 (29.4)	11 (19.6)	0.141
Improvement	59 (25.5)	9 (16.1)	0.132
No improvement	97 (42.0)	32 (57.1)	0.041‡
Notable improvement + improvement	127 (55.0)	18 (32.1)	0.002‡
Notable improvement + complete recovery	75 (32.5)	15 (26.8)	0.083
Overall improvement	134 (58.0)	24 (42.9)	0.041‡

*$n = 231$; †$n = 56$. ‡Indicates statistical significance ($p < 0.05$)

0.041; Table 2). There were no significant differences between the two groups in terms of improvement, notable improvement and complete recovery rates. However, when notable improvement and improvement rates were combined, the notable improvement plus improvement rate in the batroxobin group (55.0 per cent) was significantly higher than that in the non-batroxobin group (32.1 per cent) ($p = 0.002$; Table 2).

The difference in hearing recovery rate stratified by different initial hearing loss levels was investigated. The hearing recovery rates of patients in the batroxobin and non-batroxobin groups with initial hearing loss of less than or equal to 90 dB HL were compared, as well as those of patients with initial hearing loss exceeding 90 dB HL. Apart from the significant difference in the notable improvement plus improvement rate between the batroxobin group and the non-batroxobin group with an initial hearing loss of less than or equal to 90 dB HL ($p = 0.043$; Table 3), there were no significant differences in terms of no improvement, improvement, notable improvement and complete recovery rates between the two groups with an initial hearing loss of less than or equal to 90 dB HL and an initial hearing loss exceeding 90 dB HL.

The hearing recovery rates of patients in the batroxobin and non-batroxobin groups with initial hearing loss of less than or equal to 100 dB HL were compared, as well as for those with initial hearing loss exceeding 100 dB HL. The results showed no significant difference in terms of no improvement, improvement, notable improvement and complete recovery rates between the two groups with initial hearing loss of less than or equal to 100 dB HL. In patients with initial hearing loss exceeding 100 dB HL, the overall improvement rate in the batroxobin group (41.6 per cent) was significantly higher than that in the non-batroxobin group (16.7 per cent) ($p = 0.012$; Table 4). Although there were no significant differences between the two groups in terms of improvement, notable improvement and complete recovery rates, the improvement plus notable improvement rate in the batroxobin group (40.6 per cent) was significantly higher than that in the non-batroxobin group (16.7 per cent) ($p = 0.016$; Table 4).

The correlation between the number of times batroxobin was used and hearing recovery rate in patients with profound sudden SNHL whose initial hearing loss exceeded 100 dB HL was also investigated. A total of 106 patients with initial hearing loss exceeding 100 dB HL were divided into six groups based on the number of times batroxobin was used. Although there was a significant difference in the constituent ratio between groups based on the frequency of batroxobin use ($p = 0.026$; Table 5), Spearman correlation analysis showed no linear correlation between the number of times batroxobin was used and the overall improvement rate ($p = 0.678$; Table 5). In light of the limited number of patients using batroxobin one to two times and five to six times, a combined analysis of patients using batroxobin was conducted. The results showed that the overall improvement rates of using batroxobin two to three times compared with four to five times were 40.0 and 40.1 per cent, respectively, with no significant difference ($p = 0.961$; Table 5). It was concluded that using batroxobin two to three times was enough to reach an effective therapeutic plateau, and increasing the number of times batroxobin was used did not improve the overall improvement rate in patients with profound sudden SNHL whose initial hearing loss exceeded 100 dB HL.

Discussion

The aetiology of profound sudden SNHL is currently unclear, but it is believed to be associated with vascular embolism or

Table 3. Comparison of hearing recovery rates related to initial hearing levels (90 dB HL)

	Initial hearing loss ≤90 dB HL			Initial hearing loss >90 dB HL		
Degree of hearing recovery	Batroxobin group* (*n* (%))	Non-batroxobin group† (*n* (%))	*p*	Batroxobin group‡ (*n* (%))	Non-batroxobin group** (*n* (%))	*p*
Complete recovery	6 (9.2)	3 (30.0)	0.174	1 (0.6)	1 (2.2)	0.388
Notable improvement	26 (40.0)	1 (10.0)	0.137	42 (25.3)	10 (21.7)	0.619
Improvement	13 (20.0)	1 (10.0)	0.749	46 (27.7)	8 (17.4)	0.155
No improvement	20 (30.8)	5 (50.0)	0.401	77 (46.4)	27 (58.7)	0.139
Notable improvement + improvement	39 (60.0)	2 (20.0)	0.043§	88 (53.0)	18 (39.1)	0.096
Notable improvement + complete recovery	32 (49.2)	4 (40.0)	0.838	43 (25.9)	11 (23.9)	0.784
Overall improvement	45 (69.2)	5 (50.0)	0.401	89 (53.6)	19 (41.3)	0.139

*$n = 65$; †$n = 10$; ‡$n = 166$; **$n = 46$. §Indicates statistical significance ($p < 0.05$)

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Table 4. Comparison of hearing recovery rates related to initial hearing levels (100 dB HL)

	Initial hearing loss ≤100 dB HL			Initial hearing loss >100 dB HL		
Degree of hearing recovery	Batroxobin group* (*n* (%))	Non-batroxobin group† (*n* (%))	*p*	Batroxobin group‡ (*n* (%))	Non-batroxobin group** (*n* (%))	*p*
Complete recovery	6 (4.8)	4 (15.3)	0.123	1 (0.9)	0 (0.0)	0.595
Notable improvement	52 (41.6)	10 (38.4)	0.767	16 (15.0)	1 (3.3)	0.159
Improvement	32 (25.6)	5 (19.2)	0.492	27 (25.4)	4 (13.3)	0.162
No improvement	35 (28.0)	7 (26.9)	0.911	62 (58.4)	25 (83.3)	0.012§
Notable improvement + improvement	84 (67.2)	15 (57.7)	0.353	43 (40.6)	5 (16.7)	0.016§
Notable improvement + complete recovery	58 (46.4)	14 (53.8)	0.489	17 (16.0)	1 (3.3)	0.132
Overall improvement	90 (72.0)	19 (73.1)	0.911	44 (41.6)	5 (16.7)	0.012§

*$n = 125$; †$n = 26$; ‡$n = 106$; **$n = 30$. §Indicates statistical significance ($p < 0.05$)

Table 5. Correlation analysis between frequency of batroxobin use and hearing recovery in patients with initial hearing loss exceeding 100 dB HL

No. times batroxobin used	Total cases (*n*)	Overall improvement in hearing (*n* (%))	No improvement in hearing (*n* (%))	Between-group comparison *p*-value	Spearman correlation analysis *p*-value	Co-efficient R_s
1	3	2 (50.0)	1 (50.0)	0.026*†	0.678	0.041
2	15	10 (83.3)	5 (16.7)			
3	45	14 (31.1)	31 (68.9)			
4	32	10 (31.2)	22 (68.8)			
5	10	7 (70.0)	3 (30.0)			
6	1	1 (100.0)	0 (0.0)			
2–3	60	24 (40.0)	36 (60.0)	0.961‡		
4–5	42	17 (40.1)	25 (59.9)			

The chi-square and Kruskal–Wallis tests were used for comparing groups based on the number of times batroxobin was used, and Spearman correlation analysis was used to examine the correlation between the number of times batroxobin was used and the overall improvement rate. *Kruskal–Wallis test. †Indicates statistical significance ($p < 0.05$). ‡Chi-square test. No. = number of

thrombosis of the common cochlear artery or its spiral branches.[15] The common cochlear artery is the primary blood supply artery of the cochlea, and its branches are terminal arteries without collateral circulation.[16] Normal cochlear function also requires a significant amount of energy generated by aerobic metabolism, and is highly susceptible to reduced blood flow and oxygen supply.[17] When occlusion occurs, therefore, the corresponding areas immediately become ischaemic and hypoxic, resulting in hearing impairment.

Batroxobin can reduce the viscosity of whole blood and plasma, decrease vascular resistance, increase blood flow, and improve peripheral and microcirculatory disorders;[18] therefore, it can be used to treat sudden SNHL.[11] There are currently limited clinical studies examining the efficacy of batroxobin in treating profound sudden SNHL, with some studies focusing only on the efficacy of batroxobin used alone. This study used combination therapy, both with and without batroxobin, to treat profound sudden SNHL, and compared the differences in efficacy between the two treatment methods.

Several studies have reported on the efficacy of batroxobin in the treatment of sudden SNHL. Suzuki *et al.*[14] reported complete recovery and overall improvement rates of 27.1 and 50.0 per cent, respectively, for sudden SNHL with initial hearing greater than 40 dB HL treated with batroxobin alone. Kubo *et al.*[12] reported a complete recovery rate of 30.5 per cent and an overall improvement rate of 57.3 per cent using batroxobin alone to treat sudden SNHL with initial hearing loss exceeding 55 dB HL. These studies explored the effectiveness of batroxobin monotherapy in treating sudden SNHL that was moderate to severe. The current study found that the complete recovery and overall improvement rates of combined batroxobin therapy for profound sudden SNHL exceeding 80 dB HL were 3.0 and 58.0 per cent, respectively. Although the initial hearing of sudden SNHL patients in this study was greater than 80 dB HL, the overall improvement rate of these patients receiving combined batroxobin therapy was similar to that reported in the above studies. However, the complete recovery rate of patients receiving combined batroxobin therapy in this study was significantly lower than that reported in previous studies, possibly due to the worse initial hearing loss of patients in this study.

Kubo *et al.*[12] used batroxobin for sudden SNHL that did not respond to corticosteroids, and obtained favourable results. It has also been reported that batroxobin, rather than corticosteroids, was more suitable for patients with profound sudden SNHL.[13,14] That study found that overall improvement rate was significantly higher in the combined batroxobin therapy group compared to the combined non-batroxobin therapy group. The notable improvement plus improvement rate in the combined batroxobin therapy group was also significantly

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higher than in the combined non-batroxobin therapy group. These results suggest that, for profound sudden SNHL, combined batroxobin therapy can lead to a better improvement rate compared to combined non-batroxobin therapy.

- There is controversy over batroxobin use in sudden sensorineural hearing loss (SNHL) treatment
- Batroxobin use can increase the overall improvement rate of combination therapy for profound sudden SNHL with initial hearing loss exceeding 100 dB HL
- Batroxobin use does not increase the overall improvement rate for cases with initial hearing loss of less than or equal to 100 dB HL
- There is no linear correlation between the number of times batroxobin is used and overall improvement rate

According to a previous report, the efficacy of batroxobin treatment for sudden SNHL with initial hearing loss of less than 80 dB HL was lower than that of high-dose corticosteroids.[14] However, for sudden SNHL with initial hearing loss exceeding 80 dB HL, there was no significant difference in efficacy between batroxobin and high-dose corticosteroids.[14] This study found that combined batroxobin therapy did not decrease the hearing threshold and increase the overall improvement rate compared to combined non-batroxobin therapy for profound sudden SNHL with initial hearing loss of less than or equal to 100 dB HL. However, for profound sudden SNHL with initial hearing loss exceeding 100 dB HL, the decrease in hearing threshold in the combined batroxobin therapy group was significantly higher than that in the combined non-batroxobin therapy group. In addition, a significantly higher overall improvement rate of 41.6 per cent was observed, with an improvement plus notable improvement rate of 40.6 per cent in the combined batroxobin therapy group, compared to 16.7 per cent and 16.7 per cent for the combined non-batroxobin therapy group. These results indicate that batroxobin can decrease the hearing threshold and increase the overall and improvement plus notable improvement rates of combined therapy for profound sudden SNHL with initial hearing loss exceeding 100 dB HL. Based on these findings, combination therapy with batroxobin should be considered as a potential treatment option for profound sudden SNHL with initial hearing loss exceeding 100 dB HL, but not for profound sudden SNHL with initial hearing loss of less than or equal to 100 dB HL.

Few studies have shown that batroxobin alone can improve the efficacy of sudden SNHL.[12–14] However, previous studies have not yet reached a consensus on the number of times batroxobin should be used in the treatment of sudden SNHL. Moreover, there has been no report on the correlation between the number of times batroxobin is used and hearing recovery in patients with profound sudden SNHL. Given the high cost of batroxobin and the finding that increased use of batroxobin can increase the risk of systemic bleeding in patients,[19,20] it is necessary to explore the number of times batroxobin should be used in patients with profound sudden SNHL. This study further explored the effect of frequency of batroxobin use in combination therapy on the efficacy of profound sudden SNHL with initial hearing loss exceeding 100 dB HL. The results suggested no significant difference between the combined use of batroxobin two to three times compared with four to five times. In addition, the combined use of batroxobin two to three times resulted in the maximum overall improvement rate, indicating that further increases in the frequency of batroxobin use will not lead to a higher overall improvement rate.

Conclusion

There is controversy over the use of batroxobin in the treatment of sudden SNHL. This case–control study showed that batroxobin decreased the hearing threshold and increased the overall and improvement plus notable improvement rates of combination therapy for profound sudden SNHL with initial hearing loss exceeding 100 dB HL, but not for profound sudden SNHL with initial hearing loss of less than or equal to 100 dB HL. There was no linear correlation between the number of times batroxobin was used and the overall improvement rate. Moreover, using batroxobin two to three times in combined batroxobin therapy for profound sudden SNHL with initial hearing loss exceeding 100 dB HL resulted in the maximum overall improvement rate.

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Competing interests. None declared

References

1 Chandrasekhar SS, Tsai Do BS, Schwartz SR, Bontempo LJ, Faucett EA, Finestone SA *et al.* Clinical Practice Guideline: sudden hearing loss (update). *Otolaryngol Head Neck Surg* 2019;**161**:S1–45
2 Editorial Board of Chinese Journal of Otorhinolaryngology Head and Neck Surgery; Society of Otorhinolaryngology Head and Neck Surgery, Chinese Medical Association. Guideline of diagnosis and treatment of sudden deafness (2015) [in Chinese]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2015;**50**:443–7
3 Chinese sudden hearing loss multi-center clinical study group. Prospective clinical multi-center study on the treatment of sudden deafness with different typings in China [in Chinese]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2013;**48**:355–61
4 Zheng H, Dai QQ, Zhou L, Feng NY, Qiu JH, Chen Y *et al.* Multi-center study on the treatment of sudden total deafness [in Chinese]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2013;**48**:379–84
5 Fusconi M, Chistolini A, de Virgilio A, Greco A, Massaro F, Turchetta R *et al.* Sudden sensorineural hearing loss: a vascular cause? Analysis of prothrombotic risk factors in head and neck. *Int J Audiol* 2012;**51**:800–5
6 Passamonti SM, Di Berardino F, Bucciarelli P, Berto V, Artoni A, Gianniello F *et al.* Risk factors for idiopathic sudden sensorineural hearing loss and their association with clinical outcome. *Thromb Res* 2015;**135**:508–12
7 Perlman HB, Kimura R. Experimental obstruction of venous drainage and arterial supply of the inner ear. *Ann Otol Rhinol Laryngol* 1957;**66**:537–46
8 Zhang L, Lu SH, Li L, Tao YG, Wan YL, Senga H *et al.* Batroxobin mobilizes circulating endothelial progenitor cells in patients with deep vein thrombosis. *Clin Appl Thromb Hemost* 2011;**17**:75–9
9 Qin J, Xu Z, Shi D, Chen D, Dai J, Teng H *et al.* Deep vein thrombosis after total hip arthroplasty and total knee arthroplasty in patients with previous ischemic stroke. *Int J Low Extrem Wounds* 2013;**12**:316–19
10 Xu G, Liu X, Zhu W, Yin Q, Zhang R, Fan X. Feasibility of treating hyperfibrinogenemia with intermittently administered batroxobin in patients with ischemic stroke/transient ischemic attack for secondary prevention. *Blood Coagul Fibrinolysis* 2007;**18**:193–7
11 Oya R, Horii A, Akazawa H, Osaki Y, Inohara H. Prognostic predictors of sudden sensorineural hearing loss in defibrinogenation therapy. *Acta Otolaryngol* 2016;**136**:271–6
12 Kubo T, Matsunaga T, Asai H, Kawamoto K, Kusakari J, Nomura Y *et al.* Efficacy of defibrinogenation and steroid therapies on sudden deafness. *Arch Otolaryngol Head Neck Surg* 1988;**114**:649–52

https://doi.org/10.1017/S0022215123001512 Published online by Cambridge University Press

13 Shiraishi T, Kubo T, Okumura S, Naramura H, Nishimura M, Okusa M *et al*. Hearing recovery in sudden deafness patients using a modified defibrinogenation therapy. *Acta Otolaryngol Suppl* 1993;**501**:46–50
14 Suzuki H, Furukawa M, Kumagai M, Takahashi E, Matsuura K, Katori Y *et al*. Defibrinogenation therapy for idiopathic sudden sensorineural hearing loss in comparison with high-dose steroid therapy. *Acta Otolaryngol* 2003;**123**:46–50
15 Michel O. The revised version of the German guidelines 'Sudden idiopathic sensorineural hearing loss' [in German]. *Laryngorhinootologie* 2011;**90**:290–3
16 Nakashima T, Naganawa S, Sone M, Tominaga M, Hayashi H, Yamamoto H *et al*. Disorders of cochlear blood flow. *Brain Res Brain Res Rev* 2003;**43**:17–28
17 Shi X. Physiopathology of the cochlear microcirculation. *Hear Res* 2011;**282**:10–24
18 Kawakami M, Makimoto K, Yamamoto H, Takahashi H. The effect of batroxobin on cochlear blood flow. *Acta Otolaryngol* 1992;**112**:991–7
19 Ding J, Zhou D, Hu Y, Elmadhoun O, Pan L, Ya J *et al*. The efficacy and safety of batroxobin in combination with anticoagulation on cerebral venous sinus thrombosis. *J Thromb Thrombolysis* 2018;**46**:371–8
20 Carr ME Jr, Carr SL, Tildon T, Fisher LM, Martin EJ. Batroxobin-induced clots exhibit delayed and reduced platelet contractile force in some patients with clotting factor deficiencies. *J Thromb Haemost* 2003;**1**:243–9

https://doi.org/10.1017/S0022215123001512 Published online by Cambridge University Press