**Original Article**

The Role of Fibrinolysis in Adhesive Otitis Media (AOM)

ZOU Yi-hui, HUANG De-liang, YANG Shi-ming, HAN Dong-yi

Abstract Objective To study the effects of Batroxobin on otitis media with effusion (OME), an early stage of Adhesive Otitis Media (AOM), for the purpose of expanding our understanding of the role of fibrinolysis in the pathogenesis of AOM. Method Forty cases of OME (45 ears) were randomly selected to receive intratympanic administration of Dexamethasone at 5 mg/ml (Group 1 or G1), Batroxobin at 1 BU/ml (Group 2 or G2) or Batroxobin at 2 BU/ml (Group 3 or G3). Pre- and post-treatment changes in clinical symptoms, the Air conduction Hearing Threshold (AHT) in pure tone audiometry and average AHT over 0.25 to 2 kHz were compared. Results Data from 31 cases (33 ears) were available for analysis. AHTs among three groups were similar prior to treatment \( P > 0.05 \). The rate of normal hearing following treatment in G3 was 70% or 7 / 10, higher than in G1 (41.7% or 5 / 12) and G2 (54.5% or 6 / 11) \( P < 0.05 \). The rate of improvement following treatment was 81.8% or 9/11 and 80.0% or 8 / 10 in G2 and G3, respectively, higher than that in G1 (50.0% or 6 / 12) \( P < 0.05 \). Conclusions Therapeutic effects of intratympanic injection of Batroxobin on OME is superior to traditionally used Dexamethasone. In addition, higher concentration of Batroxobin appears to be superior to lower concentrations. These findings confirm that fibrinolysis plays a pivotal role in the pathogenesis of middle ear adhesion and that fibrinolytic medicine can prevent or reduce adhesion development in the middle ear.

Key words Batroxobin, otitis media with effusion, adhesive otitis media, fibrinolysis

Introduction

Adhesive otitis media (AOM) is an important cause of hearing loss. Adhesion in the middle ear is irreversible once formed. Therefore, the most effective clinical intervention for AOM is to prevent or mitigate adhesion formation in the middle ear. Currently, AOM is regarded as a later stage or sequelae and complication of all types of otitis media \(^1\). In the clinic, late stage otitis media with effusion (OME) often is seen to progress to AOM, supporting this view. Studies of peritoneal adhesion indicate that reduction of local fibrinolysis is a key factor in peritoneal adhesion formation \(^2, 3\). In addition, the characteristics of adhesion in the peritoneal and tympanic cavities are similar. We, therefore, speculated that fibrinolysis also played a pivotal role in middle ear adhesion \(^4\) and hypothesized that, if so, the fibrinolytic medicine, Batroxobin, would prevent or reduce adhesion formation and accelerate recovery from OME. Here, we investigate the effect of Batroxobin on OME in comparison to Dexamethasone, an agent widely used in OME treatment, in order to elucidate the role of fibrinolysis during adhesion formation in the middle ear.

Material and Methods

1. Patient inclusion criteria: 1) reported fullness and obstruction in the ear, hearing loss and tinnitus; 2) over 0.25–2kHz, air conduction hearing threshold (AHT) on pure tone audiometry >25 dB HL, bone conduction ≤ 25dB HL and air and bone gap ≥10 dB \(^5\); 3) type B or C tympanogram; 4) presence of intratympanic fluid on tympanometry; 5) no other present diseases.

2. Treatment groups Patients were randomly selected to receive intratympanic injection of dexamethasone sodium phosphate at 5 mg / ml (Group 1 or G1), Batroxobin (made in Japan) at 1 BU / ml (Group 2 or G2) or Batroxobin at 2 BU / ml (Group 3 or G3).

3. Patient data Of the 40 cases (45 ears) studied, 7 (10 ears) were excluded due to presence of sensorineu-
ral component in their hearing loss and 2 cases (2 ears) dropped from the study, resulting in 31 cases (33 ears) meeting the inclusion criteria and enrolled in the study. The distribution of age, gender and course of disease were similar among the three treatment groups (see Table 1).

4. Treatment After sterilizing the external auditory meatus with 75% ethanol and topical tympanic membrane anesthesia, tympanotomy was performed and the middle ear drained. 0.5 ml of either dexamethasone sodium phosphate at 5 mg/ml (G1), Batroxobin at 1 BU/ml (G2) or Batroxobin at 2 BU/ml (G3) was injected into the tympanic cavity. After the procedure, patients were placed on Cefalexin at 0.5 g tid for 5 days and followed up on the 3rd, 7th, 14th and 28th post-operation days. Treatment was repeated 1–2 times if deemed necessary. AHT was tested before and after treatment.

5. Outcomes assessment
5.1 Efficacy assessment. Treatment efficacy was assessed 4 weeks after treatment based upon AHT over 0.25 to 2 kHz and improvement of clinical symptoms. The following criteria were used: 1) Complete resolution: AHT at all frequencies were <25 dB HL with no residual symptoms; 2) Significant improvement: AHT at all frequencies improved by more than 30 dB with complete resolution or significant improvement of clinical symptoms; 3) Improvement: AHT at all frequencies improved by 15 dB to 30 dB with noticeable symptom improvement; 4) Failure: AHT improvement was less than 15 dB with no symptom improvement. The outcome differences among groups were examined using $\chi^2$ test.

5.2 Audiometric data assessment. Pre- and post-treatment AHT changes and differences in post-treatment AHT among groups over 0.25 to 2 kHz were assessed using variance analysis.

Results
1. Symptoms: All but 2 ears in G1 showed complete resolution or improvement of clinical symptoms.
2. Therapeutic efficacy: See Table 2–3 for changes in symptoms and AHT over 0.25 to 2 kHz.
3. Audiometric data changes: See Table 3 and Figure 1 for AHT changes over 0.25 to 2 kHz in three groups before and after treatment.
Discussion

According to reports, decreased local fibrinolysis plays a pivotal role in the pathogenesis of peritoneal adhesions [2, 3]. As the activity of plasminogen activator (PA), the most important factor in fibrinolysis, in effusion of the middle ear, is reduced [6, 7], Effective prevention and treatment of OME with the fibrinolysis medicine, Batroxobin [8], have been reported in an experimental model and the authors' previous works have shown that PA plays a role in adhesive formation in the middle ear [9], we hypothesize, therefore, that fibrinolysis is also an important factor in the pathogenesis of middle ear adhesion through mechanisms similar to that in peritoneal adhesion. Adhesion formation can be caused by many factors, including infection, allergy, surgery, injury, eustachian tube dysfunction, etc. Damage to the mucosa of middle ear leads to inflammatory responses and repair which involve several complex biological processes and at least five separate, but interrelated, systems. Mucosal damage can result in injury of vascular endothelium and subsequent exudation of all blood constituents, including fibrinogen, plasminogen and fibronectin (Fn), all of which can collect in the middle ear. Fibrinogen reacts with thrombin to create fibrin monomer that can polymerize. Fibrin polymers then come into contact with coagulation factors such as factor XIIIa and become insoluble. Eventually, insoluble fibrin polymers interact with large proteins, such as Fn, to produce the fibrin gel matrix. Adhesion formation or adhesion–free re–epithelialization of the fibrin matrix is an alternative pathway, which depends on fibrinolytic activities. At sufficient levels of fibrinolytic activities, the fibrin gel matrix can be completely lysed. Otherwise, the fibrin gel matrix remains and serves as the progenitor to adhesions by forming a band or bridge between two apposed mucosa surfaces coated with it. The band or bridge becomes the basis for the organization of an adhesion. Usually, within 5 to 7 days, it can be determined whether the fibrin gel matrix has persisted or been lysed [2–4], consistent with findings in animal models of middle ear adhesion formation [10].

There are three sources of fluid in OME: blood contents from the middle ear mucosa discharged into the cavity, secretions arising from mucosa epithelium metaplasia, and proliferation of mucosa glands. Related to the first source are three models of pathogenesis based on blood vessel permeability: 1) bubble proliferation, 2) loosening contact between endothelial cells, and 3) endothelium destruction. In mild cases, the first two conditions preponderate and the exudation consists of salt and low molecular weight proteins. In severe cases where the third circumstance occurs, a great variety of blood components can be exuded [11]. The latter two fluid source of OME typify chronic reactions where the aforementioned blood vessel reaction underlies and persists throughout the inflammation process.

Fibrin (coming from fibrinogen) deposition in the middle ear seems to be a prerequisite for adhesion formation. Fibrinogen comes from the blood during the inflammatory process and is a high molecular weight protein. It is exuded in severe cases that destroy the vessel’s endo-

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Table 3 Pre– and post–treatment AHT (dB HL)

<table>
<thead>
<tr>
<th>Groups</th>
<th>0.25 kHz Pr</th>
<th>0.5 kHz Pr</th>
<th>1.0 kHz Pr</th>
<th>2.0 kHz Pr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Po</td>
<td>Po</td>
<td>Po</td>
<td>Po</td>
</tr>
<tr>
<td>G1</td>
<td>30.4</td>
<td>28.3</td>
<td>34.6</td>
<td>26.7</td>
</tr>
<tr>
<td>G2</td>
<td>34.5</td>
<td>24.5</td>
<td>35.0</td>
<td>19.5</td>
</tr>
<tr>
<td>G3</td>
<td>34.5</td>
<td>15.5</td>
<td>32.0</td>
<td>15.0</td>
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</tbody>
</table>

Note 1: Pr (pre–treatment): no differences among the three groups (P >0.05)
2. Po (post–treatment): G3 lower than G2 and G1 (P <0.05), no difference between G2 and G1 (P >0.05)
3. More pre– and post–treatment AHT change in G3 and G2 than in G1 (P<0.05) and no difference between G2 and G3 (P >0.05)

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Fig.1 Average pre–and post–treatment AHT changes over 0.25 to 2 kHz. Solid lines: pre–treatment, and dashed lines: post–treatment. There are more pre– and post–treatment AHT changes in G3 and G2 than in G1 (P<0.05) and no difference between G2 and G3 (P>0.05)
The quantity of high molecular weight proteins released during effusion, such as fibrinogen and Fn, varies based upon the extent of mucosa damage, thus the varying degrees of development of adhesion in the middle ear.

Once formed, adhesion is irreversible. Giving medications that promote fibrinolysis to decompound fibrinogen and dissolve gel matrix before adhesion development can prevent or reduce adhesion in OME, as well as accelerating recovery.

The current work compared the therapeutic effects between Batroxobin and Dexamethasone. The conditions of the three groups in this study were similar, exhibiting equivalent hearing loss ($P > 0.05$). Medical intervention prior to entering the study was also comparable as was the study methodology, allowing studying effects from pharmacological differences between the two medications. The main role of Batroxobin is to promote fibrinolysis, which is realized by decomposing fibrinogen, promoting the release and activity of tissue PA (tPA), and reducing its inhibitors, such as $\alpha_2$ – PI, PAI$ ^{[12]} $. Dexamethasone works through its anti-inflammatory, antitoxic and antishock capabilities and through inhibition of growth of capillaries and fibroblasts, which can prevent adhesion development at later stages of inflammation. Our results indicate that therapeutic effects of Batroxobin are better than those of Dexamethasone on OME, and that Batroxobin at 2 BU/ml is superior to Batroxobin at 1 BU/ml. This suggests that fibrinolysis is a major factor in middle ear adhesion formation and pathogenesis of AOM and those Batroxobin–like medicines may prevent or reduce adhesion development in the middle ear.

We therefore conclude that fibrinolysis is an important factor in pathogenesis of middle ear adhesion and that application of medicines that promote fibrinolytic process and removing exuded fibrinogen in the middle ear in time can prevent / reduce adhesion formation and development of AOM.

References


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