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Randomized controlled trial of juzen-taiho-to in children with recurrent acute otitis media☆

Makoto Ito [a], Yumiko Maruyama [b], Ken Kitamura [c], Toshimitsu Kobayashi [d], Haruo Takahashi [e], Noboru Yamanaka [f], Yasuaki Harabuchi [g], Hideki Origasa [h], Tomokazu Yoshizaki [i,*]

[a] *Department of Pediatric Otolaryngology, Tochigi Children's Hospital, Jichi Medical University, Tochigi, Japan*
[b] *Department of Otolaryngology, Kurobe Civic Hospital, Kurobe, Japan*
[c] *Department of Otolaryngology-Head and Neck Surgery, Tokyo Medical & Dental University, Tokyo, Japan*
[d] *Department of Otolaryngology-Head and Neck Surgery, Tohoku University School of Medicine, Sendai, Japan*
[e] *Department of Otolaryngology-Head and Neck Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*
[f] *Department of Otolaryngology-Head and Neck Surgery, Wakayama Medical University, Wakayama, Japan*
[g] *Department of Otolaryngology-Head and Neck Surgery, Asahikawa Medical University, Asahikawa, Japan*
[h] *Biostatistics and Clinical Epidemiology, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan*
[i] *Department of Otolaryngology-Head and Neck Surgery, Graduate School of Medical Science, Kanazawa University, Japan*

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ABSTRACT

Objective: Recurrent acute otitis media (AOM) in young children is rapidly increasing worldwide. Repeated antibiotic use leads to antibiotic-resistant pathogen development. Complementary and alternative medicine approaches have been suggested as a supplemental treatment option to conventional antimicrobial medicine. This randomized, parallel-group, open-label, non-herbal medicine controlled trial assessed the efficacy of a traditional Japanese herbal medicine, juzen-taiho-to (JTT) for AOM prevention in otitis-prone children.

Methods: Children prone to recurrent AOM aged 6–48 months were recruited from 26 otolaryngology clinics in Japan and received conventional AOM treatment based on Japanese guidelines with or without 2 daily oral doses of JTT (0.10–0.25 g/kg/day). The mean number of AOM episodes, coryza episodes, and duration of total antibiotic administration per month were compared during 3-month intervention.

Results: At least one episode of AOM was diagnosed in 71% of JTT-group and 92% of control participants during follow-up. JTT administration reduced the frequency of AOM episodes by 57% compared with children who received conventional treatment alone (0.61 ± 0.54 vs. 1.07 ± 0.72 AOM instances/month; $P = 0.005$) and also significantly decreased number of coryza episodes ($P = 0.015$) and total antibiotic administration ($P = 0.024$).

Conclusions: This is the first report of recurrent AOM prevention by herbal medication. JTT appears to effectively prevent recurrent AOM in children. Subsequent double-blind studies are needed to confirm the beneficial effects of JTT on recurrent AOM and upper respiratory tract infections.

☆ *Clinical Trial Registration*: UMIN-CTR: ID: UMIN000002871.

Abbreviations: AOM, acute otitis media; CAM, complementary and alternative medicine; JTT, juzen-taiho-to; MEE, middle ear effusion; NKT, natural killer cells; URT, upper respiratory tract.

* Corresponding author at: Department of Otolaryngology-Head and Neck Surgery, Graduate School of Medical Science, Kanazawa University, 13-1 Takaramachi, Ishikawa, Kanazawa, Japan. Fax: +81 72 234 4265.
E-mail address: tomoy@med.kanazawa-u.ac.jp (T. Yoshizaki).

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1. Introduction

Otitis media is very common in children. By 2 years of age, most children (70%) experience at least one episode of acute otitis media (AOM) [1–5]. A subpopulation of children, representing 5–10% of the general population, are otitis-prone, having experienced at least 3 separate episodes of AOM within a 6 months, or more than 4 episodes in 1 year [6–8].

The increase in the number of otitis-prone children and the rapid emergence of drug-resistant bacteria associated with AOM are now generating increasing concern. β-Lactamase-nonproducing ampicillin-resistant strains of *Haemophilus influenzae* and penicillin-resistant *Streptococcus pneumoniae* are particularly common and cause recurrent AOM in Japan [9–11]. In otitis-prone children, the effectiveness of repeated antibiotic therapy for each new infection and prophylactic antibiotic therapy to prevent AOM relapse is quite limited. Furthermore, recurrent use of antibiotics leads to the development of antibiotic-resistant pathogens [12,13] and the imbalance of the normal nasopharyngeal bacterial flora [14]. Surgical insertion of a tympanostomy tube can have a significant role in maintaining a 'disease-free' state [15–17], but clinicians should consider the possible adverse effects of grommet insertion, such as transient or recurrent otorrhea, tympanosclerosis, focal atrophy and persistent perforations which may require repair.

In addition to these conventional treatments for AOM, complementary and alternative medicine (CAM) approaches have been suggested as a supplementary choice for the treatment of recurrent AOM [18–20], because CAM treatments such as herbal medicine and probiotics are commonly used to treat pediatric upper respiratory tract (URT) viral infections in Europe, United States and Asia [21–23]. Viruses play an important role in middle ear viral and following bacterial infection because a URT viral infection usually precedes AOM. *Echinacea*, *Lactobacillus rhamnosus* GG (probiotic), mao-to and kakkon-to (herbal medicine) are considered to reduce the risk of acute URT infections [21,23–25], but no confirmative evidence has shown that these products reduce the incidence of recurrent AOM [24,25].

The unique role played by traditional Japanese herbal medicine, a type of pharmaceutical-grade multi-herbal medicine, is gradually attracting worldwide attention. More than 100 herbal medicines have been used clinically for centuries to treat a wide variety of diseases with very few side effects. Despite, safety and tolerability of most CAM treatments are not precisely defined, all Japanese herbal medicines are standardized and manufactured on a modern industrial scale under strict scientific quality controls. Juzen-taiho-to (JTT) is one of the Japanese herbal medicines that comprises 10 different herbs, and is administered to patients in various weakened conditions, including post-surgery patients and patients with chronic illnesses, where it can alleviate general symptoms such as fatigue, pale complexion, anemia and loss of appetite [26,27]. JTT is used clinically to strengthen the immune functions of patients with various diseases, including cancer, hepatitis. JTT has been suggested to upregulate the host immune system [28–30] and reported to have therapeutic effects against bacterial infection such as perianal abscess [31]. A recent report suggested the beneficial effects of JTT in reducing the episodes of AOM in otitis-prone children [32,33]. JTT has been known for lipopolysaccharides (LPS)-like immunostimulatory activity [34,35]. JTT and LPS induce similar gene expression profiles in monocytes [36,37]. Montenegro et al. suggested the emerging theory of bacterial contribution to the immune-boosting activity of JTT, called ''herbal probiotics'' [38].

JTT is composed of ten crude drugs, of which the quality is controlled by Japanese Pharmacopia XIII. JTT was prepared as follows. A mixture of Astragali radix (3.0 g), Cinnamomi cortex (3.0 g), Rehmanniae radix (3.0 g), Paeoniae radix (3.0 g), Cnidii rhizome (3.0 g), Atractylodis Lanceae rhizome (3.0 g), Angelicae radix (3.0 g), Ginseng radix (3.0 g), Hoelen (3.0 g), and Glycyrrhizae radix (1.5 g) was added to 285 ml of water and extracted at 100 °C for 1 h. The extracted solution was filtered and the filtrate was spray-dried to obtain the dry extract powder (2.3 g).

The aim of this study was to examine the possible effect of JTT in reducing the incidences of recurrent AOM in young children in a strict diagnostic framework. The primary and secondary endpoints were to investigate whether JTT could reduce the number of infectious episodes of AOM (primary endpoint) as well as URT infection (coryza), the duration of antibiotic administration and the number of children who underwent tympanostomy tube insertion and time (days) until tympanostomy tube insertion during the intervention in otitis-prone children (secondary endpoints). We conducted a randomized, parallel-group, open-label, non-herbal medicine (conventional treatment only) controlled trial between December 2009 and October 2011 to assess the efficacy of JTT for the prevention of AOM in children with recurrent AOM.

2. Methods

2.1. Study settings

The study was conducted according to the principles of the Declaration of Helsinki (as amended in Somerset West, South Africa 1996) and was approved by the Institutional Review Board at each participating university and hospital (Approval No. 2009-032 5587). An independent external group was appointed to monitor the study progress and the safety of the participants.

2.2. Subjects

Children aged 6–48 months who were otitis prone (as documented in their medical records) were recruited from 26 otolaryngology clinics including university hospitals, general hospitals, and private clinics in Japan during December 2009 to October 2011. Children with unwillingness to participate; congenital malformations of the ears, nose, or throat; known allergy to JTT; or receiving immune therapy (e.g., immunoglobulin and steroids) or other Japanese herbal medicine were excluded from the study. Children with tympanostomy tube insertions were also excluded from the study.

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