Study Protocol

Otological Safety Profile of 100% Manuka Honey Application in Tympanoplasty: A Double-blinded Randomized Controlled Trial

Formulated on 5th May 2021

Revised on 20th November 2022

Background

Chronic suppurative otitis media (CSOM) is the chronic inflammation of the middle ear mucosa characterized by intermittent or continuous ottorhea from the ear canal that can be mucopurulent or serous in nature, through a perforation of the tympanic membrane that has occurred for two months or more.Two types of CSOM are recognized, a mucosal disease (safe type) and an epithelial disease (unsafe type).[1,2]

CSOM is included in the ten most commonly found diseases in the field of Ear Nose Throat Head and Neck Surgery (ENT-HNS) in Indonesia, and ranks first in its prevalence. The prevalence of CSOM in Indonesia based on a survey by the Ministry of Health of the Republic of Indonesia in 1993-1996 was 3.1%,[3] and according to the criteria of the World Health Organization (WHO) Indonesia was considered to have a high prevalence rate. When calculated based on the total population of Indonesia, which is currently 250 million, it is estimated that Indonesia has 7.8 million people who suffer from CSOM. Patient data from the Otology Division of the ENT-KL National Hospital Dr. Cipto Mangunkusumo (RSCM) for the 2010-2020 period also showed a similar value, Where CSOM was the number one cause of patient visits to the outpatient clinic and the most surgeries carried out each year.4 The impact caused by CSOM is very large, namely hearing loss, restrictions on activities related to water, as well as the risk of fatal complications.[1]

Developments in the field of ENT-KL, especially otology, have made this disease treatable with a high success rate. One of the therapeutic options for CSOM is middle ear surgery. The aim of this surgery the prevention of reinfection through closure of the TM. However, graft failures can still occur. This failure can be caused by poor vascularization around the edge of the perforation due to chronic infection that results in low secretion of growth factors needed for the wound healing.

Throughout history, honey has been recognized for its healing properties. The use of honey for its medicinal properties dates back to 2200 BCE. The main content of honey is sugar (75-79%) and water (20%).[11,14,15] Other ingredients are protein, vitamin B complex, minerals and antioxidants such as flavonoids, ascorbic acid, catalase, and selenium. Honey also contains enzymes such as invertase, amylase, and glucose oxidase.[11] Oryan et al.[16] wrote that the therapeutic effect of honey on wound healing occurs through the following mechanisms: 1) antimicrobial activity; 2) debridement function; 3) anti-inflammatory function; 4) improving the immune system; 5) antioxidant function; 6) stimulate tissue regeneration and repair.

A number of studies have shown a positive effect of honey on cell proliferation, especially keratinocyte cells which play a very important role in the process of closing tympanic membrane

perforations. Chaudhary, et al.[17] conducted a study using honey on human immortal keratinocytes (HaCaT) cultures. They found that the dilution of honey that gave the most effective effect was 0.1%. The wound healing rate in the cell layer was found to be the highest at 0.1% honey dilution and the lowest at 0.25% dilution. Calli et al.[18] conducted a study on guinea pigs to evaluate the effect of honey on the healing of tympanic membrane perforations. They found that the group of animals that received honey drops showed a greater success of perforation closure than the control group that received drops of physiological saline solution. The results of histological examination also showed that the connective tissue was thicker and had a better woven arrangement in the group with the honey intervention.

Tympanoplasty is a surgical procedure that has a high level of difficulty and cost, and has a risk of failure. The failure rate for closure of the MT perforation ranges from 21% to 33%. One of the most common failures in this operation is that the MT perforation does not close due to poor vascularization and very low growth factor secretion in the perforated area. Honey has been widely studied for its benefits in wound healing,[19] but the effect of Manuka honey on the tympanic membrane re-epithelialization process in CSOM patients has not been researched, given the differences in wound healing of the tympanic membrane and other parts of the skin. This research is expected to provide a new method that can increase the success of the tympanic membrane closure.

Research Objectives

- To test the otological safety of 100% medical grade manuka honey given at the time of tympanoplasty.

Research Design

This study uses a comparative, randomized and prospective clinical trial design to determine the effect of honey in increasing tympanic membrane re-epithelialization post tympanoplasty. The clinical study uses 100% medical grade manuka honey to determine the safety of its use in the healing process of tympanic membrane perforation after tympanoplasty. The subjects of the clinical study are CSOM patients of the mucosal type who underwent tympanoplasty at the Cipto Mangungkusumo hospital. During this research procedure, evaluation of the effect of ototoxicity will be carried out on all patients with the click stimulated ABR starting from the first subject. If an ototoxicity effect is indeed found, it will immediately be reported to an independent team outside the research team for an interim analysis to see the causal relationship with the treatment. Other side effects of administering manuka honey during and after the study reported by patients were immediately noted and evaluated.

Methods

The in vivo study was a randomized, controlled, double-blind clinical trial on adult patients (18 - <46 years old) diagnosed with tubotympanic chronic suppurative otitis media (CSOM) undergoing tympanoplasty at Cipto Mangunkusumo General Hospital (CMGH) from June 2021 – August 2022. Patients who had previously received surgical treatment for CSOM in the same ear or had recurrent or residual disease and those whose pathology showed suspicion of tumors were excluded from the study. Patients were randomly divided into intervention and control groups using the Robust Randomization App (RRApp)[122] with a simple random sampling method and a ratio of 1: 1. Patients were blinded to the group assignments. During tympanoplasty, after filling the middle ear with gel foam and placing the graft, gel foam soaked in MH (MANUKApli topical gel, ManukaMed®) was placed in the external ear canal in the intervention group, while the control group only received a gel foam packing. The outer third of the ear canal was filled with an antibiotic tampon. The ear tampon is removed two weeks after the procedure and all patients applied six drops of 0.3% of ofloxacin twice daily for five days. Patient's symptoms were followed up at a weekly basis for the duration of six weeks. The BERA test was done at week 5. An audiometry test was done at week 6 to evaluate possible hearing loss. At 3 to 6 weeks post-tympanoplasty, patients were not given any ear drops.

For the in vivo study, the Mann-Whitney U test was used for unnormalized distributed continuous data. Categorical data were analyzed by using the Chi-square test with an alternative Fisher's exact test. The correlation of two numerical variables was analyzed by the Pearson correlation test for normally distributed data and Spearman correlation for data with non-normal distribution. The normality test was the coefficient of variation (COV) and the Shapiro-Wilk test. All tests were carried out in two-tailed with a significance level of 0.05. All data were processed and analyzed using Microsoft Excel 2021 and the Statistical Package for The Social Sciences (SPSS) version 26. All graphs were created using GraphPad Prism 9.1.0. This study was approved by the ethical committee of the Faculty of Medicine, Universitas Indonesia (no. KET 469/UN2.F1/ETIK/PPM.00.02/2021).