



(RESEARCH ARTICLE)



Erdosteine for mucociliary transport in benign chronic suppurative otitis media

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Abstract

Background: Current treatment for CSOM is still unsatisfactory, many factors contributed in this condition. Impaired mucociliary clearance of the Eustachian tube can be a predisposing factor for recurrent otitis media and slow healing of the middle ear mucosa, local circulation and improvement of middle ear pressure. During process of middle ear infection, mucus production commonly found, the middle ear and the Eustachian tube are disturbed. The erdosteine effects of increase epithelial mucociliary transport are well documented. Objectives: To investigate the effectiveness erdosteine in mucociliary transport of benign CSOM.

Method: sixteen (16) patients with benign CSOM were experimental research, using pretest-posttest control group design method with random sampling. The two main comparisons were transport mucociliary time compared to a) erdosteine and b) no erdosteine.

Result: The study analyzed the interval time of mucociliary transport between pretest and posttest was measured in studied patients. The transition time from pretest to posttest with erdosteine from 24:36:22 to 16:28:32 minutes ($p=0,006$) and without erdosteine from 22:12:39 to 19:18:19 minutes ($p=0,029$). There is a difference in transportation time before and after administration of erdosteine.

However, there were no significant difference in mucociliary transport time from pretest to posttest between 2 groups ($p=0.682$).

Conclusions: The results of our study indicate that erdosteine is correlated with increased mucociliary transport. Eventhough the interval time have no significance different between erdorsteine group and without erdorsteine group.

Keywords: Erdosteine; Mucociliary transport; Chronic suppurative otitis media; Middle ear

1. Introduction

Chronic Suppurative Otitis Media (CSOM) is represented as chronic inflammation of the middle ear and mastoid cavity, manifested with persistent or recurrent ear discharge through the tympanic membrane perforation with duration more than 2 months (1, 2).

Current treatment for CSOM is still unsatisfactory, many factors contributed in this condition. Impaired mucociliary clearance of the Eustachian tube can be a predisposing factor for recurrent otitis media and slow healing of the middle ear mucosa, local circulation and improvement of middle ear pressure. In some studies it is said that a properly

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functioning Eustachian tube can affect the function of the middle ear. Good tubotympanic mucociliary drainage is a favorable prognostic factor in the outcome of therapy and the success of middle ear reconstructive surgery(3, 4).

In the infection process of CSOM, inflammatory cells also spontaneously release oxidants and continuing production of secret due to transform the structure of the middle ear epithelium. Mucolytics work by diluting secret with break down mucopolysaccharide threads from mucus so the viscosity can reduce, easier to expel, and restore function of mucociliar clearance(5).

Currently, erdostein as mucolytics used in acute and chronic respiratory infections case. Working as a mucoactive agent and mucoregulator, also has other positive effects such as antioxidant, increasing epithelial mucociliary transport, anti-bacterial adhesive, and anti-inflammatory. As an anti-inflammatory agent, erdostein inhibit cytokines and TNF- α . Dal Negro et al and Maurizio's study stated that the positive effect of Erdostein was better than other mucoactive agents in the treatment of chronic respiratory infections (5, 6).

Erdostein is also given as adjuvant therapy in rhinitis or rhinosinusitis. In a study conducted by Hoza JF et al on 60 patients with chronic rhinosinusitis accompanied by polyps, erdostein administration was able to improve the patient's complaint due to erdostein's anti-inflammatory effect and could be given concurrently with antibiotics and steroids, no side effects were found. Meanwhile, in cases of middle ear infection, mucolytic administration not yet become a standard treatment because of the lack of research (7).

The ENT Clinical Practice Guidelines describes benign CSOM therapy with systemic or topical antibiotics, ear toilet, and avoid water come in to the ear (8). Based on the high cases of CSOM, the rate of treatment failure and disease recurrence, so in the current study we investigate the effectiveness erdosteine in mucociliary transport of benign CSOM.

1.1. Prevalence

The prevalence of the disease in the world shows the wide variation, the most common in low-income and middle-income countries. At the developing countries it is about 65-330 million (4-33.3%) patients, while 60% (39-200 million) of them have conductive hearing loss. More than 90% of this disease is found in tropical and subtropical countries such as South-East Asia, Pacific and Africa and these cases are rare in America, Europe, Middle East and Australia (9, 10).

The prevalence of CSOM in Indonesia is 3.8%. Sanglah Hospital Denpasar reported that 382 patients with CSOM from 2014-2016. Zainoel Abidin Hospital Banda Aceh showed that the incidence of CSOM in 2018 was 380 patients (11, 12).

2. Material and methods

The study was approved by institutional review boards of dr Zainoel Abidin Hospital and Universitas Syiah Kuala Banda Aceh. An experimental research study, using pretest-posttest control group design method with random sampling. There were two groups, the erdostein group (treated with oral antibiotics Ciprofloxacin 2x500 mg, aural toilet H2O2 3% 3x10 drops and oral mucolytic Erdostein 2x300 mg) and the control group (without erdostein). The patients who diagnosed with benign CSOM and attended outpatient clinic ENT Department at Zainoel Abidin Hospital Banda Aceh Indonesia. Random sampling was utilized.

The sample in this study were patients with benign CSOM and otorrhea, the age between 18-65 years old, and agreed to participate in this study. On the contrary, CSOM patients without otorrhea, ENT carcinoma, upper respiratory tract infections, rhinitis allergy, postoperative ear, anatomical abnormalities, pregnant women, and had taken mucolytics two weeks previously were excluded.

The samples were collected from patients with benign CSOM and had otorrhea. The patient rinsed before and after the examination and was not informed about the kind of taste would feel. The patient lies with the head tilted to the contralateral side of the ear being examined for 5 minutes then the external auditory canal was cleaned using a cotton, 0.1 ml of saccharin solution 5% was dripped into the tympanic cavity through the perforation, observed with ear microscope. Counted time by stopwatch until the patient feels the sweet taste. The samples outpatients and given therapy for 7 days, according to group.

Both of groups evaluated on 8th day, they performed the same procedure to dripped saccharin solution, counted the time and compare between pretest-posttest and between treatment group-control group.

3. Results

3.1. Characteristics demographic

There were 3 (18.8%) patients in each the age group of 18-25 years, 26-35 years, and 55-65 years. there were 5 (31.3%) patients in the age group of 36-45 years, 2 (12.5%) patients in the age group of 46-55 years. Majority of the patients were males (62.5%) compared to females (37.5%).

3.2. Clinical characteristics

In the present study, 9 (56.3%) patients had otoreea, 5 (31.3%) had hearing loss, 1 (6.3%) had tinnitus, and 1 (6.3%) had ear pain. Out of 16 patients, 8 (50%) patients had CSOM in 1-5 years, some 8 (50%) patients are more than 5 years. None of the patients had CSOM less than 1 year. Ear complain repair showed the otorrhoea were reduced during the post-test, namely 9 people (56.3%). There were complaints of persistent tinnitus in 1 patient and hearing loss in 5 patients.

3.3. Mucociliary transport

In this study, mean saccharin clearance time in erdostein group pre-test and post-test were found to be 11.56 and 14.15 min with time difference mucociliary were 8.7 min. In group without erdostein group pre-test and post-test were 12.39 and 12.48 min with time different mucociliary were 3.64 min.

4. Discussion

The age range of participants in this study was ranging from 36 to 45 years and mean age was 39 years. In another similar study, the age of patient range from 25 to 44 year age group (37.4%)(13). However, according to another study, the largest prevalence of CSOM was the age group 1 to 10 years is 52.8% (14). The incidence of CSOM almost begins with recurrent otitis media in children, rarely after adulthood. Infectious factors usually come from the nasopharynx reaching the middle ear through the Eustachian tube. This is related to the size and location of the Eustachian tube which is shorter and flatter and the immunological function was still low, making it easier to get middle ear infections in children(15, 16).

The two classic symptoms CSOM are otorrhoea and conductive deafness. Usually, patients complain of pain or discomfort in the ear and tinnitus(8). This is in line with this study, it was found that patients with active phase safe type CSOM who had the most ear complaints were otorrhoea as many as 9 people (56.3%) and hearing loss as many as 5 people (31.3%) followed by complaints of tinnitus as many as 1 person (6.3%) and ear pain as much as 1 person (6.3%). While suffering from CSOM, an inflammatory process occurs that releases various inflammatory mediators. This process due to the proinflammatory cytokines TNF-, IL1- β , and IL-8 play an important role in mucus production by middle ear goblet cells, then caused mucociliary dysfunction in the middle ear, mucus build up and ultimately decrease mucociliary transport in the tube Eustachius(17).

Otorrhoea is the most common complaint in this study because the inflammatory process will affect the middle ear mucociliary transport system where goblet cells increase so that mucus production will also increase. Chao et al in Sari et al reported that the anterior two thirds of the Eustachian tube had the most active mucociliary transport activity (17). Based on the length of suffering CSOM, it was found that CSOM 1-5 years were 8 patients (50%) and >5 years were 8 patients (50%). The result was different with the research at ENT outpatient at Malang, in his research complaining ear discharge more than 5 years were 66.7%, while 16.67% had complaints 1-5 years and <1 year. Duration of the disease also shows the relation between the duration of complaints.(17) Factors cause otitis media become chronic include inadequate therapy, high virulence, Eustachius tube dysfunction, allergies, low body resistance, poor environment and social economics (18, 19). According to the authors, difference in this study due to the majority of the samples were the productive age group and they were more aware of their ear complaints. The productive age is productive in working, socializing, high activity so recover from illness is high and related to seeking treatment. In this study, it was found that in the treatment group there was a difference between the mean mucociliary transport time between the pretest and posttest.

The average mucociliary transport time in the treatment group became faster, from 24:36:22 minutes (SD \pm 11:56:09) to 16:28:32 minutes (SD \pm 14:15:04) with a time difference of 08:07:50 minutes. Likewise in the control group where the mean post-test mucociliary transport time became faster from 22:12:39 minutes (SD \pm 12:39:32) to 19:18:19 (SD \pm 12:48:12) with a mean difference of 03:64:20 minutes. This is in line with the research at Dr. Wahidin

Sudirohusodo hospital, Labuang Baji and Pelamonia Makasar hospital conducted a study on patients with active otitis media with effusion (OME) based on the category of mucociliary transport time before and after 7 days of conservative treatment. They saw a change transport time between the first day (before conservative treatment) and seventh day (after treatment), the results time before treatment were 1638.06 seconds (27 minutes 18.06 seconds) and the average transport time on the seventh day (after treatment) was 1009.13 seconds (16 minutes 49.14 seconds). In this study showed a significant correlation between the length of suffering OME with mucociliary transport time in the pre-test and post-test ($p < 0.05$). Bivariate analysis in this study used paired t-test and independent t-test in each control and treatment group. Before the paired t-test was performed on both groups, a normality test was performed and the results were normally distributed. From the results of the paired t-test in the treatment group ($p=0.006$) and the control group ($p= 0.029$), there were found difference between pre-test and post-test mucociliary transport times. An independent t-test was carried out to test the difference in mucociliary transport time post-test and it was found that no difference between the control and treatment groups ($p=0.682$).

Conservative treatment given in their study included ear toilets, topical antiseptic (boric acid tampons), oral systemic antibiotics (cefadroxil) and oral corticosteroids. (20) Transformation in the mean mucociliary transport time became faster in the same group. This happened after giving therapy to both groups. A study states, after medical therapy in otitis media patients, the mucosa in the middle ear will healing in 2-3 weeks to 3 months, if there were complaints of recurrent upper respiratory tract infections such as rhinitis, sinusitis, tonsillitis and so on, they will be cured. In this study, the administration of therapy for both groups in 7 days was based on the recommended dose of Erdosteine 2x300 mg every day for 7 days and Erdosteine binding remain stable up to 7 days(6, 21). The mean pretest mucociliary transport time in the both groups were same. This is probably due to the average sample of the study suffering from OME for more than 5 years. The duration of OME affects the speed of mucociliary transport. Prolonged obstruction in the middle ear due to infection resulted in permanent changes in the mucosa and bone in the middle ear pre-test ($p=0.007$) between the effect length of stay and the time of mucociliary transport at the pre-test. This was also seen in the post-test ($p=0.010$) between the effect length of suffering and time of mucociliary transport at the post-test.(22) The most complaints from OME were otorrhea, where after treatment the complaints were reduced at 9 patients (56.3%). In this study, the selection of the antibiotic was Ciprofloxacin as the most effective antibiotics for the treatment OME and proven effective against OME(23). The results of paired t-test in the treatment group, it was found that there was a difference between the time of mucociliary transport between the pretest and posttest ($p=0.006$). Treatment group was given additional therapy Erdosteine mucolytic 2x300 mg/day for 7 days accompanied by Ciprofloxacin 2x500 mg and H2O2 3%, it was seen that Erdosteine administration had an effect on the mucociliary transport time. This result is different from another study that regarding the administration of a mucolytic (N-acetylcysteine) to OME benign, before and after treatment, in both group, there were no significant difference in transport time and decrease transport time. However, in their study, subjectively found an improvement in mucociliary transport time with administration of N-acetylcysteine but it was not statistically significant (17). According to the authors, one of the reasons for difference results, erdosteine has more positive effects than other mucociliary agents, has the best antibacterial anti-adhesive activity. The ability of bacteria to adhere to mucosal cells is associated with the surface of the bacteria having fimbriae. The active metabolite of Erdosteine is able to reduce the adhesion of bacteria to the host cell by means of the sulfhydryl Erdosteine molecule opening disulfide bonds in the fimbriae so that it interferes with the fimbriae bond with the host cell (5).

Cuneyt et al said that the mucolytics administration, analgesics and steroids in the treatment of otitis media, especially otitis media with effusion with very thick secretions because mucolytic agents can break down polysaccharides so that it will reduce mucus viscosity and improve middle ear mucociliary transport so that mucus is easier to expel. (24) Cuneyt M, Joseph ED, Ellen MM. Adjuvan Therapy Otitis Media in Advance Therapy of Otitis Media. Hamilton, London: Decker Inc. 2004;185-88)

Dalnegro et al mentioned that the combination of Erdosteine and several antibiotics, the effect that occurs not only increases the ability of antibiotics but also extends the inhibitory effect of bacterial adhesive to human mucosal cells when compared with antibiotics alone, showing Erdosteine's ability to enhance the anti-adhesion effect of antibiotics (5).

The treatment group was also given the antibiotic Ciprofloxacin and the mucolytic Erdosteine so that it was hoped that it would not only improve mucociliary transport but also increase the effect of antibiotics against bacterial infections so that the healing of OME would increase. The selection of the antibiotic Ciprofloxacin as the therapy for OME in this study was based on Abraham's research, where Ciprofloxacin, Gentamicin, Ceftriaxone and Amikacin were the most effective antibiotics for the treatment of OME(1).

5. Conclusion

To find out which one is better between giving Erdosteine and not giving Erdosteine, then an independent T-test is then performed, which is a test used to test the mean or mean of the two different subjects. The results showed that there was no difference in mucociliary transport time between the control and treatment groups with $p=0.682$ ($p>0.05$). The results of this study may be found in the length of time suffering from CSOM. The length of time suffering from CSOM was the same between the treatment and control groups, so that the mean results of mucociliary transport did not differ.

Based on statistical analysis, there was no difference in mucociliary transport time when Erdosteine was given or without Erdosteine, but this study found there are difference in mucociliary transport time of the treatment group was greater than that of the control group where there was an average change in mucociliary transport time from pretest to posttest. Mucociliary transport becomes faster and was follow decreased otorrhoea in the patient's complaints after administration of Erdosteine. Of course, giving Erdosteine can be considered as additional therapy in cases of active phase safe type CSOM.

Compliance with ethical standards

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Disclosure of conflict of interest

There was no conflict of interest in this research

Statement of ethical approval

The study has been approved by the Health Research Ethics Committee of the Faculty of Medicine at Syiah Kuala University with a number of Ethical contributions KEPPKN Registration Number: 1171012P (Description of Ethical Expedited "Ethical Expedited" Number: 031/EA/FKRSUDZA/2020)

Statement of informed consent

All study participants provided informed written consent prior to study enrollment.

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