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Hospital clinical trial: Homeopathy (*Agraphis nutans* 5CH, *Thuya occidentalis* 5CH, *Kalium muriaticum* 9CH and *Arsenicum iodatum* 9CH) as adjuvant, in children with otitis media with effusion

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ABSTRACT

Background: Otitis media with effusion (OME) is the most common cause of paediatric hearing loss. No single treatment has proved its effectiveness. There is a lack of evidence-based medicine studies in the area of homeopathy.
Method: A prospective randomized, double blinded interventional placebo control study was conducted. Patients, from 2 months to 12 years, with OME diagnosed by pneumatic otoscopy (PNO) and tympanometry, were randomized into two groups. Both groups received aerosol therapy (mucolytics and corticosteroids). In addition, the experimental group (EG) received homeopathy (*Agraphis nutans* 5CH, Thuya Occidentalis 5CH, *Kalium muriaticum* 9CH and *Arsenicum iodatum*), and the placebo group (PG) placebo, both of them for 3 months. Patients were evaluated by PNO examination and tympanometry at baseline, at 45 and 90 days.
Results: 97 patients were enrolled. In the EG, 61.9% of individuals were cured (PNO went from negative in the 1st visit to positive in the 3rd visit) compared with 56.8% of patients treated with placebo. 4.8% of patients in the EG suffered a recurrence (positive PNO in the 2nd visit changed to negative in the 3rd visit) while 11.4% did in the PG. No significant difference was found. Adverse events were distributed similarly, except in the case of upper respiratory tract infections, which were less frequent in EG (3 vs. 13, p: 0.009).
Conclusion: The homeopathic scheme used as adjuvant treatment cannot be claimed to be an effective treatment in children with OME.
Trial registration: EUDRACT number: 2011-006086-17, PROTOCOL code: 55005646.

Otitis media with effusion (OME), a non-purulent effusion of the middle ear, has been identified as a significant health problem for children in the early years of life. Recovery is spontaneous in most cases, but recurrence is common [1,2]. Some authors argue that OME is a normal evolutionary process within children development, 30–40% of pre-schoolers developing OME in the context of an upper respiratory tract infection (URTI) [3]. It is commonly accepted that OME begins to decline at about 6–7 years of age. The aetiology of OME is multifactorial and URTI, immature immune systems and poor functioning of the Eustachian Tube play an important role in children. Other factors contributing to the recurrence and maintenance of OME include age, perinatal factors, environmental factors, pharyngeal reflux, nursery care, allergy and exposure to cigarette smoke [2,4–10]. Diagnosis can be made by simple otoscopy, pneumatic otoscopy (PNO), optical microscopy, tympanometry or combinations of these procedures. Current clinical guidelines recommend the use of PNO for the diagnosis of OME [4,5,7,8,11] due to its high sensitivity (94%) and specificity (80%) [5,12].

Despite its frequency, it is not always clear how OME should be managed medically or when surgery should be recommended. Therefore differences of opinion between paediatricians and ENT

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specialists, are often found, which increase the uncertainty surrounding this pathology [5].

According to the American Academy of Paediatrics [7] and the British Clinical Guideline NICE [4], there is no guaranteed medical treatment that has proved to be efficacious in randomized controlled trials. Antihistamines and decongestants are considered ineffective and are not recommended for the treatment of OME. Antibiotics and corticosteroids have no proven long-term effectiveness, so their use is not routinely recommended either. Complementary and alternative medicine have a grade D recommendation in the clinical guidelines, as its usefulness can neither be confirmed nor discounted, and there are few relevant clinical studies published about these options [4,6–8,13,14]. Although there are some observational studies [14–16] and only one randomized controlled-blinded study with homeopathy, they focused in Acute Otitis media (AOM) [17]. Despite widespread doubts concerning the efficacy of homeopathic therapy, previous observational studies have demonstrated that its use is safe, also in the paediatric population [15,17]. Also, there is an increasing demand and consumption of homeopathic medicine in Spain, where approximately 30% of the population has used it at least once and 27% use it regularly, a percentage that reaches 36–40% in the paediatric population [13,18–20]. Also, a draft ministerial order in 2013 published by the Spanish Ministry of Health of Spain has given rise to a diversity of opinions among the medical and scientific community and the general population. Due to the absence of effective medical treatment and the high rate of spontaneous resolution of OME, the latest recommendations suggest a *"watch and wait"* strategy, consisting of active observation without any medical or surgical intervention for 3 months. This strategy is widely supported by all current clinical guidelines (Recommendation type A) [2,4,6,8].

In the current study we test the hypothesis that a protocoled homeopathic management of OME in childhood would: (i) Recover or reduce the recurrence of OME diagnosed with PNO and tympanometry; considering negative PNO (absence of tympanic motility) and type B tympanograms as pathological; and positive PNO (presence of tympanic motility) and type A or C tympanograms as absence of OME, (ii) reduce the rate of otological complications of OME (Number of AOM, eardrum perforation or mastoiditis) and (iii) be a safe treatment for children, recording adverse events (mild, moderate and severe) occurring during the 3 months of treatment.

To the best of our knowledge, this is the first randomized controlled blinded in OME involving homeopathy.

1. Methods

1.1. Design

A double blind, placebo-controlled, and randomized parallel-group Phase III study was carried out. There were no changes to the trial design before starting recruitment that could have affected the trial quality.

1.2. Participants (inclusion and exclusion criteria)

Patients aged from 2 months to 12 years with OME diagnosed by PNO examination (Halogen HPX with insufflation n° 25021 from Welch Allyn) were enrolled. Informed consent was provided by the parents of the participants.

1.3. Study settings

The study took place at the Department of Otorhinolaryngology and Head-Neck Surgery at Toledo Hospital Complex from January 1st, 2013 to December 31st, 2013 (enrollment period). Patients were referred to our tertiary health care Hospital by primary care paediatricians who had diagnosed OME, using simple otoscopy. The waiting time from diagnosis by paediatrician to evaluation by otolaryngologist was less than 3 months. The research team counted on the collaboration of 4 ENT specialists, a specialist in Biomedical Research and a Paediatric Specialist in Homeopathy. A Contract Research Organization (CRO) was recruited for pharmacovigilance, monitoring and statistical analysis purposes.

Once one of the four ENT specialists had confirmed the presence of OME with PNO and the parents had accepted to take part into the study by signing the informed consent, the patient was enrolled to the clinical trial. All examiners had more than 4 years of experience using PNO routinely. The patient's follow-up was always performed by the same clinician who had included the patient in the study.

The exclusion criteria included in this clinical trial were several conditions that may interfere with the resolution of OME: Neonatal screening fail, receptive language disorder, neurosensorial hearing loss, autism, craniofacial abnormalities, Down Syndrome, middle or internal ear malformation, ciliary motility disorders, cholesteatoma, acute mastoiditis, acute otitis media, recent vaccination (less of 30 days), obstructive sleep apnea, tympanic perforation or Timpanostomy tubes, adenoidectomy, lactose or glucose intolerance, treating asthma, corticoid, antihistamine or mucolytics therapy.

A Paediatric Specialist qualified with more than 30 years of experience in Homeopathy performed the homeopathic regimen selected. He is a registered member of the Society of Homeopaths of Spain. The homeopathic products selected are supposed to interact at the level of adenoids, Eustachian tube and fluidity of the effusion.

1.4. Randomization and trial interventions

After application of the inclusion and exclusion criteria, the children included in this study were randomly divided into 2 groups, the experimental group (EG) and the placebo group (PG). Treatment assignment was set up with a permuted-block randomization algorithm and a masking plan was followed to guarantee the double-blindness.

The EG received aerosol therapy (Model Aapex Mini-Nebe 230V-50Hrz 0.6A) consisting of one session every 24 h for 20 days of 1 vial of Ambroxol hydrochloride (7.5 mg/ml), 1 vial of Budesonide (0.25 mg/ml suspension), and 2 cc of physiological saline. The subjects also received homeopathic treatment A (*Agraphis nutans* 5CH and Thuya Occidentalis 5CH) with a dosage of 5 granules of each, once a day, preferably in the evening and homeopathic treatment B (*Kalium muriaticum* 9CH and *Arsenicum iodatum* 9CH) with a dosage of 5 granules, twice a day. The PG received the same therapeutic drugs scheme with aerosol therapy and placebo treatment instead of the homeopathy treatment. Boiron Laboratories prepared the homeopathy and placebo treatment, following European Good Manufacturing Practice (EGMP) requirement. Al of the active principles are licensed in Spain, where the trial took place.

Patients visited the trial centre on days 0 (1st baseline visit), 45 (2nd visit) and 90 (3rd visit) for the complete 3-month treatment protocol. A 4th safety follow-up telephone call was also performed, as shown in Fig. 1. At baseline 1st visit, demographic, clinical variables and ENT examination, including PNO (Digital Macro View-Model 23810) and tympanometry (Model GSI-Auto-Tymp Version 2), were carried out. All the primary and secondary outcomes were recorded in the Data Collection Logbook of the trial in each visit. Patients' empty aerosol containers and homeopathic-placebo tubes were checked in each visit, in order to measure the adherence to the treatment consider as done when the patient consumed at least