

Clinical evaluation of unani ear drops herbotic for earache

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Abstract: An ear infection (acute otitis media) is most often a bacterial or viral infection that affects the middle ear. Children as compared to adults are more prone to infections. A study has been conducted on 200 patients with herbal medicine Herbotic and allopathic drug Ofloxacin for the treatment of otitis media. The efficacy of test and control drug was monitored before and after treatment and diagnosed on clinical history, clinical presentation and pathological investigation. This study was a case control, multicenter, prospective randomized authentic allopathic controlled, two arm parallel group clinical trial. The data on clinical proforma was gathered between April 2014-March 2015 and subjected to statistical analysis. From the statistical results it was concluded that Herbotic and Ofloxacin are equally effective for the treatment of earache, effect being confirmed by physicians and patients alike.

Keywords: Earache, test drug Herbotic, control drug Ofloxacin, efficacy.

INTRODUCTION

Ear pain (otalgia) is one of the most common reasons for visits to primary care physicians and medical care providers. Causes include inner ear infections (otitis media), external ear infections (otitis externa), foreign bodies and trauma (Adour *et al*, 1981; Alshekhli, 1980). Otitis media is the most common cause of ear pain, occurs primarily in young children, peaks during the winter months and is associated with respiratory infections (Frankel, 1973). In contrast, otitis externa is regularly associated with swimming and diving (often called "swimmer's ear"), (Gibson *et al*, 1994; Goethals 1972; Kreisberg *et al* 1971), affects all ages (Kuttila *et al* 2004; Malik *et al*, 1975; Olsen, 1986) and peaks during the summer (Sataloff *et al*, 1984). However, because outer ear infections can develop anywhere from hours to days after exposure, they may not always be accurately attributed to swimming or other water exposures (Scarborough *et al*, 2003). Moisture, humidity and water in the ear canal are thought to remove the protective lining (cerumen, or ear wax) and increase the pH, increasing susceptibility to infection. Among divers, otitis externa was associated with a change in the normal microbial flora from gram-positive to gram-negative species shortly after immersion (Shah *et al*, 2003). *Pseudomonas aeruginosa*, *Staphylococcus epidermidis* and *Staphylococcus aureus* are the bacterial agents most frequently isolated from the ear canal of those diagnosed with otitis externa. Inflammation of any type in the ear causes pain, swelling, and redness. Otitis externa exhibit, gradual development of an earache; individuals with mild cases may describe an itch instead of pain; touching or pulling on the ear helix (upper rim) worsens the pain; hearing loss; ringing or buzzing sounds in the ear; blocked or full sensation in the ear; swelling of

the ear (Rareshide *et al*, 1990). Otitis media show pain in the ear and hearing loss; ringing or buzzing sounds in the ear; full or plugged sensation in the ear; fever and occasionally, discharge from the ear (Reichert, 1933). Diagnosis is done by the cause of an earache by taking a patient history and performing a local examination of ear, nose and throat. The health care practitioner often uses an Otoscope to look into the ear canal to evaluate the canal and the eardrum. Laboratory tests are done by a sample of drainage from the ear is sent to the laboratory in an attempt to identify the specific bacteria causing the infection. Sending the sample to the laboratory is not necessary in most cases and usually is reserved for infections that do not respond to normal treatment. (Vaamonde, 2004)

MATERIALS AND METHODS

This was randomized clinical case control study conducted on the outdoor and indoor patients in ShifaulMulk Memorial Hospital for Eastern medicine, Hamdard University, Karachi, Pakistan, and Govt. Tibbia College Bahawalpur. Case taking of the patients suffering from above mentioned disease would follow as follows history taking and physical examination.

Eligibility

Ages eligible for study: 02-70 Years and genders eligible both male and female. Inclusion Criteria: The patients suffering from earache, pain in one or in ear, all socio-economic status involving lower, middle and high status population. Exclusion Criteria: Any chronic diseases i.e. cardiovascular, neuronal, and congenital disorders, Medical conditions that would confound the efficacy evaluation, Medical conditions in which it would be unsafe to use an alpha-blocker, Use of concomitant drugs that would confound the efficacy evaluation, any

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accidental injury. Study Type: A randomized, case-controlled multicenter clinical trial to evaluate the efficacy and safety of two dosing regimens (Herbal verses allopathic) in subjects.

Herbal and allopathic drugs

Herbal ear drops, Herbotic (test drug), Oxifloxacin (control). The formulation of this dosage form was presented to FEM ethical committee. Ofloxacin Otic solution 0.3% is a sterile aqueous anti-infective (anti-bacterial) solution for otic use. The recommended dosage regimen for the treatment of otitis externa is: For pediatric patients (from 6 months to 13 years old): Five drops (0.25mL, 0.75mg Ofloxacin) instilled into the affected ear once daily for seven days. For patients 13 years and older: Ten drops (0.5mL, 1.5mg Ofloxacin) instilled into the affected ear once daily for seven days.

Consent

All patients gave verbal or written, informed consent for their participation, and the protocol was approved by the appropriate Independent Ethics Committee of Faculty of Eastern Medicine.

STATISTICAL ANALYSIS

All the data collected at Shifa-Ul-Mulk Memorial Hospital for Eastern Medicine, Hamdard University Karachi, and Govt. Tibbia College Bahawalpur was subjected to statistical analysis to determine the level of significance of cross sectional study. SPSS for Windows Version 18.0 was used and applied for statistical analysis of data, was verified and checked for range and consistency with customized data entry and processing programs (Microsoft Access XP2007). Each cross sectional study report including the entered data, was recorded electronically. Data was analyzed with statistical Analysis Software SPSS, version 18.0.

The test group

Test group n=100 was developed following inclusion criteria and were treated with Herbal Ear Drops 2-4 times daily for 12 days following 3 week follow up visits.

The control group

Similarly control group n=100 was developed following inclusion criteria and were treated with Allopathic twice daily for 3 weeks following follow ups.

Method of preparation of dosage form

The herbal dosage form was designed as follows and given in table 1.

Collection and identification of herbs

The selected herbs for earache were purchased from the local market at Joria Bazar, Karachi, Pakistan. Organoleptic evaluations and certain physical and

chemical test for the validations of herbal medicines were carried out in the Pharmacognosy lab of Faculty of Eastern Medicine under the supervision of Prof. Dr. Usman Ghani Khan and also Research & Development Laboratory/Quality Control Laboratory of Herbion Pakistan (Pvt.) Limited. All herbs and one gum were cleaned and examined for their impurities and adulteration at Herbion R&D Facility. Physical and chemical tests were than performed to determine whether the herbs may be used for the extraction process. Water was used as solvent for extraction with water to herb ratio of 10:1 in stainless steel, double jacketed extractor. The herb was treated with solvent for about 1.5-2.0 hours at 90-100°C. The decoction thus obtained was allowed to cool and then filtered through stainless steel sieve no. 350. The same procedure was adopted for rest of herbs.

Spray Dried Powdered Extract Preparation: The decoctions of the above raw material were then transferred to a pilot scale spray dryer to get the individual powdered extract. The glass parts including cyclone, spray cylinder as well as collection container, collection bottle, screw cap and filter were thoroughly checked before starting of spray drying operation. The decoction container was placed near the spray dryer unit and the suction tube was inserted into the container whereby sealing all other openings. The compressed air valve was switched ON present at the main switch panel. The inlet temperature was set up to 100°C. The "Start" button was switched and then the aspirator capacity was set up to 65% till the inlet temperature reaches to 100°C and outlet temperature reaches to 60-75°C. After that, the air pressure was adjusted through regulator up to 200 bars and the feed pump was started by rotating knob clockwise by setting it to 20 SPM.

The powder was then started to collect and powders were released and thereby transferred into an air-tight container to be used for direct compression of ear drops transferred for final packaging and the ear drops were filled in HDPE plastic bottle.

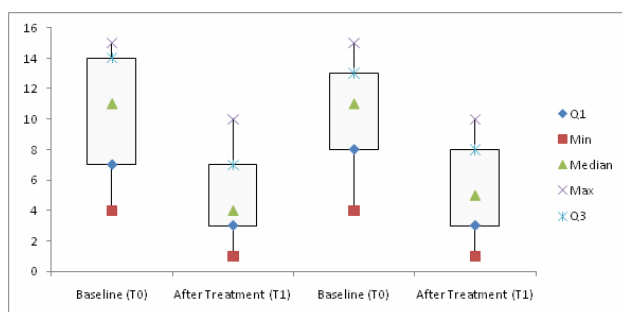
Data collection

The research data was collected for this study included history taking and physical examination, filling of clinical trial proforma, use of case record, file and documents. The clinical trial proforma along with clinical reports attached here which clearly specifies the clinical feature and information such as diagnosis, prescription and dosage form administration, efficacy evaluation and clinical assessment.

RESULTS

The trials executed at Shifaul Mulk Memorial Hospital, Faculty of Eastern Medicine, Hamdard University and Government Tibbia College Bahawalpur. The patients

who were sustained the inclusion criteria were selected for this research project. A patient questionnaire also serve as a data sheet having documented with the subjects at entry that record the information concerning the sex and age of the subjects, clinically. The purpose of the present investigation was to compare the eastern/herbal medicine with allopathic medicine so as to assess its ultimate effects for its curative function. Controlled studies include a group given a comparison treatment of allopathic to one group and the second group traditional medicine to establish effectiveness and safety by standard parameters. As such the constituents of dosage form design of coded Herbal Ear Drops as reported on the formulation exert therapeutic activity; therefore, this study has been compared with standard therapy such as Ofloxacin.



Graph 1: Comparative analysis in intensity of symptoms between two treatment groups.

The patients were registered from the general O.P.D. This study trial was supervised by the ethical committee of the Hamdard University. Safety of the subject in clinical trial based on earache was derived from the earlier studies. Multiple primary variables in the sign and symptoms were quite sufficient to cover the range effect of the therapy. Applying the designed format collected the data out of 200 patients of earache, 100 patients were treated with Herbatic 100 patients were treated with Ofloxacin. The parameters that were taken in signs and symptoms for otalgia were ear Congestion and ear ache, ear inflammation.

Distribution of the patient

The patients for test and control drug were registered from general OPD in the hospital. Generally the cases established the supportive treatment in the form of complete rest. The age distribution of patients classified into the different class intervals ranging the age starting from 02 years to above 60 years. The age distribution of 100 patients that was recorded having 5 class intervals (see table 2).

Comparative analysis and clinical response

The comparative clinical study conducted on Herbal Ear Drops has been done to assess the clinical responses. The therapeutic evaluation of the drug was made on the basis

of improvement in the subjective signs and symptoms, clinical assessment, biochemical and serological assessment at periodic intervals during the course of treatment.

Ear congestion and earache

This complains has been recorded on the herbal test drug herbal ear drop Herbatic and Ofloxacin and the effects that were observed on the patients. Patients presenting with complaint of ear congestion and pain-exhibited improvement of this condition in 58.12% of patients and 21.87% of patient did not improve with herbal drugs. The effects of Ofloxacin in respect to anorexia only 85.94% of the patient indicated complete improvement as compared 47.05% patients showed no improvement and in addition 19% showed reverse effect. The overall effects of Herbatic were better than Ofloxacin (table 3).

Ear inflammation

The heart burn is the most common complaint in patient suffering from ear inflammation treated with herbal medicine and showed that effective in 81.25% of the patient and not effective in 18.75%. While in case of control drug only 55.88% of the patients had shown complete improvement. It indicates that test drug has shown better response than control drug. Chi-Square test was applied and p value was calculated 0.0357 which is significant see table 4

Comparative analysis of intensity of symptoms

A comparative analysis was done in the level of intensity of symptoms between two treated groups i.e. test and control groups before and after the treatment. Wilcoxon Signed Rank Test was applied to see the statistical difference. It was concluded from this statistical analysis that Herbatic (Test) possesses greater value to lower down the intensity of symptoms as compared to Ofloxacin (Control) as represented in graph 1.

DISCUSSION

The overall analysis has been shown in the different tables and the signs and symptoms improvement in patients are enumerated which shows the performance at the baseline and treatment completed. According to the statistical analysis 66% of the cases got complete relief and 34% of the patients had shown minimum or no effects in test group. While the control drug have superior efficacy in this respect by showing that 71% of the cases got complete relief and 29% of patient had shown no response. Comparison of data recorded by participants relating to these variables showed no significant differences between test and control groups ($p > 0.05$). Chi-Square Test was applied and p-value was calculated as 0.3244, which is greater than 0.05 indicating that Test and control therapy is equally significant in the treatment of Hepatitis.

Table 1: Test drug Herbotic unit composition

No	Ingredients	Part used	Quantity/1000 ml
1	Azadirachta indica - Neem	Seed	8.210 ml
02	Tea tree Oil	Essential Oil	3.532 ml
03	Eucalyptus Oil	Essential Oil	3.000 ml
04	Clove Oil	Essential Oil	0.201 ml
	Excipients		
05	Methyl Paraben	-	30.00 mg
06	Propyl Paraben	-	1.500 mg

Table 2: Patient age distribution and frequency

Treatment groups	Sex	Mean	Number (n)	Standard Deviation
Test drug	Male	28.14	55	7.43
	Female	27.82	45	7.01
	Total	26.55	100	7.40
Control drug	Male	27.95	58	6.80
	Female	29.49	42	6.82
	Total	28.37	100	6.83
Total	Male	27.75	103	6.91
	Female	28.30	81	6.71
	Total	27.46	200	6.56

Table 3: Improvements of test and control drugs Ear Congestion & Ear Ache

Name of Drug	Improved	Not Improved	p value
Herbotic	25 (78.12%)	7 (21.87%)	0.0407
Ofloxacin	18 (52.94%)	16 (47.05%)	

Table 4: Improvements of test and control drugs Ear Inflammation

Name of Drug	Improved	Not Improved	p value
Herbotic	26 (81.25%)	6 (18.75%)	0.0357
Ofloxacin	19 (55.88%)	15 (44.11%)	

Table 5: Overall improvement in severity of symptoms in Test Herbotic by Wilcoxon

Overall severity of symptoms				
Baseline (T0)		After treatment (T1)		
Median	IQR	Median	IQR	p value
11	7-14	4	3-7	0.006

Table 6: Improvement in Intensity of symptoms with Herbotic Wilcoxon Signed Rank Test

Symptoms	Intensity of symptoms				
	Baseline (T0)		After treatment (T1)		
	Median	IQR	Median	IQR	p value
Ear congestion and Ear ache	2.5	2-3	1	1-2	0.05
Inflammation	2	1-3	0.5	0-1	0.02

Table 7: Overall severity of symptoms in Ofloxacin by Wilcoxon Signed Rank Test

Overall severity of symptoms				
Baseline (T0)		After 1 moth of treatment (T1)		
Median	IQR	Median	IQR	p value
11	8-13	5	3-8	0.0113

Table 8: Improvement in intensity of symptoms with Ofloxacin

Symptoms	Intensity of symptoms				
	Baseline (T0)		After treatment (T1)		
	Median	IQR	Median	IQR	p value
Ear congestion and ear ache	2.5	2-3	1.5	1-2	0.05
Inflammation	2	1-3	1	0-1	0.02

Table 9: Comparison in intensity of symptoms between two treatment groups by Wilcoxon Signed Rank Test

Herbotic					Ofloxacin				
Before treatment (T0)		After treatment (T1)			Before treatment (T0)		After treatment (T1)		
Median	IQR	Median	IQR	p value	Median	IQR	Median	IQR	p value
11	7-14	4	3-7	0.006	11	8-13	5	3-8	0.011

Table 10: Drug compliance and cost effectiveness comparison

Remarks of the Patients	Treatment Group		Total	p value
	Herbotic	Ofloxacin		
Drug Compliance	Bad	10	21	0.0079
	Good	90	69	
Cost Effectiveness	Costly	3	75	0.0001
	Cost effective	97	15	

Improvement in associated symptoms

There was a significant improvement in associated symptoms in test group as compared to control group when observed between these two treated groups at the end of therapy. We recorded the intensity of symptoms as absent: 0, mild: 1, moderate: 2 and severe: 3 at baseline (T0), and after treatment (T1) through median values, interquartile ranges (IQR) and Wilcoxon signed-rank test was applied to calculate differences in median values. It was concluded that Herbal Ear Drops (Test) has greater response in the improvement of symptoms as compared to control therapy as discussed above.

As the above study conducted denotes that the curative function of eastern/herbal formulation is almost similar to control. Generally the patients that were under research study had also monitored by prescribing authentic eastern/herbal medicine prescribing according to clinical manifestation prevail. In this vast therapy there is lot much combination to alleviate the symptoms and to give strength to body by natural source medicine. For this we have used some combination of medicine additional to the Herbotic for contracting associated signs and symptoms and to get complete relief. It is also necessary for physician when they are prescribing medicine to the patient they must consider weather and temperament and then prescribe the specific medicine and some necessary dietary restriction, it will results in high cure rate for all the diseases. These dosage forms are generally used in the eastern practice and not the compulsory part of this study. It is generally describing the pattern of eastern treatment and their combination for achieving complete cure. The overall improvement is given in tables 5-8

Ear Congestion & Ear Ache (T0: median 2.5, range 2-3; T1: median 1, range 1-2), inflammation (T0: 2, range 1-3; T4: median 0.5, range 1-2)

Ear congestion and earache (T0: median 2.5, range 2-3; T1: median 1, range 1-2), inflammation (T0: 2, range 1-3; T1: median 0.5, range 1-2), (T0: 2, range 2-3; T1: median 1, range 1-2), all showed statistically significant improvement after treatment with Eardrop.

Comparative analysis of intensity of symptoms between treatment groups

Comparative analysis was done in the level of intensity of symptoms between two treated groups i.e. test and control groups before and after the treatment. Wilcoxon signed rank test was applied to see the statistical difference after calculating the median values and interquartile ranges. It was concluded from this statistical analysis that Eardrop (Test) possesses greater value to lower down the intensity of symptoms as compared to Ofloxacin therapy (Control) (tables 9 & 10)

The object of this study was to compare herbal medicine Eardrop and Ofloxacin and to see whether these may represent a platform for the development of novel therapeutics. It was observed that there is a marked improvement in overall subjective signs and symptoms when treated with Herbotic compared to Ofloxacin. There was a noticeable improvement in ear congestion and earache, Inflammation.

Drug compliance and cost effectiveness

Compliance of the treatment and cost effectiveness of the both therapies used for the treatment of Earache was also analyzed during the course of treatment (table 10).

The analysis through chi-square test revealed marked difference between two treated groups in term of cost effectiveness and drug compliance ($p < 0.05$). The comments about drug compliance and cost effectiveness were obtained at the end of treatment. The purpose is to determine whether the information obtained from the patients have any significant hearing and difference between the treatment groups.

Adverse effects profile

All the patients enrolled in the study were evaluable for safety. Side effects were defined as sign and symptoms that first occurred or became more severe during the course of treatment. The majority of adverse events were assessed as mild in severity and self-limiting in nature. Therefore, none of the patients withdrew from the study due to these adverse events. Adverse events categorized by the clinical investigator as possibly or definitely drug related in patients administered Ofloxacin showed side effects such as headache (02 patients), were the most common drug related events among control recipients and no side effects were recorded in test treated recipients. No life threatening side effects recorded in any group. It is because of the fact that plant drug selected for the treatment of earache does not contain any chemical agent that may trigger the adverse drug reaction response. This can be explained further that chemical components of the plant drugs altogether are low in the frequency of occurrence and even administered together in synergistic fashion exhibit pronounced type of effective response for curative action.

CONCLUSION

The finding from this study demonstrated the following salient clinical assessment, there was statistically significant difference when comparing the effectiveness of herbal medicine Eardrop to Ofloxacin for the treatment of Earache as described in the thesis. This is clearly evident that Eardrop possesses a therapeutic value for the treatment of Earache associated symptoms but also the eradication rate of Earache is superior with Eardrop as compared to Ofloxacin (Control drug). Chi-square test was used to analyze the statistical difference. From the statistical results obtained out of clinical response it was concluded that Eardrop is effective for the treatment of Earache associated symptoms, the effect being confirmed by physicians and patients alike.

There was no such adverse effect with the use of Eardrop and this has found good acceptability by all treated patients. The principal objective on herbal medicine Eardrop as compared to Ofloxacin is to determine whether these may represent a platform for the development of novel therapeutic. The efficacy of herbal formulation is a characteristic of a complex mixture of chemical compounds present in different herbs used as

multiple dosage form design. The results from this research study have clearly revealed the evidence of efficacy of test drug Eardrop for the improvement of Earache associated symptoms as compared to Ofloxacin.

The approach of this scientific clinical study validates the Unani medicine, so in its ultimate result, it leads to new class of therapeutics.

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