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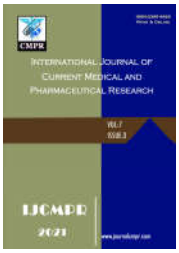

Research Article

NOVEL MAGNETIC DOSAGE FORM FOR THE LOCAL TREATMENT OF INFLAMMATORY DISEASESIN OTORHINOLARYNGOLOGY

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ABSTRACT

Introduction: Design of Magnetic Drug Delivery Systems one of the object researching to modern pharmaceutical science. The dosage form with the magnetite nanoparticles in the form of ointment was created with active ingredients trimecaine, methyluracil, dioxidine on the base of PEG 400/1500 mixture for topical treatment of otorhinolaryngological infectious diseases such as tonsillitis. Use of such a magnetic formulation with its applying and fixing via an external magnet on the tonsils will allow improving the efficacy of local treatment. Pharmacological studies of the proposed method of treatment were evaluated by the dynamics of the main clinical symptoms observed in the treatment of compensated forms of chronic tonsillitis.
Methodology: Magnetic ointment was applied directly to the surface of the tonsil and the posterior wall of the pharynx. Permanent magnet was applied to the outer part of the mandible in the area of the projection of the tonsils and the posterior wall of the pharynx for a period of 5 to 10 minutes.
Results: 126 people diagnosed with chronic tonsillitis were examined and treated. Simple form - 54 patients and toxic-allergic form of I degree - 72 patients. It was found that bacterialcontamination of themucousmembrane of the posteriorwall of thepharynx and tonsils was normalizedduringtreatment and did not increase after one month.
Conclusion: Usage of magnetic ointment in the treatment of compensated forms of chronic tonsillitis has a total therapeutic effect; allows eliminating inflammation of the palatine tonsils, to prevent the development of relapses of the disease and its complications.

INTRODUCTION

Chronic tonsillitis is a widespread disease of the pharynx in adults and especially in children. The inflammatory process in the tonsils leads to pathological changes in them, which disrupts the immunological function of the body, while the tonsils themselves become a source of infection [1-4]. According to the latest data, the prevalence of chronic tonsillitis is 12-15% of cases [1].

The problem of treating chronic tonsillitis, despite the abundance of proposed therapy methods, remains unresolved at this time. In the middle of the 20th century, surgical methods of treatment were mainly used. However, a deeper study of the functions of the Pirogov-Waldeyer lympho pharyngeal ring forced to reconsider the views of clinicians on the rational treatment of chronic tonsillitis in favor of conservative methods [1, 5-9].

At the same time, the many proposed therapeutic effects and techniques indicate the lack of a clear understanding of the capabilities of medicine in relation to a specific patient with this pathology. Due to the fact that systemic antibiotic treatment often leads to a decrease in the general reactivity of the body, disorders of the gastrointestinal tract, mycoses, an increase in the resistance of microorganisms to drugs - in the treatment of chronic tonsillitis, local antibacterial, anti-inflammatory and immunomodulatory therapies are becoming increasingly common.

The lack of effectiveness of all modern methods of conservative therapy for chronic inflammation of the tonsils lies in the impossibility of exposure to drugs throughout the amygdala and reaching the focus of infection at any of its localization. Therefore, the development of new non-invasive methods for the treatment of chronic tonsillitis remains an urgent direction in solving this problem.

According to the results of research conducted jointly with the Department of Otorhinolaryngology of Kharkiv State Medical University and ENT Clinic "Dynasty" scientists of the National University of Pharmacy have selected the optimal composition of magnetic ointment for the treatment of inflammatory diseases of the pharynx and tonsils [10, 11]. This ointment belongs to the magnetic dosage forms, and contains a

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magnetic filler - magnetite (Fe_3O_4), trimecaine, methyluracil, dioxidine, PEG 400/1500 mixture.

Magnetic nanotechnology is widely used in modern pharmaceutical science[12]. Magnetite nanoparticles (Fe_3O_4) are used as magnetic material of Magnetic Drug Delivery Systems [13-16].

Due to its magnetic properties, the developed magnetic ointment, after application to the tonsils and (or) the pharyngeal wall, can be fixed with an external magnet and for a long time cause a healing effect. This will allow for effective conservative local treatment of inflammatory diseases of the pharynx and tonsils, eliminate (reduce) the need for oral medications, which will increase the pharmacotherapeutic effect and is safer and more rational.

The goal of the work: investigate the main properties of the developed drug with a magnetic component: qualitative and quantitative composition of the active substances of the ointment, density, saturation magnetization, pharmacological properties.

MATERIALS AND METHODS

Analysis of the qualitative and quantitative composition of the active substances of the ointment was performed on a liquid chromatograph type Milichrome A-02 with a microcolumn, which was filled with a sorbent with a non-polar phase. Solutions of standard samples of dioxidine, methyluracil and trimecaine and a solution of the test ointment in a water-alcohol mixture were prepared. According to the method of determining the density of solid fats and wax, the density of magnetic ointment was determined. The saturation magnetization of the developed ointment was determined by the bridge method using a magnetic flux meter F - 190, with an electromagnet.

The study of the properties of the pharmacological drug was performed on the basis of ENT Clinic "Dynasty" Kharkiv, Ukraine.126 people diagnosed with chronic tonsillitis were examined and treated (Table 1). Simple form - 54 patients and toxic-allergic form of I degree - 72 patients.

All patients were divided into three groups (n = 42). In the main group of patients were treated with magnetic ointment using magnetophoresis. Magnetic ointment was applied directly to the surface of the tonsil and the posterior wall of the pharynx. Consumption of ointment was determined by the size of the pharynx and tonsils (from 4 to 10 g). After that, a permanent magnet was applied to the outer part of the mandible in the area of the projection of the tonsils and the posterior wall of the pharynx for a period of 5 to 10 minutes. Patients in the comparison group were treated with magnetic ointment (ointment was applied directly to the surface of the tonsil and posterior pharyngeal wall) without the use of magnetophoresis. The course of treatment in groups was 5 procedures, the procedure was performed once a day.

Patients in the control group underwent traditional therapy - washing the gaps of the tonsils, vitamin therapy, immunomodulatory therapy, Patients in the control group underwent traditional therapy - washing the gaps of the tonsils, vitamin therapy, immunomodulatory therapy, Ultraviolet heater, Ultrahigh Frequency Therapy.

Patients were examined before the course of treatment, immediately after its completion and 1 month after the end of therapy. In order to diagnose pathological changes and assess the general condition of patients used clinical data (history, palpation of cervical lymph nodes, patient complaints), endoscopic (otopharyngoscopy), microbiological (bacteriological examination of smears from the surface of the tonsils by the method of Gold with inoculation on blood agar) and immunological studies (content of C-reactive protein, Circulating Immune Complexes (CICs) of anti-streptolysin-O (ASLO), IgA, IgG, rheumatoid factor in the blood, as well as SIgA, IgG).

Statistical processing of the obtained results was performed by the traditional Student's method using MS Exel 2007 spreadsheets and BMPD software package.

Table 1 Distribution of patients by the gender, age and forms of chronic tonsillitis

Initialdataofpatients			Maingroup (n=42)		Comparativegroup (n=42)		Controlgroup (n=42)	
			absolute	%	absolute	%	absolute	%
Simpleshape	M	upto 20 years	1	2.38	1	2.38	-	-
		21-30 years	3	7.14	4	9.52	3	7.14
		31-40 years	3	7.14	2	4.76	3	7.14
		41-50 years	2	4.76	1	2.38	3	7.14
		over 51 years	-	-	1	2.38	-	-
	W	upto 20 years	2	4.76	1	2.38	-	-
		21-30 years	2	4.76	3	7.14	2	4.76
		31-40 years	3	7.14	3	7.14	4	9.52
		41-50 years	1	2.38	2	4.76	2	4.76
		over 51 years	1	2.38	-	-	1	2,38
Toxic allergic form I degree	M	upto 20 years	-	-	2	4.76	1	2.38
		21-30 years	4	9.52	3	7.14	2	4.76
		31-40 years	5	11.9	6	14.29	5	11.9
		41-50 years	2	4.76	-	-	1	2.38
		over 51 years	1	2.38	1	2.38	3	7.14
	W	upto 20 years	2	4.76	-	-	1	2.38
		21-30 years	6	14.29	4	9.52	5	11.9
		31-40 years	3	7.14	5	11.9	4	9.52
		41-50 years	1	2.38	2	4.76	2	4.76
		over 51 years	-	-	1	2.38	-	-

RESULTS

Given the composition of the magnetic ointment, the functional purpose of the individual ingredients, as well as the nature of the dosage form, complete chemical control (qualitative and quantitative) was subject to dioxidine, methyluracil and trimecaine. For the analysis of the developed ointment we offered a chromatographic method, namely high-performance liquid chromatography. The use of this method allowed to determine the active substances without their prior separation from the water-alcohol extract of the ointment.

According to the results of chromatographic analysis, it was found that the retention times of the peaks of the investigated magnetic ointment solution coincide with the retention times of the peaks of the working standard sample of dioxidine, methyluracil and trimecaine, which is a qualitative characteristic of the active substances. Quantitative content of active substances (dioxidine 1.0±0.1mg/g, methyluracil 4.0±0.4 mg/g, trimecaine 3.0±0.3 mg/g) was determined according to the calculated ratios of average values of peak ares from chromatograms of the investigated solution and solutions of standard samples. This is fully confirmed by prescription data. The absence of impurities was established by the presence of other zones of delay peaks on the chromatogram. The selected chromatographic parameters ensure the fulfillment of all conditions that allow to obtain reliable results: a high degree of separation of the peaks of trimecaine, dioxidine and methyluracil, a low value of the relative standard deviation for the peak areas [8].

In order to validate the methods of ointment research and its standardization, some physicochemical properties of the ointment were studied, so the density of the magnetic ointment was 1.356 g/mL.

When studying the magnetic properties of the developed ointment, it was determined that the experimentally established value of the saturation magnetization - 27.5 kA/m, completely coincides with the theoretically calculated, which is depended on the volumetric concentration of magnetite and saturation magnetization (I_m = 340 kA/m).

Given that the magnetization of the ointment is a function of the quantitative content of the magnetic filler and its personal nature, the coincidence of theoretical and experimentally determined values of the saturation magnetization can be a criterion for qualitative and quantitative values of magnetic filler.

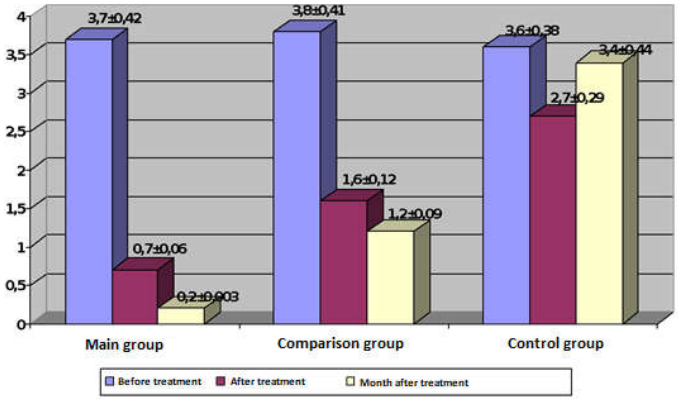

Figure 1 Dynamics of microbiological parameters of the mucous membrane of the posterior pharyngeal wall and palatine tonsils

According to the results of microbiologicalstudies (Fig. 1) it was found that inpatients of the main group bacterial contamination of the mucousmembrane of the posteriorwall of the pharynx andtonsils was normalized duringtreatment and did not in crease one month aftert reatment.

Table 2 Dynamics of the content of rheumatological and humoral immunological parameters of patients' blood

Research groups		Name of indicatot				
		CEC, units of optical density	ASLO, IU/mL	C-reactive protein, mg/L	Rheumatoidfactor, IU/mL	IgA, mg/mL
Maingroup	beforetreatment	174±9.3	286±14.1	7.4±0.52	26.3±2.2	1.17±0.19
	aftertreatment	112±6.8	172±11.8	3.1±0.22	13.7±1.8	2.11±0.25
	monthaftertreatment	58± 3.4	69± 4.7	1.8±0.09	8.1±9.4	2.61±0.18
Comparisongroup	beforetreatment	186±8.9	293±15.6	7.2±0.69	27.5±3.6	1.13±0.2
	aftertreatment	164±7.2	207±12.3	4.3±0.35	19.3±2.1	1.82±0.15
	monthaftertreatment	162±7.8	164±12.1	3.7±0.24	16.9±2.8	2.11±0.21
Controlgroup	beforetreatment	179±9.8	288±16.4	7.3±0.59	25.3±3.4	1.21±0.16
	aftertreatment	171±8.6	247±15.3	6.6±0.51	21.6±2.9	1.31±0.21
	monthaftertreatment	166±8.1	326±18.6	8.2±0.64	24.1±3.7	1.12±0.13
Indicatorsofthenorm		to 130	to 200	to 5	to 20	2.21-4.65

Notes. The difference in the groups is significant at p <0.05: from the norm (indicators "before treatment"), from the data "before treatment" (indicators "after treatment") and from the data "after treatment" (indicators "month after treatment")

Table 3 Dynamics of SIgA and IgG content in patients' saliva

Research groups		*Name of indicator*	
		SIgA, g/L	*IgG, g/L*
The main group	Before treatment	0.32±0.10	0.31±0.10
	After treatment	0.45±0.24	0.18±0.06
	Monthaf tertreatment	0.52±0.16	0.06±0.01
Comparison group	Before treatment	0.34±0.12	0.28±0.08
	After treatment	0.41±0.19	0.16±0.03
	Monthaf tertreatment	0.44±0.21	0.09±0.03
Controlgroup	Before treatment	0.31±0.11	0.32±0.11
	After treatment	0.39±0.17	0.22±0.07
	Monthaf tertreatment	0.38±0.17	0.27±0.08
Indicators of thenorm		0.49-0.56	до 0.08

Notes. The difference in the groups is significant at p <0.05: from the norm (indicators "before treatment"), from the data "before treatment" (indicators "after treatment") and from the data "after treatment" (indicators "month after treatment").

The results of studies of rheumatological and humoral immunological parameters of blood (Table 2) and saliva (Table 3) of patients in the experimental groups, convincingly indicate a reduction in the risk of autoimmune complications in patients of the main group, its storage in patients of the control group and increased risk in patients. It was also found that there was no significant increase in serum lgA in patients of the comparison and control groups.

DISCUSSION

Pharmacological studies of the proposed method of treatment were determined by the dynamics of the main clinical symptoms observed in patients before and after treatment. According to the analysis of the obtained results, the main

group found no pain in the pharynx and joints, the disappearance of pus in the lacunae of the tonsils and hyperemia of the posterior pharyngeal wall, lowering body temperature from sub febrile to normal, a significant reduction in regional lymph nodes (lymphadenitis). Congestive hyperemia of the palat in earches (Gizasign) and swellingin the upperpole of thetonsils (Zach'ssign) aftert reatment in the main group was observed in a small number of patients and was slightly pronounced. Thus, there is a normalization of the main clinical symptoms in patients of the main group and this trend is maintained for a month after completion of therapy in contrast to patients in the control group and the comparison group.

When conducting microbiological studies, the dynamics of growth of pyogenic group A streptococciwasdetermined. For the relative quantitative assessment used a scale: 1 point - contamination to 10^3, 2 points - contamination 10^3-10^6, 3 points - contamination 10^6-10^9, 4 points – contamination more than 10^9.

In patients of the comparison group there was a decrease in the contamination of pyogenic streptococcus group A, but to a lesser extent. In patients of the control group there was a slight decreasein bacterial contamination immediately after treatment. A month later, there was a return of indicators almost to baseline. This indicates a risk of recurrence.

The dynamics of the content of immunoglobulins in saliva indicates a decrease in inflammatory reactions in the tonsils of patients in the main group and their storage in the comparison group and the control group.

CONCLUSION

The use of a magnetically controlled ointment in the treatment of compensated forms of chronic tonsillitis has a total therapeutic effect. In this case, the pathogenic flora is replaced by saprophytic flora and the normal biosensors of the pharynx and palatine tonsils are restored.

Application of this method of treatment allows eliminating inflammation of the palatine tonsils, to prevent the development of relapses of the disease and its complications, which is impossible when using other modern drug and physiotherapy methods of treatment.

When using a magnetically controlled ointment in the treatment of compensated forms of chronic tonsillitis, a stable effect is achieved, proven by the results of clinical, microbiological and immunological research methods 1 month after completion of therapy.

The method of treatment of compensated forms of chronic tonsillitis does not require expensive equipment; its use is possible in medical institutions of any level and technical equipment. It is also possible to use it in out-of-hospital conditions (when the doctor leaves the house), which greatly facilitates the implementation of our methodology in practical healthcare.

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