O.A. Zorina, N.B. Petrukhina, L.M. Kozlova
Sechenov First Moscow State Medical University, Russian Federation

Treatment of aphthous stomatitis in adolescents

Author affiliation:
Kozlova Lyudmila Mikhailovna, sophomore at the faculty of dentistry of the First Moscow State Medical University

Address: 16, Timura Frunze Str., Moscow, 119992; **tel.:** +7 (499) 245-37-97

Article received: 14.03.2014. **Accepted for publication:** 14.05.2014.

Relevance: *therapeutic tactics at infectious inflammatory conditions of oral and pharyngeal mucosae includes prescription of the drugs featuring antimicrobial, anti-inflammatory and analgesic action. A combination of tyrothricin (antibacterial agent), benzocaine (topical anesthetic agent) and benzalkonium chloride (antiseptic) has been in use in clinical practice for years.* ***The study was aimed at*** *comparing the clinical efficacy of the drug based on the listed active substances and other stomatological agents in adolescents with aphthous stomatitis.* ***Results:*** *comparable efficacy of the drugs under study has been observed. No side effects have been observed within the period of the drug's use. A possibility to use one drug for treatment facilitates oral care and improves compliance of patients.*
Keywords: *aphthous stomatitis, treatment, tyrothricin, combined drugs, efficacy, safety, adolescents.*

INTRODUCTION

Imbalanced oral protection system may result in the development of infectious-inflammatory diseases of various mucosal segments. One of the most frequent nosologies is stomatitis – inflammation of oral mucosa characterized by development of various elements of mucosae of the mouth and the lips.
Stomatites may be catarrhal, ulcerative or aphthous depending on clinical manifestations.
Catarrhal stomatitis is the most frequent disorder of oral mucosa. It is usually caused by poor oral hygiene, dental diseases, dental deposits and oral dysbiosis. Gastrointestinal tract diseases, such as gastritis, duodenitis and colitis, may also cause catarrhal stomatitis. Oral mucosa becomes edematous, painful, hyperemic, covered with white or yellow deposit; hypersalivation is observed [1-3].
Ulcerative stomatitis may develop spontaneously or be caused by advanced catarrhal stomatitis. This disease develops especially often in the patients with gastric ulcer or chronic enteritis. Ulcerative stomatitis affects the mucosa throughout. Initial symptoms of these two types of stomatitis are similar; however, ulcerative stomatitis is subsequently characterized by body temperature increase up to 37.5 ^{o}C, asthenia, headache, enlargement and painfulness of lymph nodes. Food intake is accompanied by severe pain [4].
Aphthous stomatitis is characterized by singular or multiple aphthae (oval or roundish, not larger than a lenticular seed, distinct boundaries – narrow red rim, greyish-yellow deposit in the center) on oral mucosa. Aphthous stomatitis may be caused by gastrointestinal tract diseases, allergic reactions, viral infections and rheumatism. The disease sets on with general malaise, body temperature increase and pains in the mouth where aphthae have developed [5, 6].
Therapeutic tactics at infectious-inflammatory diseases of oral and pharyngeal mucosae involves prescription of drugs with anti-inflammatory, antimicrobial, analgesic and immunocorrecting effect, local antiseptics, decongestants and hyposensitization drugs [7].

Topical drugs administered in the form of gargles, insufflations, inhalations, slowly disintegrating tablets and lozenges usually suffice in the event of stomatitis and/or gingivitis.
A combination of tyrothricin (antibacterial drug), benzocaine (topical anesthetic) and benzalkonium chloride (antiseptic) has been in clinical use for years [3, 8].
Tyrothricin. Ca. 300 antibiotics may be considered products of amino acid condensation with formation of peptide bonds. Unlike normal proteins, their molecular mass does not exceed 3,000; they are comprised of certain amino acids and have a tendency to cyclization and hypercyclization.
The main biogenic peculiarity of polypeptide antibiotics is that a specific enzyme complex is used in the course of synthesis thereof (although this fact remained disputable for many years). It has been demonstrated that the common protein synthesis system containing mRNA complex with ribosomes is not involved in synthesis thereof. The main argument in favor of this fact is the presence of the amino acids not commonly found in proteins; another argument is the incapability of the known protein synthesis inhibitors to suppress biosynthesis of these antibiotics. Cyclic peptides comprised of L- and D-amino acid residues are the most widespread chemically analyzed antibiotics of this group. These are antibiotics formed by bacteria (tyrocidines, gramicidins, bacitracins, polymyxins, nisins, bacillomycins etc.) and actinomyces (etamycins, echinomycins etc.).
Tyrothricin is one of the most widely used polypeptide antibiotics.
Tyrothricin was first afforded in 1939 by R. Dubeau from bacterium *Bacillus brevis* extracted from soil. Tyrothricin producer – *B. brevis* – is an aerobic spore-forming rod. Spores are formed as bacilli and are usually located in the central part of the bacterial cell. Peritrichous flagellation enables bacteria to be wandering and Gram stainable, dilute gelatin and hydrolyze starch. Optimal growth temperature – ca. 37 ^{o}C.
Tyrothricin features bacteriostatic and bactericidal effect on gram-positive bacteria and, primarily, on pyococci. The benefit of tyrothricin is that it affects several pathogenic microbes (e.g., fecal streptococcus), that are not affected by penicillin or sulfonamides. Gram-negative bacteria are resistant to the antibiotic. Tyrothricin solutions and stable emulsions is used is medical practice, primarily as an antiseptic. The antibiotic is a poor diffuser, which is why it may be used for long-term bacteriostatic effect of topical application if needed [9].
In 1941 it was established that tyrothricin consists of two different polypeptides: they were isolated and named tyrocidine and gramicidin. In 1950 it was established that tyrocidine fraction is heterogenous and consists of three polypeptides similar in amino acid composition: tyrocidines A, B and C. Gramicidin fraction of tyrothricin also appeared heterogenous; it consists of four polypeptides: gramicidins A, B, C_D and D [8].
Benzocaine is a topical ether-structured poorly water-soluble anesthetic. Benzocaine topically and reversibly prevents development of pain impulses in sensory nerve terminals (receptors) and conduction thereof through nerve fibers. Painful sensation temporarily subsides; this process is followed by recovery of perception of cold, heat, touch and pressure.
Benzocaine decreases penetrability of cationic membranes, especially of sodium ions and, in higher concentrations, of potassium ions as well. Depending on the concentration, this may result in decreased excitability of nerve fibers.
Anesthetic effect of topical drugs may decrease in the inflamed tissue due to probable pH alteration [10]. Benzocaine has an undoubted advantage over the known surface anesthetics – efficacy thereof depends on the tissue pH to a small degree only: more than 80% of benzocaine is not ionized at pH 7.4 [11].
Benzalkonium chloride is bactericidal against staphylococci, streptococci, gram-negative bacteria (intestinal and pseudomonas aeruginosa, proteus, klebsiella etc.), anaerobic bacteria, fungi and mold. If affects strains of the bacteria resistant to antibiotics and other chemotherapeutic drugs; suppresses staphylococcal plasma coagulase and hyaluronidase; prevents secondary contamination of wounds with hospital microbial strains; it is *in vitro* active against *Neisseria gonorrhoeae, Chlamydia spp., Trichomonas vaginalis, Human herpesvirus 2*

and *Staphylococcus aureus*, does not affect *Mycoplasma spp.* and only slightly affects *Gardnerella vaginalis, Candida albicans, Haemophilus ducreyi* and *Treponema pallidum* [12].

The combination of active substances (tyrothricin + benzocaine + benzalkonium chloride) has been in use in Germany since 1964, in Luxemburg – since 1965, in Slovakia – since 1996, in Austria – since 1999. The drug (trade name – Dorithricin [Medice Pharma GmbH & Co. KG, Germany]) has been in use in Hungary, Belarus, Singapore, Vietnam, Azerbaijan, Georgia and other countries for many years. The drug is used for infectious-inflammatory oral diseases accompanied by pain syndrome (pharyngitis, laryngitis, gingivitis and stomatitis).

We analyzed experience of using this drug for aphthous stomatitis in adolescents at the department of dentistry at the Institute of Professional Education for Doctors of the Sechenov First Moscow State Medical University. The study was aimed at comparing clinical efficacy of the drug based on the mentioned active substances with other dental drugs in adolescents with aphthous stomatitis. The study involved 112 adolescents aging from 12 to 16 years (average age of the children – 13.2±2.1 years) – 61 girls and 51 boys, who were evenly distributed into the study group and the control group – 56 persons each. The overwhelming majority of the children had odontogenic foci of the infection: 47 patients in the study group (83.9%) and 45 patients in the control group (80.4%). Many patients had just recovered from a viral infection (37.2 and 41.07%) or had chronic gastrointestinal tract diseases (39.2 and 41.07% in the study group and the control group, respectively). All the adolescents involved in the study were diagnosed with moderate aphthous stomatitis.

The data on ethiopathogenetic factors contributing to the development of aphthous stomatitis observed in the adolescents is given in tb. 1.

Aphthae were localized in the children as follows: mucosa of the lateral tongue surface (12 adolescents [21.4%] and 14 adolescents [25%] in the study group and the control group, respectively), mucobuccal folds (11 adolescents [19.6%] and 9 adolescents [16.07%]), mucosae of the lips and the cheeks (12 adolescents [21.4%] and 11 adolescents [19.6%]; mixed localization (21 adolescents [37.3%] and 22 adolescents [39.3%]).

All the patients underwent application of proteolytic enzymes in order to remove deposits from the surface of aphthous elements. The study group patients were prescribed Dorithricin. According to the leaflet, the patients would slowly dissolve 1 tablet in the mouth every 3 hours (6 tablets per day). Treatment lasted for 7 days. The control group patients were prescribed 5% anesthetic emulsion QID and dental gel Metrogyl Denta, which produces not only anti-inflammatory, but also antiseptic (chlorhexidine) and antibacterial (metronidazole) effect. The gel would be put on the affected site of the oral mucosa 2 times per day for 7 days.

Dynamics of intensity of the main clinical symptoms in the setting of the performed therapy on a 10-point visual analog scale is given in tb. 2.

In both groups of patients, we revealed a statistically significant decrease in intensity of the main symptoms by the 3rd day of treatment: statistically significant decrease in intensity of pain syndrome, hyperemia, edema, hypersalivation and reduction in fibrinous deposit (see tb. 2, pic. 1). We observed further improvement of the condition by the 5th day of the performed therapy; intensity of the residual symptoms was not clinically significant by the 7th day.

Dynamics of clinical symptoms in the study group patients and the control group patients in the setting of the performed therapy was comparable. No statistically significant differences were observed (tb. 3, pic. 2).

Analysis of the obtained results demonstrated comparable efficacy of a complex drug for aphthous stomatitis in the study group adolescents and concomitant prescription of anesthetic emulsion and dental gel for the control group children.

Compliance coefficient of the drug was 98.4% (2,316/2,352*100%) in the study group; of anesthetic emulsion – 96.9% (1,520/1,568*100%), of dental gel – 94.38% (740/784*100%). On the basis of the calculated coefficients, we may assume that use of one combined drug for mouth cavity care in adolescents is preferable.

No adverse effects have been registered throughout the treatment of aphthous stomatitis.

CONCLUSION

The performed clinical observation demonstrated efficacy and safety of Dorithricin for aphthous stomatitis in adolescents. The drug' clinical efficacy is comparable with combined treatment using anesthetic emulsion and Metrogyl Denta. The possibility to use only one drug for the purpose of treatment facilitates mouth cavity care and improves compliance of the patients.

REFERENCES

1. Anisimova I. V., Nedoseko V. B., Lomiashvili L. M. *Zabolevaniya slizistoi obolochki rta i gub (klinika, diagnostika)* [Diseases of Mucosae of the Mouth and Lips (Clinical Pattern, Diagnosis)]. St. Petersburg, OOO «MEDI-izdatel'stvo», 2005. 92 p.
2. Barer G.M., Ionov V. A. *Cathedra – Cathedra*. 2008; 6 (4): 24–27.
3. Danilevskii N.F., Leont'ev V.K., Nesin A.F. et al. *Zabolevaniya slizistoi obolochki polosti rta* [Diseases of Oral Mucosa]. Moscow, OAO «Stomatologiya». 2001, 271 p.
4. Rabinovich I.M., Banchenko G.V. *Klinicheskaya stomatologiya – Clinical stomatology*. 1998; 3: 26–28.
5. Drobot'ko L. H., Strakhova S. Yu. *Khronicheskii retsidiviruyushchii aftoznyi stomatit* [Chronic recurrent aphthous stomatitis]. Available at: http://www.rmj.ru/articles4376.htm
6. Strakhova S. Yu. *Novye lekarstvennye preparaty v kompleksnom lechenii ostrogo gerpeticheskogo stomatita u detei. Avtoref. dis. … kand. med. nauk* [New Drugs for Complex Treatment of Acute Herpetic Stomatitis in Children. Author's abstract]. Moscow, 2000. 24 p.
7. Rees T. D., Binnie W. H. Reccurent aphthous stomatitis. *Dermatol Clin*. 1996; 14: 243–256.
8. Egorov N. S. *Osnovy ucheniya ob antibiotikakh* [Antibiotics: Basic Principles]. Moscow, Vysshaya shkola, 1989. 456 p.
9. Lancini D., Parenti F. *Antibiotiki* [Antibiotics]. Moscow, Mir, 1985. 460 p.
10. Dinnendahl V., Fricke U. Benzocain. In: Dinnendahl V., Fricke U., editors. Arzneistoffprofile (ASP). Frankfurt-Main, Govi-Verlag GmbH, 1982.
11. Adriani J., Taylor M. K. Benzocaine`s Properties and Uses as a Topical Anesthetic. *Anesthesiology*. 1990; XVII (1): 27–33.
12. Woo S. B., Sonis S. T. Recurrent aphthous ulcers: A review if diagnosis and treatment. *JADA*. 1996; 127: 1202–1213.

Table 1. Ethiopathogenetic factors contributing to the development of aphthous stomatitis in the adolescents under study

Ethiopathogenetic factors	Study group		Control group	
	Absolute amount	%	Absolute amount	%
Odontogenic infection	47	83.9	45	80.4
Gastric or duodenal ulcer	11	19.6	10	17.85
Gastritis	8	14.3	9	16
Colitis	3	5.3	4	7.2
Blood diseases	2	3.5	1	1.7
Past acute viral infections	21	37.2	23	41.07
Past toxic injuries	11	19.6	18	16.1

Table 2. Dynamics of intensity of the main clinical symptoms in the setting of the performed therapy

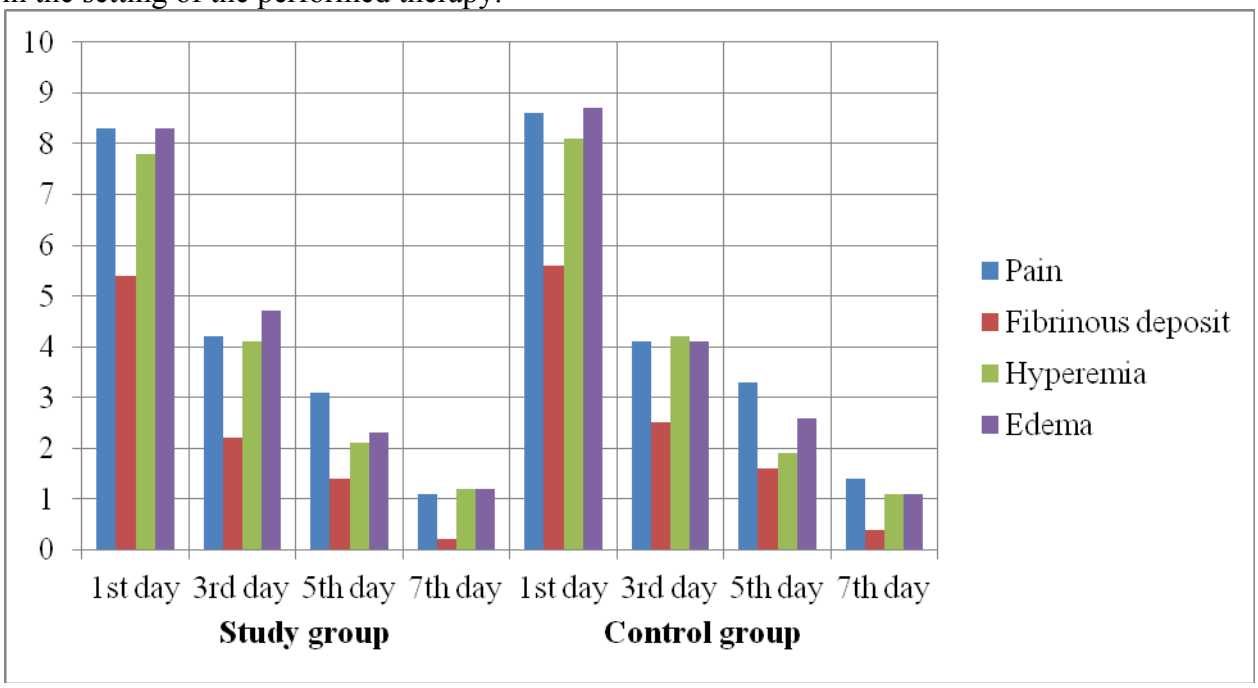
Symptoms	Day	Study group				Control group			
		1st	3rd*#	5th*	7th*	1st	3rd*#	5th*	7th*
Pain		8.3±1.4	4.2±1.2	3.1±0.4	1.1±0.2	8.6±1.5	4.1±1.4	3.3±0.8	1.4±0.3
Fibrinous deposit		5.4±1.2	2.2±1.4	1.4±0.5	0.2±0.06	5.6±1.3	2.5±1.1	1.6±0.3	0.4±0.07
Hyperemia		7.8±1.4	4.1±1.2	2.1±0.6	1.2±0.2	8.1±1.7	4.2±1.3	1.9±0.3	1.1±0.2

Edema	8.3±1.3	4.7±1.1	2.3±0.7	1.2±0.3	8.7±1.5	4.1±1.2	2.6±0.3	1.1±0.2
Hypersalivation	6.7±1.5	3.4±1.1	2.1±0.4	0.7±0.1	5.9±1.0	3.5±1.2	2.4±0.6	0.9±0.1

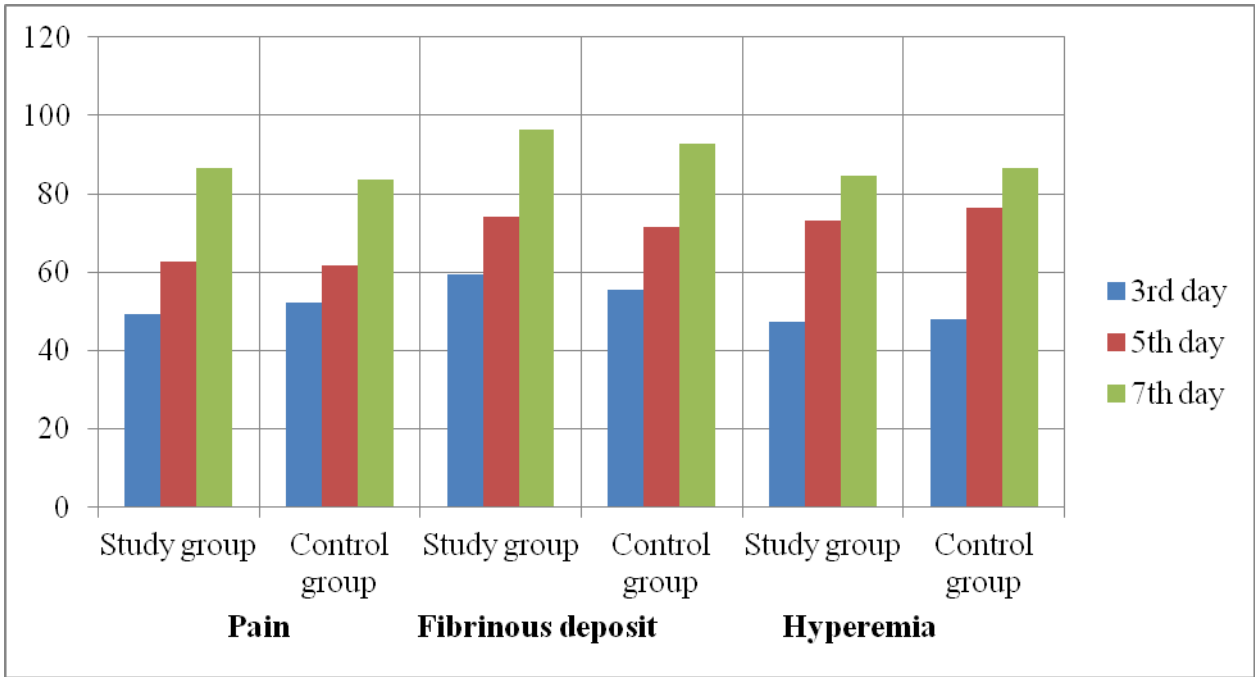
Table 3. Dynamics of the main clinical symptoms in the setting of the performed therapy (Δ%)

Parameter	**Day**	**Study group**			**Control group**		
		3rd	**5th**	**7th**	**3rd**	**5th**	**7th**
Pain		49.4	62.65	86.7	52.32	61.62	83.72
Fibrinous deposit		59.25	74.07	96.3	55.35	71.42	92.85
Hyperemia		47.43	73.07	84.61	48.1	76.54	86.41
Edema		43.4	72.3	73.5	52.9	70.11	87.35
Hypersalivation		49.3	68.65	89.55	40.7	42.4	84.74

Pic. 1. Intensity of the main clinical symptoms in the study group and the control group patients in the setting of the performed therapy.



Pic. 2. Dynamics of clinical symptoms in the setting of the performed therapy in the study group and the control group patients (Δ%).


120
100
80
60
40
20
0
Study group
Control group
Study group
Control group
Study group
Control group
Pain
Fibrinous deposit
Hyperemia
3rd day
5th day
7th day