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EFFICACY OF COMBINED RECTAL CREAM "DILATIL" (DILTIAZEM/LIDOCAINE/METHYL-URACIL) IN PRE-CLINICAL STUDY ON A MODEL OF ACUTE COMPLICATED ANAL FISSURE

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Aim. To assess efficacy of a new rectal cream "Dilatil" (diltiazem/lidocaine/methyluracil) (D) in pre-clinical study on a model of acute complicated anal fissure (ACAF).

Materials and Methods. Animal model of anal fissure, macroscopic assessment, enzyme-linked immunosorbent assay, statistical Student's and Wilcoxon's tests.

Results. At the end of the study, in the D group, the severity of the pathological process was statistically lower than in the Control pathology (CP) and N groups. Levels of IL-6, IL-10, and TNF- in the homogenate of anodermal tissue (HAT) in the D group were significantly lower compared to CP. The level of IL-6 was significantly lower in the D group compared to the N group.

Conclusions. Better efficacy of D vs N was observed in a pre-clinical study, which was also confirmed by the level of IL-10 in HAT tissue at the end of the experiment.

Keywords: rectal cream, anal fissure, Dilatil, Nifecain, macroscopic assessment, enzyme-linked immunosorbent assay, IL-10, IL-6, HIF-1α, TNF-α, calcium channel blockers, diltiazem.

Anal fissure (AF) affects a significant percentage (2%) of the adult population. Among proctological diseases, hemorrhoids and anal fissures rank first and third in frequency, respectively1. According to 2022 clinical guidelines for the treatment of anal fissures by the American Society of Colon and Rectal Surgeons, conservative treatment of acute anal fissures is safe and, as a rule, should be the first-line treatment (strong recommendation based on moderate-quality evidence, grade 1B) 2. However, conservative treatment is effective in approximately half of patients with anal fissures 3. Compared to topical nitrates, the use of calcium channel blockers for chronic anal fissures has similar effectiveness but a better safety profile (lower frequency and severity of side effects), and they can be used as first-line treatments (strong recommendation based on moderate-quality evidence, grade 1B)2. According to the current understanding of pathogenesis, pain is caused by spasms of the internal anal sphincter, which leads to impaired blood circulation in the area of the anal fissure (AF), hypoxia, and inflammation, which contribute to tissue damage on one hand and delay healing, thus causing pain again, leading to a "vicious cycle." 4,5,6 As of now, there are no soft medicinal forms in Ukraine that can comprehensively affect the key links in the pathogenesis of anal fissures — sphincter spasm, inflammation, tissue damage, and quickly relieve pain, the most unpleasant symptom containing calcium channel blockers. Therefore, the development of a new rectal cream capable of achieving this is both relevant and promising.

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The work was aimed at assessing the efficacy of rectal cream D in a pre-clinical study on a model of ACAF.

Methods. The total macroscopic pathology process severity was assessed on a scale from 0 to 10 points based on the sum of the 5 following parameters: severity of edema, hyperemia, local bleeding, purulent-necrotic processes, and anatomical defect (each parameter was assessed on a scale from 0 to 2 points). The protein concentration of IL-10, IL-6, HIF-1α, and TNF-α in HAT was analyzed in the homogenate of anodermal tissue using the enzyme-linked immunosorbent assay (ELISA) method. The study was conducted on 26 non-linear male white rats, weighing 200–240 g, using a model of ACAF. The animals were divided into four experimental groups: Intact Control (IC) ($n = 6$). Control Pathology (CP) ($n = 8$). Treatment with D ($n = 6$) — rats treated with D were administered into the anal canal using an insulin syringe with a blunt needle (0.3 ml, once daily throughout the treatment period). Treatment with N ($n = 6$) — rats treated with N administered into the anal canal using an insulin syringe with a blunt needle (0.3 ml, once daily throughout the treatment period). Pathology modeling lasted 4 days. The further treatment phase lasted 12 days. The results were analyzed using parametric (Student's t-test) and non-parametric (Wilcoxon test) methods. A significance level of $P < 0.05$ was considered statistically significant.

Results and Discussion. At the end of the study in the D group, the severity of the pathological process was statistically lower than in the Control pathology (CP) and N groups (Fig. 1).

Levels of IL-6 (Fig. 2, $P = 0.03$), IL-10 (Fig. 3, $P = 0.01$), and TNF-α (Fig. 4, $P = 0.02$) in the homogenate of endodermal tissue (HAT) in the D group were significantly lower compared to CP.

The level of IL-6 ($P = 0.001$) was significantly lower in the D group compared to N (Fig. 2). A trend toward a lower level of hypoxia factor HIF-1α (Fig. 5, $P = 0.065$) was observed in the D group compared to CP.

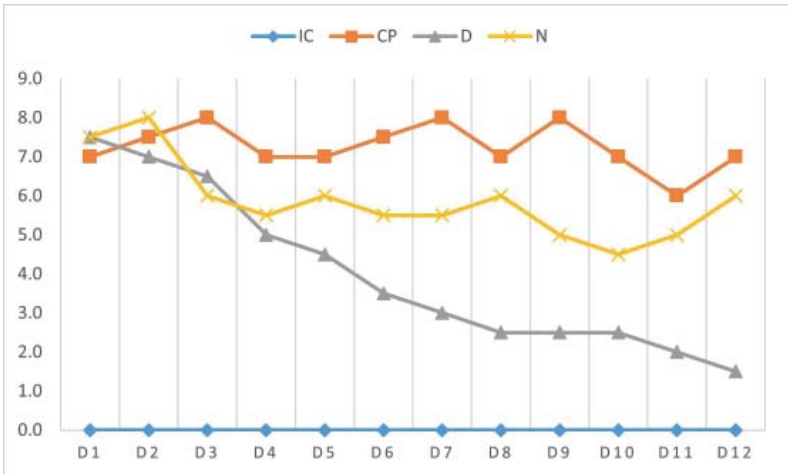

Fig. 1. **Macroscopic assessment of pathology process severity**

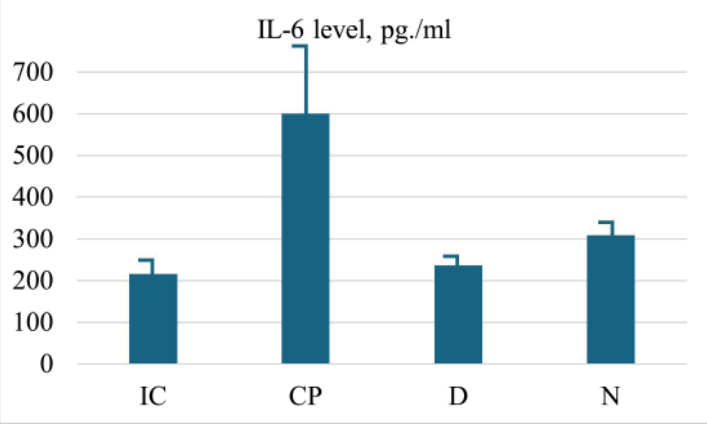

Fig. 2. **IL-6 levels in HAT after 12 days of treatment (pg/ml)**
* — difference between groups is statistically significant ($P < 0.05$)

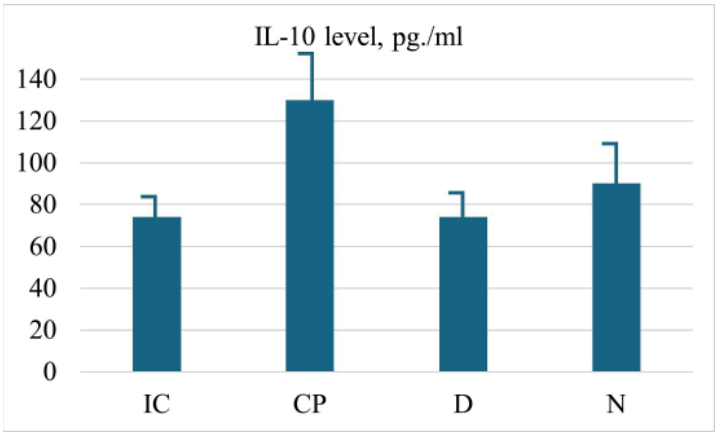

Fig. 3. **IL-10 levels in HAT after 12 days of treatment (pg/ml)**
* — difference between groups is statistically significant (P <0.05)

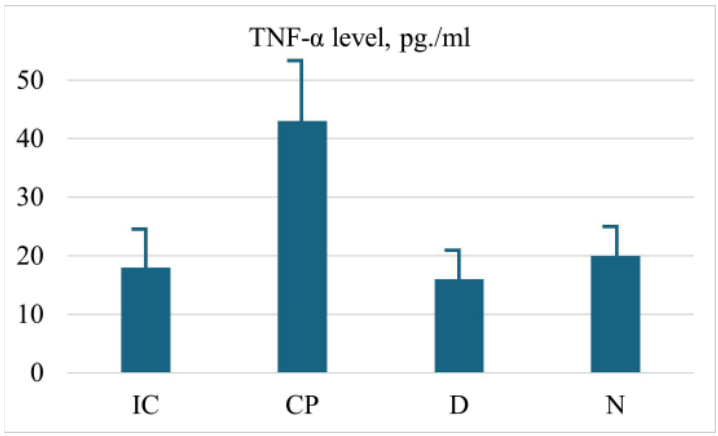

Fig. 4. **TNF-α levels in HAT after 12 days of treatment (pg/ml)**
* — difference between groups is statistically significant (P <0.05)

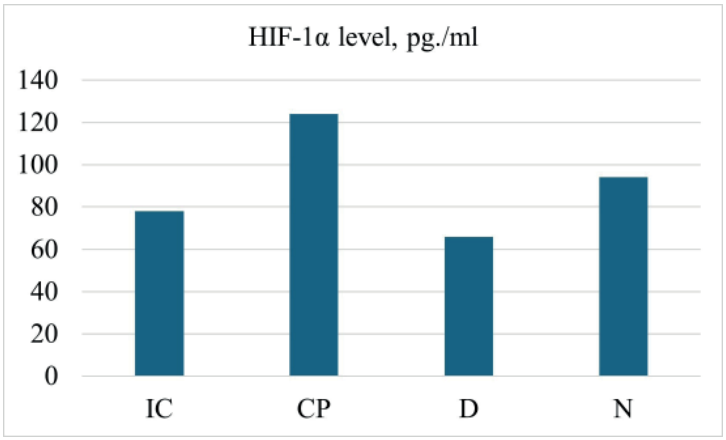

Fig. 5. **HIF-1α levels in HAT after 12 days of treatment (pg/ml)**

Study results indicate a higher therapeutic efficacy of the investigational medical product Dilatil than the comparison Nifecain, which is probably related to Dilatil's complex composition. The components of Dilatil affect the main pathogenetic mechanisms of AF. Methyl-uracil provides an anti-inflammatory effect, stimulates reparation; diltiazem (calcium channel blocker, benzothiazepine derivative) reduces spasm of the anal sphincter, provides anti-inflammatory effect; lidocaine has

an analgesic direct impact which reduces spasm of the sphincter from a significant pain symptom. Nifecain contains a calcium channel blocker of the dihydropyridine group - nifedipine and lidocaine. This conclusion is confirmed by a lower level of inflammatory, apoptosis, and hypoxia factors in the group of animals that received Dilatil cream.

Conclusions. This study confirms the perspective for conducting deeper pharmacological studies of the mechanism of action and further clinical trials of the rectal cream Dilatil, which hoas certain advantages in terms of effectiveness in the model of ACAF in the experiment in comparison with Nifecain cream.

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