

Dynamics of prostaglandin E₂ in the surgical treatment of gastroesophageal reflux disease

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Gastroesophageal reflux disease (GERD) is one of the most common gastroenterological diseases. Therefore, the issues of diagnosis and the most effective treatment of GERD are extremely relevant. Achieving a stable positive result of treatment is impossible without taking into account the pathogenetic mechanisms of the development of GERD. Particularly relevant are the little-studied issues of the influence of humoral factors on the development of GERD in the course of treatment. One of the interesting biologically active substances is prostaglandin E₂, the possible involvement of which in the mechanisms of the development of GERD is insufficiently reported.

The aim of the study is to evaluate the effect of antireflux surgery on the level of prostaglandin E₂ in blood serum and to verify that its changes after surgical treatment are associated with the decrease of gastroesophageal reflux and esophageal inflammation.

Materials and methods. 35 patients were examined with GERD who underwent laparoscopic total antireflux fundoplication. There were 26 women (74.3 %) and 9 men (25.7 %). Their age is 55.3 ± 11.3. The control group consisted of 20 practically healthy people (women – 14 (70.0 %), men – 6 (30.0 %), average age – 56.7 ± 10.6).

Immunoenzymatic analysis of prostaglandin E₂ was performed in blood plasma, which was obtained according to a standard method. Determination of prostaglandin E₂ (Prostaglandin E₂ ELISA, KGE004B, RnD Systems) was carried out by the immunoenzymatic method based on the use of the "sandwich" variant of the solid-phase immunoenzymatic analysis. The procedure was carried out on the immunoenzyme complex ImmunoChem-2100 (USA) at the Department of Clinical Laboratory Diagnostics in Zaporizhzhia State Medical University. Research on the level of prostaglandin E₂ in the main group was carried out before surgical treatment and 2–3 months after surgery by taking venous blood and using the above test systems. Statistical evaluation of the research results was performed using the Statistica for Windows 13 software package (StatSoft Inc., No. JPZ804I382130ARCN10-J).

Results. The level of prostaglandin E₂ in the blood of practically healthy people was 16.7 ± 6.1 pg/ml. In the main group, the values of prostaglandin E₂ before surgical treatment were 25.8 ± 5.7 pg/ml, after surgical treatment, they decreased to 13.5 ± 5.3 pg/ml. The detailed analysis of patients in the main group showed that the level of prostaglandin E₂ did not differ statistically in different erosive forms of esophagitis, or CLE and NERD. But it is statistically different from the level of prostaglandin E₂ in practically healthy individuals of the control group. The conducted correlation analysis indicated that the level of prostaglandin E₂ did not depend on the duration of acid exposure in the esophagus, as well as on the severity of esophagitis or the presence of CLE.

Conclusions. With effective surgical treatment of gastroesophageal reflux disease, a decrease in the level of prostaglandin E₂ after surgery is determined compared to preoperative data to the level obtained in a group of practically healthy patients. The obtained dynamics of the level of prostaglandin E₂ indicates the possibility of this hormone influencing the tone of the lower esophageal sphincter and active participation in the pathogenesis of GERD, which confirms the possibility of its use as an additional diagnostic marker of inflammation in the esophagus and a marker of the effectiveness of surgical treatment.

Ключові слова:гастроезофагеальна рефлюксна хвороба, грижа стравохідного отвору діафрагми, простагландин E₂.**Патологія. 2023.**

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Динаміка простагландину E₂ при хірургічному лікуванні гастроезофагеальної рефлюксної хвороби

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Гастроезофагеальна рефлюксна хвороба (ГЕРХ) – одне з найпоширеніших гастроентерологічних захворювань. Тому питання щодо діагностики та найбільш ефективного лікування ГЕРХ мають неабияку актуальність. Досягнення стійкого позитивного результату лікування не можливе без урахування патогенетичних механізмів виникнення ГЕРХ. Особливо актуальними є недостатньо вивчені питання щодо впливу гуморальних факторів на виникнення ГЕРХ у процесі лікування. Одна з цікавих біологічно активних речовин – простагландин E₂, можлива участь якого в механізмах виникнення ГЕРХ досліджена недостатньо.

Мета роботи – оцінити вплив антирефлюксної операції на рівень простагландину E₂ в сироватці крові та переконатися, що його зміни після хірургічного лікування пов'язані зі зменшенням гастроезофагеального рефлюксу та запалення стравоходу.

Матеріали та методи. Обстежили 35 пацієнтів із ГЕРХ, яким виконали лапароскопічну тотальну антирефлюксну фундоплакцію (26 (74,3 %) жінок, 9 (25,7 %) чоловіків). Вік пацієнтів становив 55,3 ± 11,3 року. В контрольну групу залучили 20 практично здорових осіб (14 (70,0 %) жінок, 6 (30,0 %) чоловіків), середній вік – 56,7 ± 10,6 року.

Імуноферментне дослідження простагландину E₂ здійснили в плазмі крові, яку одержали за стандартною методикою. Простагландин E₂ (Prostaglandin E₂ ELISA, KGE004B, RnD Systems) визначили імуноферментним методом, що базується на використанні «сендвіч»-варіанта твердофазного імуноферментного аналізу. Процедуру здійснили на імуноферментному комплексі ImmunoChem-2100 (США) на кафедрі клінічної лабораторної діагностики Запорізького державного

медичного університету. Дослідження рівня простагландину E_2 в основній групі здійснили до оперативного лікування та через 2–3 місяці після операції шляхом забору венозної крові та використання названих тест-систем. Статистично результати дослідження оцінили, застосувавши програмний пакет Statistica for Windows 13 (StatSoft Inc., ліцензія № JPZ8041382130ARCN10-J).

Результати. У практично здорових осіб рівень простагландину E_2 у крові становив $16,7 \pm 6,1$ пг/мл. В основній групі значення простагландину E_2 до хірургічного лікування дорівнювали $25,8 \pm 5,7$ пг/мл, після нього знизилися до $13,5 \pm 5,3$ пг/мл. Детальний аналіз структури основної групи показав, що рівень простагландину E_2 статистично не відрізнявся в пацієнтів із різними ерозивними формами езофагіту, CLE і неерозивною рефлюксною хворобою. Статистично вірогідну різницю визначили щодо рівня простагландину E_2 у практично здорових осіб контрольної групи. Кореляційний аналіз показав, що рівень простагландину E_2 не залежить від тривалості кислотної експозиції в стравоході, а також від ступеня тяжкості езофагіту чи наявності CLE.

Висновки. У разі ефективного хірургічного лікування гастроєзофагеальної рефлюксної хвороби спостерігали зниження рівня простагландину E_2 після операції порівняно з доопераційними даними до рівня, що встановили в групі практично здорових пацієнтів. Така динаміка рівня простагландину E_2 вказує на можливий вплив цього гормону на тонус нижнього стравохідного сфінктера й активну участь у патогенезі ГЕРХ. Отже, можливе його використання як додаткового діагностичного маркера запалення в стравоході та маркера ефективності хірургічного лікування.

Gastroesophageal reflux disease (GERD) is one of the most common gastroenterological diseases [13,17]. The number of patients in the population today is rapidly increasing [15,16]. In this regard, the issues of diagnosis and the most effective treatment of GERD remain relevant [14,18,21]. Achieving a stable positive result of treatment is impossible without taking into account the pathobiochemical and pathophysiological mechanisms of GERD, the study of which is increasingly attracting the attention of specialists both among therapists and surgeons [2,3,19,20]. Particularly relevant are the little-studied issues of the influence of humoral factors and their dynamics on the development of GERD during treatment [1,5,8,10,12]. One of the biologically active substances of interest is prostaglandin E_2 , the possible involvement of which in the mechanisms of GERD development is reported in separate works [4,6–8,11]. However, the available data are based on an insufficient number of studies and require further study of the pathogenetic role of prostaglandin E_2 in patients with GERD.

Aim

To evaluate the effect of antireflux surgery on the level of prostaglandin E_2 in the blood serum and to verify that its changes after surgical treatment are associated with the decrease of gastroesophageal reflux and esophageal inflammation.

Materials and methods

We examined 35 patients who underwent laparoscopic total fundoplication in the Short Floppy Nissen modification. There were 26 women (74.3 %) and men – 9 (25.7 %). Their age is 55.3 ± 11.3 . The control group consisted of 20 practically healthy individuals (women – 14 (70.0 %), men – 6 (30.0 %), mean age – 56.7 ± 10.6). The groups of sick and healthy individuals did not differ in sex ($p = 0.73$) and age ($p = 0.70$). The diagnosis of GERD was confirmed on the basis of the results obtained from the clinical manifestations analysis using valid questionnaires, video esophagogastroduodenoscopy with a lower third mucous membrane biopsy of the esophagus, and daily pH-impedance-metry. Immunoenzymatic analysis of prostaglandin E_2 was performed in blood plasma, which

was obtained according to a standard method. Previously studied samples were stored in a low-temperature freezer at a temperature of 80 C0. Determination of prostaglandin E_2 (Prostaglandin E2 ELISA, KGE004B, RnD Systems) was carried out by the immunoenzymatic method based on the use of the “sandwich” variant of the solid-phase immunoenzymatic analysis. The detection of the studied marker was carried out according to a standard procedure using the ImmunoChem-2100 immunoenzymatic complex (USA) at the Department of Clinical Laboratory Diagnostics in Zaporizhzhia State Medical University. The concentration of experimental indicators was expressed in pg/ml [22].

The criteria for inclusion in the study were confirmed GERD, consent to surgical treatment, and the absence of general contraindications to surgery. Exclusion criteria were the absence of GERD, other chronic gastroenterological diseases in the stage of exacerbation, acute surgical pathology, and refusal of operative treatment. The levels of prostaglandin E_2 in the main group were tested before surgery and 2–3 months after surgery by taking venous blood and using the above test systems. Statistical evaluation of the research results was carried out using the Statistica for Windows 13 software package (StatSoft Inc., No. JPZ8041382130ARCN10-J)

The obtained results are presented in the form of arithmetic mean and mean square deviation $M \pm s$. Differences between groups were assessed using non-parametric methods using the Mann–Whitney test, the Kruskal–Wallis test, the Wilcoxon test, Spearman’s non-parametric method, as well as with the help of the “Differential tests” submodule in the “Basic statistics and tables” module. Differences at $p < 0.05$ were considered statistically significant.

Results

The analysis of the obtained results showed that in practically healthy people the level of prostaglandin E_2 in the blood was 16.7 ± 6.1 pg/ml. In the main group, the values of prostaglandin E_2 before surgical treatment were 25.8 ± 5.7 pg/ml, which is statistically higher compared to the control group ($p < 0.05$) (Table 1). After the surgical treatment, the level of prostaglandin E_2 in the blood of the studied patients decreased to 13.5 ± 5.3 pg/ml and signi-

Table 1. The level of prostaglandin E₂ in the groups of patients under study

Parameter, units of measurement	Control group (n = 20)	1 group (n = 35) GERD	
		Before the operation	After the operation
Prostaglandin E ₂ , pg/ml	16.7 ± 6.1	25.8 ± 5.7*	13.5 ± 5.3**

*: p < 0.05 in comparison with the control group and with post-operative data; **: p < 0.05 in comparison with the preoperative data; p: the value of statistical difference.

Table 2. Characterization of the prostaglandin E₂ level and the number of patients with reflux esophagitis and columnar-lined esophagus in the studied groups of patients

Parameter, units of measurement	Control patients (n = 20)	1 group (n = 35) GERD	
		Before the operation	After the operation
Prostaglandin E ₂ , pg/ml	16.7 ± 6.1	25.8 ± 5.7*	13.5 ± 5.3**
Reflux esophagitis/CLE, n	no	21 (60.0%)*	2 (5.7%)**

*: p < 0.05 in comparison with the control group and with post-operative data; **: p < 0.05 in comparison with the preoperative data; p: the value of statistical difference; **CLE**: columnar-lined esophagus.

Table 3. Distribution of patients with various forms of esophageal mucosa inflammation and their dynamics in the studied groups

Degree of esophagitis	1 group (n = 35)		p
	Before the operation	After the operation	
NORM	–	27 (77.1 %)	0.00001
Non-erosive reflux disease	14 (40 %)	6 (17.1 %)	0.03
Erosive esophagitis (Los Angeles A, B, C)	12 (34.3 %)	–	0.0001
Columnar-lined esophagus	9 (25.7 %)	2 (5.7 %)	0.02

p: the value of statistical difference.

Table 4. Comparative characteristics of the acid exposure dynamics in the esophagus in the studied groups

Parameter, units of measurement	Control patients (n = 20)	1 group (n = 35) GERD	
		Before the operation	After the operation
Prostaglandin E ₂ , pg/ml	16.7 ± 6.1	25.8 ± 5.7*	13.5 ± 5.3**
Reflux esophagitis/CLE, n	–	21 (60.0%)*	2 (5.7%)**
Acid exposure (%)	2.1 ± 0.9	30.8 ± 27.1*	2.5 ± 1.7**

*: p < 0.05 in comparison with the control group and with post-operative data; **: p < 0.05 in comparison with the preoperative data; p: the value of statistical difference; **CLE**: columnar-lined esophagus.

Table 5. Comparative characteristics of the prostaglandin E₂ level depending on the esophageal inflammation form

Esophageal inflammation form	Number of patients	PGE ₂
NERD	14 (40 %)	23.9 ± 3.3
Erosive esophagitis (Los Angeles A, B, C)	12 (34.3 %)	26.0 ± 4.5
CLE	9 (25.7 %)	28.3 ± 8.7
P		0.1438

p: the value of statistical difference.

Table 6. Characteristics of the prostaglandin E₂ level depending on the form of esophageal inflammation in comparison with the control group

Pathological features	PGE ₂
No GERD	16.7 ± 6.1
NERD	23.9 ± 3.3*
Erosive esophagitis (Los Angeles A, B, C)	26.0 ± 4.5*
CLE	28.3 ± 8.7*

*: p < 0.05 in comparison with the control group.

ificantly differed from the preoperative values (p = 0.01), however, it did not statistically differ from the values obtained in practically healthy persons (p = 0.08) (Table 1).

During analyse there was noted the dynamics of the inflammation degree of the esophageal mucosa in the main group: the predominance of erosive forms with pronounced inflammatory lesions of the esophageal epithelium before surgery and a statistically significant decrease in inflammatory forms in the postoperative period (Table 2).

The detailed analysis of the number distribution of patients with different types and degrees of esophageal mucosa inflammation duplicates this trend (Table 3).

Similarly, there is a decrease in acid exposure in the lower third esophagus during daily monitoring in GERD patients from 30.8 ± 27.1 percent of daily preoperative monitoring to normal values of 2.5 ± 1.7 percent after surgery, which is presented in Table 4.

The detailed analysis of mucous membrane inflammation of the lower third esophagus of the main group patients before surgery showed that the level of prostaglandin E₂ did not statistically differ in various erosive forms of esophagitis, columnar-lined esophagus (CLE), and non-erosive reflux disease (NERD) (Table 5).

But it is statistically different from the prostaglandin E₂ level in practically healthy persons of the control group (Table 6).

Analysis of the correlation between the prostaglandin E₂ level and the severity of mucous membrane inflammation of the lower third esophagus showed the absence of a correlation (Fig. 1).

Fig. 1 shows that the prostaglandin E₂ level does not depend on the severity of esophagitis or the presence of CLE (p = 0.52). A similar situation is observed when analyzing the dependence of the prostaglandin E₂ level on the time of acid exposure in the lower third of the esophagus (Fig. 2).

The diagram presented in Fig. 2 also shows that the level of prostaglandin E₂ also does not depend on the duration of acid exposure in the esophagus (p = 0.33), which allows us to draw certain conclusions.

Discussion

Today, the main role of prostaglandin E₂ in the pathogenesis of GERD is attributed to its hypotensive effect on the lower esophageal sphincter and participation in the inflammatory process. There are separate works on the role of prostaglandin E₂ in the formation of the pre-epithelial barrier.

The results obtained in our work also confirm that prostaglandin E₂ is a pro-inflammatory marker of inflammation, can indicate the presence of esophagitis in GERD, and can have an effect on the tone of the lower esophageal sphincter. The effective surgical intervention led to the elimination of pathological reflux in all studied patients, as well as restoration of the esophageal mucosa in dynamics, which is visually presented in Tables 2, 3, and 4, and confirmed histologically and by daily pH-impedance-monitoring. In the postoperative period, patients with erosive esophagitis and CLE became much less compared to preoperative data. Acid exposure also

significantly decreased after the operation and reached normal values. At the same time, the prostaglandin E_2 level decreased to 13.5 ± 5.3 pg/ml, which is significantly lower than the preoperative level and the level in the control group (Table 1). Such a trend confirms the fact that against the background of the elimination of the inflammatory process in the esophagus, which is associated with the reduction of acid exposure as a result of successful surgical treatment, the level of the pro-inflammatory marker prostaglandin E_2 also decreases to the level of practically healthy patients of the control group.

At the same time, the decrease in the level of prostaglandin E_2 as a result of the reflux elimination limits the development of prostaglandin E_2 -mediated oxidative and nitrosative stress and also may lead to a decrease in its stimulating effect on the hypotonus of the lower esophageal sphincter (LES). Thereby interrupting the pathogenetic closed circle of GERD: reflux – inflammation – increased level of prostaglandin E_2 – oxidative/nitrosative stress – increased hypotonia of the LES – increased reflux. According to the data obtained during our research, there was no correlation between the level of prostaglandin E_2 , the degree of severity and the form of inflammation in the esophagus, as well as between the level of prostaglandin E_2 and the level of acid daily exposure (Fig. 1, 2). And the patients of the main group with NERD, reflux esophagitis or CLE also did not differ among themselves in terms of the level of the studied hormone (Tables 5, 6). This indicates the possible diagnostic role of prostaglandin E_2 as a marker of inflammation in erosive and non-erosive forms of GERD.

In view of the data, we received and their analysis, as well as the data indicated in the literature, we believe that currently the role of prostaglandin E_2 in the pathogenesis and diagnosis of GERD is not given enough attention, and its influence on the development of this disease is underestimated and insufficiently studied. The available data on this hormone do not reveal its involvement in the pathogenesis of GERD and its role in achieving a persistent therapeutic effect during surgical treatment, and also limit the possibility of using this hormone as a diagnostic marker and the effectiveness of surgical treatment of GERD. Our conducted research and the obtained results contribute to approaching the solution to these questions.

Conclusions

1. During the surgical treatment of gastroesophageal reflux disease, a significant decrease in the level of prostaglandin E_2 is determined after surgery compared to preoperative data to the level observed in a group of practically healthy patients.

2. The dynamics of the level of prostaglandin E_2 indicates its involvement in the pathogenesis of GERD and reflux elimination, which confirms the possibility of its use as an additional diagnostic marker of esophagitis and a marker of the effectiveness of surgical treatment.

3. Determining the level of prostaglandin E_2 in the absence of visible inflammatory changes in the esophagus, in particular with NERD, allows for an increase in the effectiveness of diagnosing the pathological process in patients with GERD.

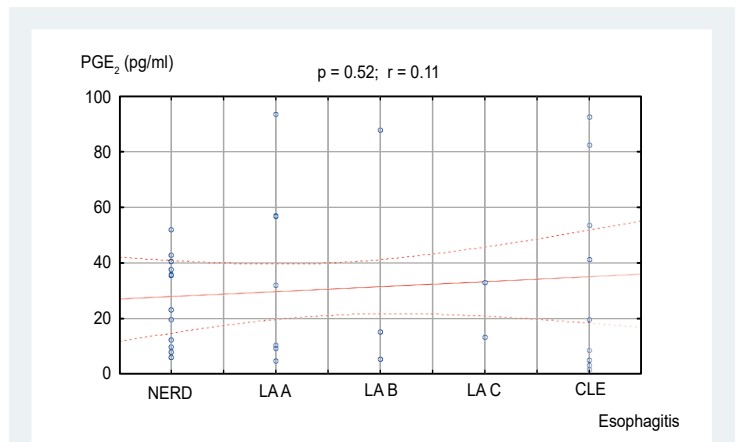


Fig. 1. Correlation between the prostaglandin E_2 level and the severity of inflammation in the mucous membrane of the lower third esophagus.

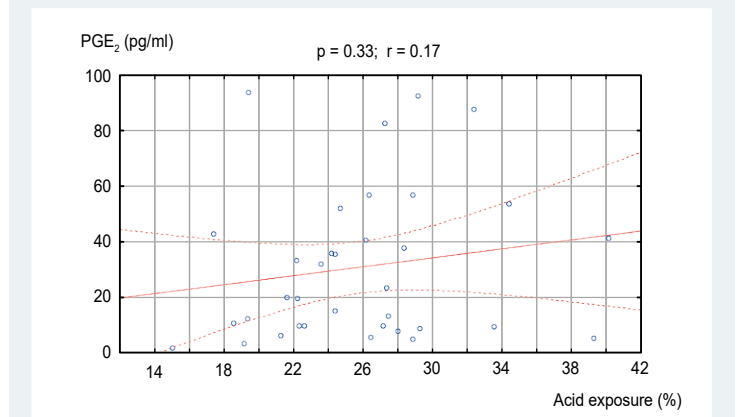


Fig. 2. Correlation between the level of prostaglandin E_2 and the time of acid exposure in the lower third of the esophagus.

4. The results of the conducted study confirm the role of prostaglandin E_2 in the pathogenesis and diagnosis of GERD and require continued work in the direction of studying the dynamics of this hormone in this disease.

Conflicts of interest: author has no conflict of interest to declare.

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