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An integrated approach to treatment of patients with complicated forms of gastroesophageal reflux disease

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Abstract

Aim. To justify the appropriateness of applying the integrated algorithm of treatment, including the sequential application of conservative antireflux treatment and antireflux surgery, in patients with complicated forms of gastroesophageal reflux disease.

Methods. The main group of the study included 554 patients with complicated forms of gastroesophageal reflux disease (erosive esophagitis in 301, peptic stricture in 36, Barrett's esophagus in 90 and a combination of several complications in 127 patients), and the control group included 229 patients with uncomplicated gastroesophageal reflux disease and indications for surgical treatment. At the diagnostic stage, fiberoptic esophagogastroduodenoscopy with chromoendoscopy using a double dye staining technique (Lugol and methylene blue) and biopsies of areas suspicious for metaplasia, as well as a barium contrast multi-positional radiographic examination of the esophagus and gastroesophageal junction were used. At the treatment stage, both groups received conservative antireflux treatment lasting 4–8 weeks, comprising lifestyle regulation, diet, antisecretory drug therapy (proton pump inhibitors — omeprazole or rabeprazole 20 mg orally twice a day, antispasmodic agent — domperidone 20 mg orally 3 times a day or itopride 50 mg orally 3 times a day), followed by either laparotomic or laparoscopic antireflux surgery. In the main group, antireflux surgery was supplemented with endoscopic argon plasma coagulation during the postoperative period in the patients with Barrett's esophagus and esophageal bougienage under endoscopic control during the pre- and postoperative period in the patients with a peptic stricture.

Results. The frequency of intraoperative [6.3% (95% CI 1.4–5.8%), p=0.0462] and early postoperative complications [41.5% (95% CI 37.4–45.7%), p=0.0011] in the main group were statistically significantly higher than in the control group. There was no clinically important difference. Frequency of late postoperative complications in the main group [5.4% (95% CI 3.7–7.6%)] did not have statistically significant differences from the control (p=0.1239). The integrated algorithm of treatment has proven to be safe with provision for the need to develop measures to reduce the overall incidence of early postoperative complications. Excellent and satisfactory immediate treatment results were achieved in 91.7% (95% CI 89.1–93.9%), and excellent and satisfactory long-term results were achieved in 91.3% (95% CI 88.7–93.5%) patients of the main group, and were statistically significantly worse than in the control group, p=0.0008 and p=0.0021 for the immediate and long-term results, respectively. The difference was attributable to the extremely high efficiency of the treatment algorithm in the control group and had no clinical significance.

Conclusion. The use of the integrated algorithm of treatment based on the implementation of antireflux surgery is appropriate in all patients with complicated forms of gastroesophageal reflux disease.

Keywords: treatment of complicated gastroesophageal reflux disease, GERD, antireflux surgery, peptic stricture of the esophagus, Barrett's esophagus, erosive reflux esophagitis.

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Background. Complicated forms of gastroesophageal reflux disease (CFGERD), which include erosive reflux esophagitis, peptic esophageal stricture, and Barrett esophagus, are registered in 15%–20% of patients with chronic GERD (1.5%–4% of the population from developed countries) [1,2]. They are characterized by a high prevalence in the population and cause significant social and economic damage since they can have an extremely unfavorable result and severe course with the development

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of malignancy, irreversible esophageal stenosis, esophageal hemorrhage, esophageal perforation, and extraesophageal complications [3,4].

The pathogenesis of GERD and erosive reflux esophagitis, as its main complication, is based on pathological gastroesophageal reflux, leading to prolonged exposure of the stomach contents to the epithelium of the esophagus and causing a damaging effect similar to a chemical burn [5]. The leading role in this is played by a disorder of the obturative function of the esophagogastric junction. It should be especially noted that hiatal hernia (HH) plays one of the main roles.

The chronic course of erosive reflux esophagitis leads to damage to the basement membrane with the formation of erosive-ulcerative esophagitis. Peptic strictures develop as a result of a long course of severe erosive-ulcerative esophagitis accompanied by damage to the submucosa [5]. Moreover, the development of Barrett esophagus is initiated and stimulated by gastroesophageal reflux, when pluripotential stem cells of the esophageal epithelium are differentiated into columnar epithelium as a result of a chronic reparative process in case of chemical damage [1,6].

Thus, the pathogenetic approach to the management of CFGERD patients should be based on treatment aimed at restoring the valve function and supporting mechanisms of the esophagogastric junction. Laparoscopic fundoplications can effectively restore the valve function of the esophagogastric junction and nowadays can be characterized as the method of choice in patients with uncomplicated GERD (NGERD) [7].

Although some guidelines and surgical schools recommend similar regimens for all CFGERD patients [8,9], the feasibility of this approach raises many questions. CFGERD patients may have a significantly higher incidence of intraoperative complications because of pronounced perivisceritis and adhesive process in the esophagogastric junction. Long-term course of CFGERD can result in changes in the mechanical and physiological properties of the distal esophagus wall, thereby increasing the frequency of relapses of gastroesophageal reflux and other postoperative complications. An unsatisfactory result in CFGERD patients may be masked by better results of treatment of NGERD patients. Difficulties arise when comparing the treatment results, which are determined in patients with various CFGERDs by heterogeneous and often incomparable criteria.

Thus, all questions resolve into the extent the approach, used to treat NGERD patients, is safe and effective in CFGERD patients. At the same time, the results of treatment of NGERD patients can be used as a criterion and guideline in research to resolve these issues.

The study aimed to substantiate the feasibility of using a complex therapeutic algorithm (CTA), including the sequential application of conservative antireflux therapy and surgical antireflux treatment, in CFGERD patients.

Material and methods. The subjects of the study were patients diagnosed with GERD who were treated in the Department of the Esophagus Surgery of the Republican Clinical Oncological Dispensary (RCOD) between January 1, 1997, and December 31, 2013, and who were registered at the dispensary for at least 6 years. All study participants were residents of the Russian Federation, and the RCOD Ethics Committee (Protocol No. 47 of April 16, 2009) approved the study.

The research was analytical retrospective by the type of structure and organization.

Study inclusion criteria included diagnosis of GERD on admission and indications for surgical antireflux treatment. Exclusion criteria were as follows: An esophageal stricture unassociated with GERD, contraindications to surgical antireflux treatment, refusal from surgical antireflux intervention for any other reason, and history of malignant neoplasms.

Endpoints included end of the follow-up period after antireflux surgery, development of esophageal adenocarcinoma, and indications for repeated antireflux surgical treatment.

The study included 846 patients who were withdrawn from the study during the follow-up period. The main group was composed of 554 patients with CFGERD [65.5%, 95% confidence interval (CI) 62.2–68.7] and the control with 292 patients with NGERD (34.5%, 95% CI 31.3–37.8). At the time of inclusion in the study, the median age of the patients was 51 years (95% CI 50–53, range 19–77 years) in the main group and 50 years (95% CI 48–51, range 18–74 years) in the control group. There were no statistically significant differences in the age of inclusion in the study between the groups. There were 61.4% of men (95% CI 57.2–65.4) and 38.6% of women (95% CI 34.6–2.8) in the main group and 48.3% of men (95% CI 42.4–54.2) and 51.7% of women (95% CI 45.8–57.6) in the control group.

The follow-up period after the antireflux surgery was 72 to 278 months in the main and control groups. The median follow-up periods were 122 and 120 months in the main and control groups.

The diagnosis was established based on the following:

– General clinical examination,

– Endoscopic examination of the esophagus

Table 1. Distribution of patients in the main group according to the type of complicated forms of gastroesophageal reflux disease (CFGERD)

Type of CFGERD	Number of patients with this CFGERD	Relative incidence of this CFGERD, %	95% confidence interval of the relative frequency, %
Erosive esophagitis	301	54.3	50.1–58.5
Peptic stricture	36	6.5	4.6–8.9
Barrett esophagus	90	16.2	13.3–19.6
Combination of several CFGERDs	127	22.9	19.5–26.7
Total	554	100	—

and stomach [fibroesophagogastroduodenoscopy (FEGDS)] with double chromoscopy with Lugol's solution and methylene blue solution and biopsy from areas with suspected metaplasia, and

– Multiplanar radiographic contrast study of the esophagus and esophagogastric junction with barium swallow contrasting.

The basis of the CTA developed and used by us, applied in patients of the main and control groups, was surgical antireflux interventions in various versions.

We performed antireflux surgeries in GERD patients for indications such as paraesophageal HH (an absolute indication for surgery), presence of any CFGERD and GERD extraesophageal manifestations, and ineffectiveness of conservative therapy for more than 10 weeks.

The CTA itself consisted of three stages:

1) conservative antireflux therapy lasting for 4–8 weeks, including lifestyle regulation, diet, antisecretory drug therapy [proton pump inhibitors (omeprazole or rabeprazole 20 mg orally twice a day) and eukinetic drugs (domperidone 20 mg orally three times a day or itoprid 50 mg orally three times a day)];

2) antireflux surgery;

3) dispensary follow-up including FEGDS with double chromoscopy and biopsy and radiographic contrast study of the esophagus and esophagogastric junction during the first 12 months of the follow-up period with a frequency of once every 6 months, then once a year or as complaints arise.

Additionally, we used the methods of treatment necessary for certain complications:

– dilatation of the esophagus in the form of bougienage under endoscopic control in the preoperative and postoperative periods with peptic stricture;

– ablation of metaplastic epithelium in the form of endoscopic argon plasma coagulation in patients with Barrett esophagus in the postoperative period.

All complications recorded during the treatment of GERD patients were associated with the surgical stage and its consequences. We distinguished intraoperative complications, early postoperative complications (developed within 3 months after surgery, which was the period during which the developed complications of laparoscopic fundoplication were predominantly transient), and late postoperative complications (developed within 3 months to 1 year after surgery).

Treatment results were divided into short-term (outcome noted during the first year of follow-up) and long-term (outcome noted during the entire follow-up period after the first year, and after this period, the frequency of satisfactory results decreased dramatically, which was associated with a decrease in the recurrence incidence of Barrett metaplasia and peptic stricture).

The threshold level of statistically significant difference was 0.05. To compare quantitative characteristics, the Mann–Whitney nonparametric statistical methods were used (two groups). CI limits for relative frequencies (fractions) were calculated using the Clopper–Pearson method, and the exact value of the significance level was calculated using the Pearson χ^2 test. The data were analyzed using the Statistica 10.0 statistical software package (StatSoft, Tulsa, OK, USA). The odds ratio (OR) and their CI were calculated using the MedCalc 14.12.0 program (MedCalc Software bvba, Ostend, Belgium).

Results. HH was registered in 509 of 554 patients in the main group (91.9%; 95% CI 89.3–94) and in 279 of 292 patients in the control group (95.5%; 95% CI 92.5–97.8, $p = 0.0448$). The duration of GERD history ranged from 0 (complaints occurred for the first time) to 480 months in the main group and from 0 to 440 months in the control group. The median duration of GERD history was 36 months in the main group (95% CI 24–36) and 24 months in the control group (95% CI 24–36; $p > 0.05$).

The distribution of patients in the main group according to the type of CFGERD (erosive reflux esophagitis, Barrett esophagus, peptic stricture, or a combination of several CFGERDs) is presented in Table 1.

The vast majority of interventions in the main and control group patients [93.1% and 93.8% (95%

CI 90.4–96.3 and 90.7–95.1), respectively] were performed using minimally invasive approaches in the variants according to Nissen, Nissen–Rossetti, Dor, or Toupet. There were no statistically significant differences in the frequency of application of different types of surgical approach between patients with CFGERD and NGERD.

Conversion to laparotomy was required in 29 cases (5.2%, 95% CI 3.5–7.4) in the CFGERD group and 7 cases (2.4%, 95% CI 1–4.9) in the NGERD group. Indications for conversion were intraoperative complications (10 cases in CFGERD and 3 cases in NGERD) and pronounced adhesive process (19 cases in CFGERD and 4 cases in NGERD). No statistically significant differences ($p > 0.05$) were noted in the frequency of conversions to laparotomy in the main and control groups.

The surgery was performed with the laparotomic approach due to the suspected (anamnesis data) pronounced adhesion process in 9 (1.6%) and 11 (3.8%) patients with CFGERD and NGERD, respectively. Simultaneous laparoscopic cholecystectomy was performed in 28 (5.1%) patients in the main group and 24 (8.2%) in the control group.

To ensure the comparability of treatment results in patients of various groups and subgroups of CFGERD, excellent results were attributed to the absence of the need for additional therapeutic manipulations and use of proton pump inhibitors (except primary argon plasma coagulation in patients with Barrett metaplasia) in the postoperative period; the results of treatment for patients who required endoscopic therapeutic manipulations in the postoperative period and/or long-term administration of proton pump inhibitors (except primary argon plasma coagulation in patients with Barrett metaplasia) and/or bougienage of the esophagus were considered satisfactory. If a repeated surgical intervention was necessary, as well as in the esophageal adenocarcinoma or esophageal stricture case, which was not possible to treat with a bougie, the treatment result was considered unsatisfactory.

The incidence of intraoperative complications was statistically significantly higher in the main group (6.3%, 95% CI 1.4–5.8) than in the control group (3.1%, 95% CI 1.4–5.8; $p = 0.0462$), with a difference of 3.2% (95% CI 0.4–6.1), OR 2.12 (95% CI 1.004–4.48). The difference was formed mainly because of the frequency of minor injuries to the intra-abdominal organs, namely, 3.1% (95% CI 1.8–4.9) in the main group versus 0.3% (95% CI 0–1.9) in the control group, with a difference of 2.7% (95% CI 1.1–4.3), OR 9.21 (95% CI 1.22–69.77).

The incidence of early postoperative complications was statistically significantly higher in the CFGERD group (41.5%, 95% CI 37.4–45.7) than in the NGERD group (30.1%, 95% CI 24.9–35.8; $p = 0.0011$), with difference of 11.4% (95% CI 4.7–18.1), OR 1.65 (95% CI 1.22–2.23). The difference was mainly associated with a higher incidence of gas-bloat syndrome, occurring in 23.3% (95% CI 19.8–27) in the study group versus 13.0% (95% CI 9.4–17.4) in the control group ($p = 0.0003$), with a difference of 10.3% (95% CI 5–15.5), OR 2.03 (95% CI 1.37–3.01).

The predominant early postoperative complications in both groups were dysphagia and gas-bloat syndrome, which caused a high frequency of early postoperative complications in both groups. These complications were manifestations of the fundoplication cuff hyperfunction syndrome (a consequence of its excessive tension during the fundoplication process) and were predominantly transient in the early postoperative period.

At a significance level of 0.05, there were no statistically significant differences between the main and control groups, both in the incidence of late postoperative complications in general [5.4% (95% CI 3.7–7.6) in the main group and 3.1% (95% CI 1.4–5.8) in the control group, $p = 0.1239$] and in the incidence of each late postoperative complication, in particular. As in the case of early complications, dysphagia and gas-bloat syndrome prevailed in the range of complications in the late postoperative period. It should be especially noted that in the late postoperative period, these complications occurred rarely in both groups (the upper limits of the 95% CI of the incidence of dysphagia were 3.3 and 2.5 and of gas-bloat syndrome were 4 and 3.5 for the main and control groups, respectively). This is of fundamental importance since in the later stages after the surgery, dysphagia and gas-bloat syndrome were already persistent and deteriorated significantly the quality of life of patients.

Thus, CTA can be characterized as unambiguously safe in terms of intraoperative and late postoperative complications. Based on the results obtained at a significance level of 0.05, it can be argued that the rates of intraoperative complications in CFGERD and NGERD patients were below 8.7% and 5.8%, respectively; the incidence of late postoperative complications was lower than 7.6% in the main group and lower than 5.8% in the control group.

The high incidence of dysphagia and gas-bloat syndrome in the early postoperative period led to a high incidence of early postoperative complications (more than 37.4% and 24.9% in CFGERD and NGERD patients). In this case, the complications were mainly of a transient nature.

Thus, CTA can be considered safe for use in patients of both groups, subject to the proviso of the

need to develop measures to reduce the incidence of early postoperative complications.

The use of CTA enabled to achieve excellent short-term treatment results in 86.6% of CFGERD patients (95% CI 83.5–89.4). With a significance level of 0.05, it can be stated that statistically significantly better short-term treatment results were achieved in the control group patients:

– The frequency of excellent short-term treatment results was statistically significantly higher ($p = 0.0001$), and the difference was 9.6% (95% CI 6–13.2), OR 3.94 (95% CI 2.05–7.55).

– The frequency of satisfactory short-term treatment results was statistically significantly higher in the CFGERD group than in the NGERD group ($p = 0.0076$), and the difference was 3.7% (95% CI 1.4–5.9), OR 3.83 (95% CI 1.33–11.05).

– The frequency of unsatisfactory short-term treatment results was statistically significantly higher in the CFGERD group than in the NGERD group ($p = 0.0008$), and the difference was 5.9% (95% CI 3–8.8), OR 3.69 (95% CI 1.64–8.28).

The use of CTA enabled to achieve excellent long-term results of treatment in 86.8% of CFGERD patients (95% CI 83.7–89.5). With a significance level of 0.05, it can be argued that statistically significantly better long-term treatment results were achieved in the control group patients:

– The frequency of excellent long-term results was statistically significantly higher in the NGERD group than in the CFGERD group ($p = 0.0001$), and the difference was 10.1% (95% CI 6.6–13.5), OR 4.77 (95% CI 2.35–9.7).

– The frequency of satisfactory long-term results of treatment was statistically significantly higher in the CFGERD group than in the NGERD group ($p = 0.0002$), and the difference was 4.5% (95% CI 2.8–6.2), OR not calculated.

– The frequency of unsatisfactory long-term results of treatment was statistically significantly higher in the CFGERD group than in the NGERD group ($p = 0.0021$), and the difference was 5.6% (95% CI 2.5–8.7), OR 2.98 (95% CI 1.44–6.18).

Discussion. Typically, the patient population with CFGERD is represented by men aged 41–60 years. In the population of NGERD patients who had indications for surgical treatment, there was no predominant gender. There were no age differences between CFGERD and NGERD patients with indications to surgical treatment. In the sample of patients with complicated forms of GERD, patients with erosive reflux esophagitis prevailed (54.3%; 99% CI 50.1–58.5). Meanwhile, CFGERD patients had a combination of two or more CFGERDs in 24.5% (99% CI 19.5–26.7) of cases.

Our data indicate the fact that HH and GERD complications can be considered concomitant diseases, as 91.9% (95% CI 89.3–94) of CFGERD patients had HH, which is a serious disorder of the normal anatomical and physiological relationships of organs of the cardioesophageal area. Effective correction of HH is possible only by surgery; thus, the extremely high prevalence of HH in CFGERD patients indicates the advisability of mandatory inclusion of antireflux surgery in the algorithm for treatment of this pathology.

There were no statistically significant differences in the duration of the GERD history between patients in the main and control groups. That is, our data indicate the fact that CFGERD is not a direct consequence of NGERD progression as a result of a long course of the disease.

Considering that laparoscopic approach for antireflux surgeries is currently the "gold standard," it is important to note that its use was possible in 93.1% (95% CI 90.7–95.1) and 93.8% (95% CI 90.4–96.3) of patients with CFGERD and NGERD, respectively. In other cases, there were contraindications for minimally invasive surgeries. At the same time, contrary to expectations, no statistically significant differences in the frequency of conversions to laparotomy during laparoscopic antireflux surgeries were recorded between patients in the main and control groups.

The methodology developed by us and tested in this work for assessing the results of treatment, depending on the need to perform various kinds of therapeutic manipulations to correct the complications that have developed during the postoperative period, in a comparative analysis of treatment results in the main and control groups, proved itself as convenient, which enables to impart the terms indicating the treatment result (excellent, satisfactory, and unsatisfactory) with a very specific meaning associated with a certain range of complications and conditions that determine the patient's well-being. The technique is easy to use, easily reproducible, and is based on objective criteria.

CTA can be characterized as safe in the treatment of CFGERD patients, including when compared with the safety of CTA in NGERD patients who have indications for surgical treatment. At the same time, some aspects are noteworthy. Thus, in the main group, intraoperative complications in general and injuries of intra-abdominal organs in particular occurred statistically significantly more often. Moreover, the incidence of intraoperative complications was low in both groups. Thus, laparoscopic fundoplications are safe in CFGERD patients; however, in this group, the chances of injury to intra-abdominal organs during antireflux

surgery are 20% higher than patients with NGERD. In our opinion, this aspect is associated with pronounced perivisceritis and adhesive process, which are characteristic of CFGERD and complicate manipulation and orientation during the surgery.

Another aspect is the high incidence of dysphagia and gas-bloat syndrome in the early postoperative period, which leads to a high incidence of early postoperative complications (more than 37.4% and 24.9% in CFGERD and NGERD patients, respectively), and despite the transient nature of these complications, it indicates the need to develop measures to prevent the syndrome of the fundoplication cuff hyperfunction. The use of a transillumination phototensometric probe developed by Sharapov et al. [7] and introduced into practice in the RCOD Department of Surgery of the Esophagus also contributed to the prevention of intraoperative complications, and it can be an example of such measures.

The use of CTA in CFGERD patients was accompanied by statistically significantly worse results than in NGERD patients. However, given that the share of short-term excellent and satisfactory results in CFGERD patients was 91.7% (95% CI 89.1–93.9) and of long-term excellent and satisfactory results was 91.3% (95% CI 88.7–93.5), it can be stated that, despite the statistically significant difference in treatment results between patients in the main and control groups, this difference is due to the high efficiency of CTA in NGERD patients and not a negative result of CTA in CFGERD patients; also, it has no clinical significance.

Thus, the study results indicate that CTA, based on the performance of antireflux surgery, used in the treatment of NGERD patients, is also effective and safe for CFGERD patients, and its use is advisable in all patients with erosive reflux esophagitis, peptic stricture, Barrett esophagus, and combinations thereof.

CONCLUSIONS

1. The developed and implemented method for evaluating and comparing treatment results is based on objective criteria, is easily reproducible, and enables to perform correct comparisons for patients with various CFGERDs and NGERD.

2. The high prevalence of HH in patients with CFGERD indicates the advisability of including antireflux surgery in the treatment algorithm for this pathology.

3. The use of laparoscopic approach during antireflux surgeries in patients with CFGERD was possible in 93.1% of cases (95% confidence interval 90.7–95.1). In other cases, there were contraindications for minimally invasive surgeries.

4. The admissibility and feasibility of using a CTA, used for treating patients with NGERD, in patients with CFGERD are confirmed by the safety and efficacy of the algorithm in this group of patients.

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