NON-INTERVENTIONAL STUDY REPORT SYNOPSIS

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OBSERVATIONAL NON-INTERVENTIONAL STUDY OF INTERNATIONAL GERDQ QUESTIONNAIRE USE FOR GASTROESOPHAGEAL REFLUX DISEASE DIAGNOSIS IN RUSSIAN CLINICAL PRACTICE

STUDY DURATION:	**FIRST PATIENT IN:** FEBRUARY 06, 2012
06.02.2012– 20.06.2012	**LAST PATIENT OUT:** JUNE 20, 2012

PROTOCOL SYNOPSIS

OBSERVATIONAL NON-INTERVENTIONAL STUDY OF INTERNATIONAL GERDQ QUESTIONNAIRE USE FOR GASTROESOPHAGEAL REFLUX DISEASE DIAGNOSIS IN RUSSIAN CLINICAL PRACTICE

Survey time

Estimated date of first subject in: February 06, 2012

Estimated date of last subject out: June 20, 2012

Study sites

2 sites located in Russian Federation

Study Objectives

Primary:

To determine the sensitivity and specificity of GerdQ questionnaire for the diagnosis of GERD in work of general practitioner in Russia

Secondary:

- To assess the relationship between the result of completing GerdQ questionnaire and the results of physical examination (endoscopy, diurnal pH-metry).
- To assess the relationship between the result of completion of GerdQ questionnaire and clinical assessment by gastroenterologist
- To study the prevalence of GERD among the study population

Study design

The study was a multicenter observational prospective study.

The study enrolled 150 patients who were routinely monitored in different units of the investigational centres (gastroenterology, nephrology, cardiology, pulmonology and general medicine units), and for whom EGD and pH-metry procedures were planned to specify the diagnosis. Patients were enrolled into the study after informed consent; however the decision regarding EGD procedure should have been taken before enrolment. Before EGD the patients were requested to complete the GerdQ questionnaire on their own; then the gastroenterologist made the preliminary diagnosis (GERD or other abnormality). After that EGD was performed and if there were no signs of esophagitis (esophageal mucosa changes, including hyperemia

and edema) on EGD, 24-hour pH-metry was performed in order to rule out endoscopy-negative GERD. Upon the completion of the examination patient questionnaire completion results and gastroenterologist's diagnosis results were compared with the objective (instrumental) examination results.

STUDY POPULATION

Target study population consisted of male and female patients aged 18 years or more routinely monitored in different units of the investigational centres (gastroenterology, nephrology, cardiology, pulmonology and general medicine units), for whom EGD and pH-metry procedures were planned to specify the diagnosis. Patients were supposed to provide informed consent and perform all the study procedures.

The study enrolled 150 patients.

ENDPOINTS

Primary endpoints:

- GerdQ questionnaire sensitivity, i.e. the percentage of GERD detection based on GerdQ questionnaire (total score ≥ 8) among patients with instrumentally-confirmed GERD.
- GerdQ questionnaire specificity, i.e. the percentage of GERD absence based on GerdQ questionnaire (total score < 8) among patients, for whom instrumental examination ruled out GERD diagnosis.

Secondary endpoints:

- GERD detection frequency among study subjects based on instrumental examination (EGD, pH-metry).
- GERD detection frequency among study subjects based on the completed GerdQ questionnaire, which corresponds to the percentage of patients with a total score ≥ 8.
- Frequency of abnormality detection upon instrumental examination (esophageal epithelium changes found on EGD, pH values deviations discovered upon pH-metry), depending on GerdQ total score.
- GERD diagnosis sensitivity by the gastroenterologist, i.e. percentage of patients, whom the gastroenterologist diagnosed with GERD before instrumental examination, among patients with instrumentally-confirmed GERD.
- GERD diagnosis specificity by the gastroenterologist, i.e. percentage of patients, for whom the gastroenterologist ruled out GERD diagnosis before instrumental examination, among patients, for whom instrumental examination ruled out GERD diagnosis.

RESULTS

150 patients were included into ITT analysis. 145 patients were included into PP analysis. The reason for this difference between ITT and PP population is the short-term pH-metry which was performed in 5 cases. Its results made it impossible to evaluate the major criterion of pH-metry.

Patients disposition (age groups, gender, ethnicity)

		ITT population		**PP population**	
		Patients number	**% of total**	**Patients number**	**% of total**
Gender	Male	72	48%	70	48.3%
	Female	78	52%	75	51.7%
	Total	150	100.0	145	100.0%
Ethnicity	Caucasian	150	100%	145	100.0%
	Asian	0	0%	0	0%
	Negroid	0	0%	0	0%
	Total	150	100.0	145	100.0%
Pregnancy (for women)	Yes	0	0%	0	0%
	No	78	100%	75	100%
	Total	78	100%	75	100%

Study subjects demographic data

ITT population:

	Valid	**Mean**	**Mean deviation**	**Median**	**25-percentile**	**75-percentile**	**Minimum**	**Maximum**
Age, full years	147	47	13	47	37	56	19	85
Body mass, kg	150	75	14	74	67	83	45	116
Height, cm	150	172	8	172	165	178	152	192
BMI, kg/m^2	150	25.32	4.11	25.04	22.22	27.77	16.82	37.56

PP population:

	Valid	**Mean**	**Mean deviation**	**Median**	**25-percentile**	**75-percentile**	**Minimum**	**Maximum**
Age, full years	142	47	13	47	37	56	19	85
Body mass, kg	145	75	14	74	67	83	45	110
Height, cm	145	172	8	172	165	178	152	192
BMI, kg/m^2	145	25.26	4.03	25.00	22.22	27.48	16.82	37.56

Study subjects baseline clinical characteristics

	ITT population		PP population	
Esophageal complaints	**Patients number**	**% of total**	**Patients number**	**% of total**
Dysphagia	2	1.3	2	1.3
Upper abdominal pain	85	56.7	81	52.6
Belching	44	29.3	42	27.3
Epigastric burning	123	82.0	118	76.6
Lump in throat or behind sternum feeling	3	2.0	3	1.9
Odynophagia	1	0.7	1	0.6
Regurgitation	65	43.3	61	39.6
Extraesophageal complaints	**Patients number**	**% of total**	**Patients number**	**% of total**
Cardiac syndrome (retrosternal pain)	1	0.7	1	0.6
Otorhinolaryngological syndrome (hoarseness, salivation)	2	1.3	2	1.2
Lung syndrome (chronic cough, dyspnoea occurring more often when lying down than standing)	3	2.0	3	1.8
Stomatological syndrome (gum erosions)	0	0	0	0

Results:

GERD diagnosis results

ITT population: The majority of patients (126 out of 150, 84%) were diagnosed with GERD on the basis of gastroenterologist's assessment. **PP population**: 122 patients out of 145 (84.1%).

ITT population: The majority of patients (90 out of 150, 60.0%) had a score of 8 or more according to the GerdQ questionnaire and were diagnosed with GERD. **PP population**: 88 patients out of 145 (60.7%).

ITT population: According to EGD data esophagitis was diagnosed in 130 patients (86.7%). GERD complications were diagnosed in 52 patients (34.7%). More than half of those patients for whom esophagitis severity grade was determined (26 subjects, 54.2%) had esophagitis severity grade A according to the Los Angeles Classification. **PP population**: esophagitis: 125 patients (86.2%), GERD complications: 50 patients (34.5%). 26 subjects out of 47 (55.3%) had esophagitis severity grade A according to the Los Angeles Classification.

ITT population: The majority of patients (132 subjects, 88%) were diagnosed with GERD according to EGD results. **PP population**: 127 subjects (87.6%).

ITT population: The majority of patients (107 subjects, 71.3%) were diagnosed with GERD according to pH-metry results (24-hour and short-term). 2 subjects were missed during analysis. **PP population**: the majority of patients (105 subjects, 72.4%) were diagnosed with GERD according to pH-metry results (24-hour in all patients). 1 subject was missed during analysis.

ITT population: According to instrumental examination results (EGD or pH-metry) the majority of examined patients (138 subjects, 92.0%) were diagnosed with GERD. **PP population**: According to instrumental examination results the majority of examined patients (133 subjects, 91.7%) were diagnosed with GERD.

Sensitivity and specificity of GerdQ questionnaire for GERD diagnosis

ITT population: According to the GerdQ questionnaire GERD was diagnosed in 90 patients (60.0% of all patients). The percentage of patients with a total GerdQ score $\geq$8 among patients with instrumentally confirmed GERD (138 subjects) was **64.5%** (89 subjects), which reflects the **sensitivity** of the questionnaire. The percentage of patients with a total GerdQ score<8 (11 subjects) among patients, for whom instrumental examination ruled out GERD diagnosis (12 subjects), was **91.7%** (11/12 subjects), which corresponds to the **specificity** of the questionnaire. Statistical analysis demonstrated, that variables (GERD diagnosis based on GerdQ questionnaire and instrumental method) are quite strongly interrelated ($p<0.001$, $\varphi=0.311$). ROC-analysis data confirmed the high sensitivity and specificity of GerdQ questionnaire for GERD diagnosis. ROC-analysis was performed in order to evaluate the accuracy and specificity of the questionnaire data. Area under curve (AUC) equalled 84.3 % (95% confidence interval 70.6%-98.0%, $p<0.001$ for study null-hypothesis regarding the equivalence of true area under curve 0.5 (50%)).

PP population: According to the GerdQ questionnaire GERD was diagnosed in 88 patients (60.7% of all patients). The percentage of patients with a total GerdQ score$\geq$8 among patients with instrumentally confirmed GERD (133 subjects) was **65.4%** (87 subjects), which reflects the **sensitivity** of the questionnaire. The percentage of patients with a total GerdQ score<8 (11 subjects) among the patients, for whom instrumental examination ruled out GERD diagnosis (12 subjects), was **91.7%** (11/12 subjects), which corresponds to the **specificity** of the questionnaire. Statistical analysis demonstrated, that variables (GERD diagnosis based on GerdQ questionnaire and instrumental method) are quite strongly interrelated ($p<0.001$, $\varphi=0.322$). ROC-analysis data confirmed the high sensitivity and specificity of GerdQ questionnaire for GERD diagnosis. Area under curve (AUC) equalled 84.8% (95% confidence interval 71.1%-98.5%, $p<0.001$ for study null-hypothesis regarding the equivalence of true area under curve 0.5 (50%)).

Abnormality detection upon instrumental examination in subgroups with different GerdQ questionnaire scores

ITT population: GERD detection frequency according to EGD data, frequency of GERD complications occurrence increases depending on GerdQ total score. Esophageal epithelium abnormalities (esophagitis) detection frequency was 73.7% in the subgroup of patients with a total GerdQ score of 3-7, 93.1% in the subgroup with a total score of 8-10 and 96.9% in the subgroup with a total score of 11-18. pH values deviations frequency discovered according to pH-metry results (pH value deviation was considered to be present in case if the time when esophageal pH was <4 constituted more than 5% of the pH-metry time) was 57.9%, 89.3% and 75.0%, respectively. **PP population**: GERD detection frequency according to EGD data, frequency of GERD complications occurrence increases depending on GerdQ total score. Esophageal epithelium abnormalities detection frequency (esophagitis) was 72.2% in the subgroup of patients with a total GerdQ score 3-7, 92.9% in the subgroup with a total score of 8-10 and 96.9% in the subgroup with a total score of 11-18. pH values deviations frequency discovered according to pH-metry results (the period when esophageal pH was <4 constituted more than 5% of the total time) was 61.1%, 88.9% and 75.0%, respectively.

Sensitivity and specificity of gastroenterologist's assessment for GERD diagnosis

ITT population: Gastroenterologist diagnosed GERD in 126 out of 150 patients (84%), whereas the instrumental method (EGD and pH-metry) detected GERD in 138 patients. The percentage of patients with GERD according to gastroenterologist's assessment among patients, for whom GERD was diagnosed instrumentally, is **90.6%** (125 out of 138 patients), which indicates the **sensitivity** of gastroenterologist's GERD diagnosis. Upon instrumental examination GERD diagnosis was ruled out in 12 out of 150 patients. In 11 of them GERD was ruled out according to gastroenterologist's assessment before instrumental diagnostics. Therefore, **specificity** of gastroenterologist's GERD diagnosis is 11/12= **91.7%**. Statistical analysis demonstrated, that variables (gastroenterologist's and instrumental GERD diagnosis) are strongly interrelated ($p<0.001$, $\varphi=-0.609$).

PP population: Upon assessment gastroenterologist diagnosed GERD in 122 out of 145 patients (84.1%), whereas the instrumental method (EGD and pH-metry) detected GERD in 133 patients. The percentage of patients with GERD according to gastroenterologist's assessment among patients, for whom GERD was diagnosed instrumentally, is **91.0%** (121 out of 133 patients), which indicates the **sensitivity** of gastroenterologist's GERD diagnosis. Upon instrumental examination GERD diagnosis was ruled out in 12 out of 145 patients. In 11 of them GERD was ruled out according to gastroenterologist's assessment before instrumental diagnosis. Therefore, **specificity** of gastroenterologist's GERD diagnosis is 11/12= **91.7%**. Statistical analysis demonstrated, that variables (gastroenterologist's and instrumental GERD diagnosis) are strongly interrelated ($p<0.001$, $\varphi=-0.623$).

RESULTS

Results according to the ITT population analysis results

1) GerdQ questionnaire sensitivity, defined as the percentage of GERD detection based on GerdQ questionnaire (total score ≥ 8) in patients with instrumentally-confirmed GERD is **64.5%** (89 out of 138 patients).
2) GerdQ questionnaire specificity, defined as the percentage of GERD absence based on GerdQ questionnaire (total score < 8) among patients, for whom instrumental examination ruled out GERD diagnosis, is **91.7%** (11 out of 12 patients).
3) GERD detection frequency based on instrumental examination (EGD, pH-metry) in order to specify the diagnosis in patients monitored by gastroenterologists due to upper GI symptoms or in case of assumption of atypical GERD was **92.0%** (138 out of 150 patients).
4) GERD detection frequency based on the completed GerdQ questionnaire (questionnaire total score ≥ 8) in patients monitored by gastroenterologists due to upper GI symptoms or in case of assumption of atypical GERD was **60.0%** (90 out of 150 patients).
5) Esophageal epithelium abnormalities (esophagitis) detection frequency upon instrumental examination (EGD) was **73.7%** in the subgroup of patients with a total GerdQ score of 3-7, **93.1%** in the subgroup with a total score of 8-10 and **96.9%** in the subgroup with a total score of 11-18. pH values deviations frequency discovered according to pH-metry results (the period when esophageal pH was <4 constituted more than 5% of the total time) was **57.9%**, **89.3% and 75.0%**, respectively.
6) Sensitivity of gastroenterologist's GERD diagnosis, defined as the percentage of patients, whom the gastroenterologist diagnosed with GERD before instrumental

examination, among patients with instrumentally-confirmed GERD is **90.6%** (125 out of 138 patients).

7) Specificity of gastroenterologist's GERD diagnosis, defined as the percentage of patients, for whom the gastroenterologist ruled out GERD diagnosis before instrumental examination, among patients, for whom instrumental examination ruled out GERD diagnosis was **91.7%** (11 out of 12 patients).

Results according to the PP population analysis results

Sensitivity and specificity of GerdQ questionnaire and gastroenterologist's assessment in **PP population** are very close to these parameters of the ITT population.

1) GerdQ questionnaire sensitivity, defined as the percentage of GERD detection based on GerdQ questionnaire (total score ≥ 8) in patients with instrumentally-confirmed GERD is **65.4%** (87 out of 133 patients).
2) GerdQ questionnaire specificity, defined as the percentage of GERD absence based on GerdQ questionnaire (total score < 8) among patients, for whom instrumental examination ruled out GERD diagnosis, is **91.7%** (11 out of 12 patients).
3) GERD detection frequency based on instrumental examination (EGD, pH-metry) for diagnosis confirmation in patients monitored by gastroenterologists due to upper GI symptoms or in case of assumption of atypical GERD was **91.7%** (133 out of 145 patients).
4) GERD detection frequency based on the completed GerdQ questionnaire (questionnaire total score ≥ 8) in patients monitored by gastroenterologists due to upper GI symptoms or in case of assumption of atypical GERD was **60.7%** (88 out of 145 patients).
5) Esophageal epithelium abnormalities detection frequency (esophagitis) upon instrumental examination (EGD) was **72.2%** in the subgroup of patients with a total GerdQ score of 3-7, **92.9%** in the subgroup with a total score of 8-10 and **96.9%** in the subgroup with a total score of 11-18. pH values deviations frequency discovered according to pH-metry results (the period when esophageal pH was <4 constituted more than 5% of the total time) was **61.1%**, **88.9%** and **75.0%**, respectively.
6) Sensitivity of gastroenterologist's GERD diagnosis, defined as the percentage of patients, whom the gastroenterologist diagnosed with GERD before instrumental examination, among patients with instrumentally-confirmed GERD is **91.0%** (121 out of 133 patients).
7) Specificity of gastroenterologist's GERD diagnosis, defined as the percentage of patients, for whom the gastroenterologist ruled out GERD diagnosis before instrumental examination, among patients, for whom instrumental examination ruled out GERD diagnosis was **91.7%** (11 out of 12 patients).