Sensitivity of upper gastrointestinal series in the diagnosis of gastroesophageal reflux in premature infants[*]

Sensibilidade da seriografia do esôfago, estômago e duodeno para o diagnóstico de doença do refluxo gastroesofágico em recém-nascidos prematuros

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Abstract   **Objective:** To determine the sensitivity of upper gastrointestinal (UGI) series, adopting the 24-h esophageal pH monitoring as the gold standard in the diagnosis of gastroesophageal reflux disease (GERD) in preterm newborns, besides describing the presence of anatomical abnormalities in the digestive tube. **Materials and Methods:** The present study included 41 neonates with average birth weight of 1,243.9 g, presenting signs/symptoms of GERD and abnormal 24-h esophageal pH monitoring (reflux index ≥ 10%). The UGI series was performed as soon as the infants' clinical conditions were considered sufficiently stable. **Results:** The 24-h pH monitoring and UGI series were performed respectively at 49.8 and 66.8 days of life. The UGI series sensitivity was of 56.1% (CI 95%: 39.9–71.2%). The reflux index was significant in 41.4%, moderate in 44.8%, and mild in 13.8% of the cases. Only one case of hiatus hernia was identified by UGI series. **Conclusion**: Upper gastrointestinal series has demonstrated low sensitivity in the diagnosis of GERD in preterm newborns and was not associated with the reflux severity as compared with pH monitoring. However, it is useful in the detection of anatomical abnormalities in the upper gastrointestinal tract.
Keywords: Gastroesophageal reflux disease; Upper gastrointestinal series; 24-h esophageal pH monitoring; Preterm newborns.

Resumo   **Objetivo:** Determinar a sensibilidade da seriografia do esôfago, estômago e duodeno (SEED) para o diagnóstico da doença do refluxo gastroesofágico (DRGE) em recém-nascidos prematuros, tendo como padrão ouro a monitoração prolongada do pH esofágico distal, e descrever a presença de anormalidades anatômicas do tubo digestivo. **Materiais e Métodos:** Foram incluídos no estudo 41 recém-nascidos, com média de 1.243,9 g, apresentando sinais/sintomas de DRGE e resultados alterados na monitoração do pH (índice de refluxo ≥ 10%). A SEED foi realizada logo que as condições clínicas dos recém-nascidos foram estáveis para a realização dos exames radiológicos. **Resultados:** A monitoração prolongada do pH e a SEED foram realizadas com 49,8 e 66,8 dias de vida, respectivamente. A sensibilidade da seriografia foi de 56,1% (IC 95%: 39,9–71,2%). Refluxo significativo foi observado em 41,4% dos casos, refluxo médio em 44,8% e refluxo pequeno em 13,8%. A SEED identificou apenas um caso de hérnia de hiato. **Conclusão:** A SEED apresentou baixa sensibilidade para a DRGE em prematuros e não se associou com a gravidade do refluxo, na comparação com a monitoração do pH, sendo, entretanto, útil no diagnóstico de alteração anatômica.
Unitermos: Doença do refluxo gastroesofágico; Seriografia; pHmetria; Recém-nascidos prematuros.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as a disorder of the distal esophagus, with frequent return of the gastric contents into the esophagus, associated with digestive and extra-digestive symptoms such as frequent regurgitation and vomiting episodes in association with low weight gain, anemia, esophagitis or respiratory complications[1,2].

Over the past two decades more studies about this disease in the neonatal period have been undertaken; however many aspects still remain to be clarified[3]. At the neonatal period, the investigation for GERD is of significant relevance, as such this entity can cause severe symptoms in neonates, particularly in preterm newborns, such as episodes of apnea, bradycardia, cyanosis and vomiting. Gastroesophageal reflux disease has also been associated with apparently life-threatening complications such as aspiration pneumonias and apnea, significantly extending the hospital stay of such neonates[2,4–13]. Although the long-term esophageal pH monitoring is still considered as the gold standard for the diagnosis of GERD, it presents the disadvantages of an invasive and expensive procedure, besides demanding specialized personnel and equipment, and for these very

reasons the method is not being used in many services[14,15].

On the other hand, upper gastrointestinal (UGI) series is a low-cost, less invasive well tolerated and it is available at most medical/clinical assistance centers. Additionally, UGI series can detect anatomical abnormalities associated with the present symptoms in the upper gastrointestinal tract, and is the conventional imaging method for the study of GERD[14,15].

The early diagnosis of GERD and associated complications in preterm newborns is of utmost importance as it allows better approaches for the treatment of such an entity, potentially shortening hospital stay length and reducing morbidity.

The purpose of this study was to evaluate the sensitivity of UGI series for the diagnosis of GERD in preterm newborns, with clinical manifestations and esophageal pH monitoring highly suggestive of the disease, as well as describing the presence of congenital upper gastrointestinal tract malformations detectable at the radiological exam.

MATERIALS AND METHODS

The research project was approved by the Committee for Ethics in Research on humans of the institution and the neonates were included in the study after a term of free and informed consent was signed by family members. A prospective descriptive study was developed with 41 preterm neonates admitted to a tertiary neonatal care unit, with symptoms suggestive of GERD. Amongst the neonates, 22 (53,7%) were boys and 19 (46,3%) were girls, with gestational age < 37 weeks, all of them weighting < 2,500 g at birth, with weight ranging between 655 g and 2,450 g. The symptoms of GERD presented by the neonates considered as indications for long-term distal esophageal pH monitoring were: xanthine resistant apnea and/or bradycardia, frequent vomiting and/or regurgitation associated with poor weight gain (< 20–30 g/day), apparent life-threatening apnea, multiple atelectasis or pneumonias, need for long-term oxygen therapy and unexplained worsening of respiratory conditions.

Prolonged (18 to 24-hours) distal esophageal pH monitoring was performed by one of the investigators, at the discretion of the unit's medical team, and only neonates whose pH monitoring results were abnormal (reflux index ≥ 10%) were chosen to participate in the study[16]. The equipment utilized for documenting and recording of the exam was a Digitrapper MkIII (Medtronic Inc.; Shoreview, MN, USA), using antimony electrodes (Medtronic Inc., Shoreview, MN, USA) positioned at the distal third of the esophagus, at the level of the T6-T7 vertebral bodies. In all of the exams, the electrode position was confirmed by means of chest X-ray. The software utilized for results analysis was the EsopHogram version 5.60C4 (Gastrosoft Inc.; Irving, TX, USA). During the exams, the neonates remained on horizontal dorsal decubitus, receiving dietary intake of 120–130 ml/kg/day every four hours by means of a gastric feeding tube. The neonates were kept without medications such as antacids, H2 blockers, xanthines or corticosteroids that could affect the exam's results for at least 48–72 hours before the examination.

The UGI series was performed as soon as the infants' clinical conditions were considered sufficiently stable, with low frequency of apnea or oxygen desaturation and with appropriate body temperature control in open cribs, thus involving low risk for transportation of the neonate to the radiology center. The neonates that could not be transported for radiological investigation for being under assisted ventilation and preterm neonates with disorders which contraindicated enteral feeding were excluded from the study.

The radiological investigation included plain chest X-ray and abdominal films and UGI series. The investigation of reflux episodes under fluoroscopic control was performed after oral ingestion of barium diluted in glucose solution or milk, administered by a bottle or by a gastric tube. The maximum amount of contrast medium was equivalent to that which the neonate would swallow in a breastfeeding, with upper digestive tract morphology and motility being studied. The quantitative evaluation of reflux by contrast-enhanced radiological study was performed with the neonate positioned on dorsal decubitus, and results were considered as abnormal in cases where more than three reflux episodes were observed in patients up to six weeks of life and more than two reflux episodes in patients above seven weeks of life[17]. For the qualitative evaluation of reflux, it was considered the height reached by the refluxate in the oesophagus. The degree of the reflux was then graded as small if below the lower third of the oesophagus, moderate if in the middle third and significant if above the middle third of the oesophagus.

The quantitative assessment of reflux episodes by means of intermittent fluoroscopy occurred over a maximum period of 5 minutes. The radioscopy flashes did not exceed 20 seconds[17].

The following descriptive variables were studied: gestational age in weeks; birth weight in grams; postnatal age in days at the moment of pH monitoring and at the day the UGI series was performed; and the results of the quantitative evaluation of reflux by pH monitoring, namely: total number of reflux episodes, duration of the longest episode, number of episodes lasting longer than five minutes, and percentage of total examination time with esophageal pH < 4, also called reflux index (RI). Abnormal results corresponded to RI ≥ 10%, at the research period[16].

The study sample size was based on the prevalence of symptoms (vomiting, apnea, decreased oxygen saturation, bradycardia, bronchospasm, oxygen dependence) identified in 18 neonates, establishing a sampling error of 15%. It was established that 41 cases would be necessary, considering that such a figure reflected the appropriate sample size for the set of symptoms.

Descriptive analyses of the sample variables were performed by calculating mean and standard deviation, minimum and maximum values, establishing sensitivity value and confidence interval of 95% (CI 95%) for the UGI series. The Student's t-test was utilized at the comparison between the radiological severity and RI. The Wilcoxon test was utilized at the comparison between days of life in which both examinations were performed. The Statistical Analysis System (SAS) version 8.2 was utilized for statistical data analysis.

RESULTS

Among the symptoms observed during the neonates' hospital stay, decreased oxy-

gen saturation was the most prevalent one, being found in 33 cases (80.5%). Other symptoms (more than one symptom/sign per neonate) were apnea, in 22 cases (53.7%), vomiting episodes in 17 cases (41.5%), cyanosis in 15 cases (36.6%), bradycardia in 11 cases (26.8%) and lastly, bronchospasm, present in three cases (7.3%).

The mean RI was 24.4% ± 12.1%, ranging between 11.3% and 60.9%. The description of the pH monitoring parameters is shown on Table 1.

On average, the radiological examination was performed at 66.8 days of life, versus 49.7 days at the pH monitoring, being this difference, between the two values, statistically significant ($p = 0.007$). Therefore, the mean interval between examinations was 17.1 days.

The sensitivity of the UGI series was 56.1% with CI 95% between 39.9% and 71.2% (Table 2). As regards the qualitative evaluation of pathological reflux episodes, 41.5% (12 cases) presented significant reflux, while 44.8% (13 cases) presented moderate reflux and 13.8% (4 cases) presented with mild reflux.

Among all performed radiological examinations, 18 cases were considered as physiological reflux, with a mean of 1.33 ± 0.55 episodes, being the minimum of 1 and maximum of 2 episodes. On the other hand, results of 23 radiological studies were considered as abnormal, with 3.78 ±1.44 episodes, ranging between 2 and 7.

Table 3 presents the description of the mean RI values according to the qualitative radiological assessment of pathological reflux episodes. No significant difference

Table 2 UGI series sensitivity, based on the long-term distal esophageal pH monitoring (gold standard).

UGI series	Reflux index ≥ 10%
Positive	23
Negative	18
Total	41

Sensitivity = 56.1%; CI 95%: 39.9–71.2%.

Table 3 Mean value of reflux index according to the radiological severity of the reflux evaluated by UGI series ($n = 41$).

Radiological severity at UGI series – affected esophageal segment	RI (%) Mean ± SD
Proximal segment ($n = 4$)	26.4 ± 9.0
Medial segment ($n = 13$)	25.9 ±12.9
Distal segment ($n = 12$)	25.4 ± 14.2

RI, reflux index; SD, standard deviation; n, number of cases. Comparison of RI between proximal/medial segments ($p = 0.47$), medial/distal segments ($p = 0.47$) and proximal/distal segments ($p = 0.45$).

was observed in RI according to the UGI series severity levels.

In the present sample, UGI series found sliding hiatus hernia in one neonate at 65 days of life. In this case, six significant reflux episodes were demonstrated, besides gastric emptying time greater than five minutes (Figure 1). At 56 days of life, pH monitoring demonstrated RI = 35.8%, with 24 episodes, all of them longer than 5 minutes, with the longest episode lasting 144 minutes.

DISCUSSION

Upper gastrointestinal series presented low sensitivity in the diagnosis of GERD

Figure 1. UGI image of a 65-day old neonate, demonstrating significant gastroesophageal reflux, in association with sliding hiatus hernia.

in a sample of preterm neonates, considering the esophageal pH monitoring as the gold standard; however it identified anatomic abnormality of the upper digestive tract in one neonate.

Several authors[15,18–21] have demonstrated higher sensitivity and specificity of pH monitoring in the diagnosis of GERD as compared with other complementary studies currently available. However few studies exclusively evaluating newborns are found in the literature.

Studies conducted in infants below one year of age, with samples between 21 and 61 neonates, demonstrated radiography sensitivity ranging between 29% and 40%[15,21]. The lower sensitivity of the radiological study, as compared with esophageal pH monitoring can be explained, among other factors, by the short fluoroscopy time (5 intermittent minutes) and by the higher density of the barium contrast medium, as compared with a normal gastric contents[15]. In the present study, we found sensitivity of 56.1% (CI 95% of 39.9–71.2%), higher than that described in the literature. However, considering that the present study evaluated exclusively preterm neonates, the authors could not establish an accurate sensitivity comparison. Few studies were found in the literature describing contrast-enhanced radio-

Table 1 Description of the study sample and results from the long-term esophageal pH monitoring and UGI series.

Variables	n	Mean	Standard deviation
Birth weight (grams)	41	1,243.9	414.1
Gestational age (weeks)	41	30	3
pH monitoring (days of life)	41	49.8	21.7
Reflux index (%)	41	24.4	12.1
Total number of episodes	39	134.0	62.1
Number of episodes > 5 minutes	37	13.3	7.5
Longer reflux episode (minutes)	41	56.4	44.1
UGI series (days of life)	41	66.8	33.6
Total number of reflux episodes at X-ray	41	2.3	2.0

n, number of neonates.

logical examination of the esophagus, stomach and duodenum exclusively in preterm neonates admitted to a neonatal unit.

The study developed by Ozelame et al.[22], which included 12 neonates in their series, has emphasized the relevance of the standardization of the radiological technique and of the radiologist's experience for the method sensitivity.

In the present study, a relevant factor to be taken into consideration was the significant difference at the moment of the two examinations performance (mean of 17 days). No data was found in the literature on the acceptable time interval, considering the necessity of stable clinical conditions of the neonate, such as weight > 2,000 g and thermal stability, for the performance of the radiological exam. Such conditions are not required for the esophageal pH monitoring, so it characterizes an advantage of this method. The two-week time difference might, in some neonates, be sufficient to promote maturation of the function of the lower esophageal sphincter and the whole digestive tube. and, as a consequence, it may cause a significant reduction in reflux episodes. By itself, such factor may be accountable for the loss of sensitivity of the radiological method in this sample.

A superficial analysis demonstrates that esophageal pH monitoring presents as disadvantages the invasive characteristic of this method and the expensiveness, besides requiring an appropriately trained physician, factors which impair its utilization in many hospitals[15]. On the other hand, UGI series is a low-cost method that is well tolerated and is able to detect anatomical abnormalities and complications such as hiatus hernia, intestinal obstruction and intestinal malrotation, as well as motility disorders[9,19,21], being available at most hospital medical centers [15].

Studies highlight the indication of UGI series for children with symptoms of GERD to identify anatomic abnormalities in the esophagus, stomach and duodenum, but not all of them report the percentage of malformations found[7,9,15,19,20]. Al-Kha-

wari et al.[15], in a retrospective study with 169 patients comparing UGI series and esophageal pH monitoring, have found a predominance of anatomic abnormalities in the age group < 1 year, including 9 patients with intestinal malrotation, 9 with hiatus hernia, and 15 with other changes in the gastroduodenal junction. In the present study sample, only one case of hiatus hernia was found, with no other anatomic abnormally being found in the upper digestive tract, a fact that may be explained by the small sample size (41 individuals) and by the fact that only neonates were studied, an age group which was not specified in the study developed by Al-Khawari et al.[15].

No data was found in the literature establishing association between RI, evaluated by esophageal pH monitoring, and the number of reflux episodes in the UGI series. Such an association was not observed in the present study, and may be an interesting aspect to be analyzed in further studies. Recently, by means of a new method for GERD evaluation – multiple intraluminal esophageal impedance – a significant association could be observed between reflux episodes extent and the acid clearance time with the presence of symptoms/signs of GERD in preterm newborns[23]. In this study, the occurrence and frequency of the symptoms depended on the most proximal extent of the reflux and the esophageal clearance time[23].

Thus, the authors conclude that UGI series demonstrated low sensitivity for GERD in preterm newborns, and it did not associate with the reflux severity as compared with the esophageal pH monitoring. However, it is useful in the detection of anatomical abnormalities in the upper gastrointestinal tract.

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