Scintigraphic scoring system for grading severity of gastro-esophageal reflux on 99mTc sulfur colloid gastro-esophageal reflux scintigraphy: A prospective study of 39 cases with pre and post treatment assessment

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ABSTRACT

Aim: The study aimed at developing a scoring system for scintigraphic grading of gastro-esophageal reflux (GER), on gastro-esophageal reflux scintigraphy (GERS) and comparison of clinical and scintigraphic scores, pre- and post-treatment. **Materials and Methods:** A total of 39 cases with clinically symptomatic GER underwent 99mTc sulfur colloid GERS; scores were assigned based on the clinical and scintigraphic parameters. Post domperidone GERS was performed after completion of treatment. Follow up GERS was performed and clinical and scintigraphic parameters were compared with baseline parameters. **Results:** Paired *t*-test on pre and post domperidone treatment clinical scores showed that the decline in post-treatment scores was highly significant, with *P* value < 0.001. The scintigraphic scoring system had a sensitivity of 93.9% in assessing treatment response to domperidone, specificity of 83.3% i.e., 83.3% of children with no decline in scintigraphic scores show no clinical response to Domperidone. The scintigraphic scoring system had a positive predictive value of 96.9% and a negative predictive value of 71.4%. **Conclusion:** GERS with its quantitative parameters is a good investigation for assessing the severity of reflux and also for following children post-treatment.

Keywords: Domperidone, gastro-esophageal reflux, scintigraphy, scoring system

INTRODUCTION

Gastro-esophageal reflux (GER) comprises of retrograde movement of gastric contents into the esophagus and is a frequently experienced benign, but symptomatic condition. At one end of the spectrum are infants with physiological reflux and at the other end are children with objective pathological sequelae comprising gastro-esophageal reflux disorder (GERD).[1] There have been different diagnostic modalities for GERD evaluation. Of these, 24 h ambulatory esophageal pH monitoring is considered to be the gold standard for diagnosing a reflux. Gastro-esophageal reflux scintigraphy (GERS) is recommended as a suitable screening test because of its physiologic and non-invasive nature, low radiation exposure and convenience of performance.[2]

Prokinetic agents are the most popular medications and the first line treatment option for a child with GERD. Of these, domperidone is commonly used, especially in the Indian scenario, because of its low cost, early onset of action and fewer side-effects as compared to other dopamine antagonists like metoclopromide. Domperidone acts by increasing sphincter tone and increasing gastric emptying.[3,4]

Though studies have established diagnostic modalities and treatment options, a standardized imaging protocol for diagnosis and evaluation of treatment response is not in place. GERS is sensitive in comparison to the other available options; however,

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besides ascertaining the presence of reflux, there is a need to understand the real time dynamics of reflux severity, which can provide quantitative dimension to the result of the test. Thus, standardization of existing protocol and establishing quantitative scintigraphic parameters will give us a better understanding of GERD and help us follow the child objectively during the treatment.

MATERIALS AND METHODS

Patients

The study approved by Institutional Review Board and Hospital Ethics Committee included a prospective evaluation of 39 consecutive cases (18 males, 21 females, age range from 6 days to 2 years) with a clinical diagnosis of GER. They were referred to our department between February 2007 and February 2009, for a 99mTc sulphur colloid GER study.

Methods

Clinical evaluation and basic investigations

Patients visiting pediatric out-patient department with complaints of cough, breathlessness, failure to thrive, recurrent episodes of vomiting were clinically assessed. Complete blood count and a postero-anterior chest radiograph (X-ray) were performed. Based on history, general examination and basic investigations, a score was assigned to the patient with clinical suspicion of GER. The scoring system was designed by pediatricians; parameters of which are in Table 1. The Hospital Ethics Committee was not in favor of 24 h esophageal monitoring, due to its invasive nature; hence, the clinical scoring system was considered as gold standard.

Scintigraphic evaluation

Patient was advised fasting 4 h prior to study. Written informed consent was taken from parents. Accompanying pediatrician secured the nasogastric (NG) tube. Feeding volume of milk was calculated as per the standard feeding formula followed in the pediatric ward of our Institution i.e., 4-6 ml/kg body weight. 5-10 ml of milk was kept separate and 300-500 μCi (11.1-18.5 MBq) of 99mTc sulfur colloid was uniformly mixed with the rest of the calculated volume. Radiolabelled milk in a syringe was slowly instilled through the NG tube, following which 5-10 ml unlabeled milk was also fed to clear the residual activity from the NG tube. NG tube was withdrawn before imaging. Patient was then positioned supine on the couch with chest and upper abdomen in the field of view, on a single head gamma camera General Electricals (GE) SPX4 with low energy high resolution parallel hole collimator. Detector was placed posteriorly for better patient co-operation. Movement of the child was prevented by strapping him/her to the couch. Radioactive marker was placed at the lower border of cricoid cartilage to mark upper esophageal junction and a static marker image [Figure 1a] was acquired for 30 s. Dynamic acquisition was then started with a frame rate of 3 s/frame for 60 min in 64 × 64 matrix, with 20% energy window centered at a photo peak of 140 keV. Before concluding the study, a static image was acquired for 1 min to detect aspiration of radioactivity in the lungs.

Data processing

The acquired data was visualized in GE default colour and dynamic images were processed to detect the presence of GER. Any spike of radioactivity visualized above the stomach was processed. Scintigraphic parameters which were developed from the data are given in Table 2.

A scoring system based on scintigraphic findings was obtained from the parameters mentioned, to derive semi-quantitative indices of GER, shown in Table 3.

Prokinetic drug treatment

A total of 0.2 mg/kg/dose Domperidone, 6-8 hourly was administered orally for a period of 6-8 weeks as decided by pediatrician.
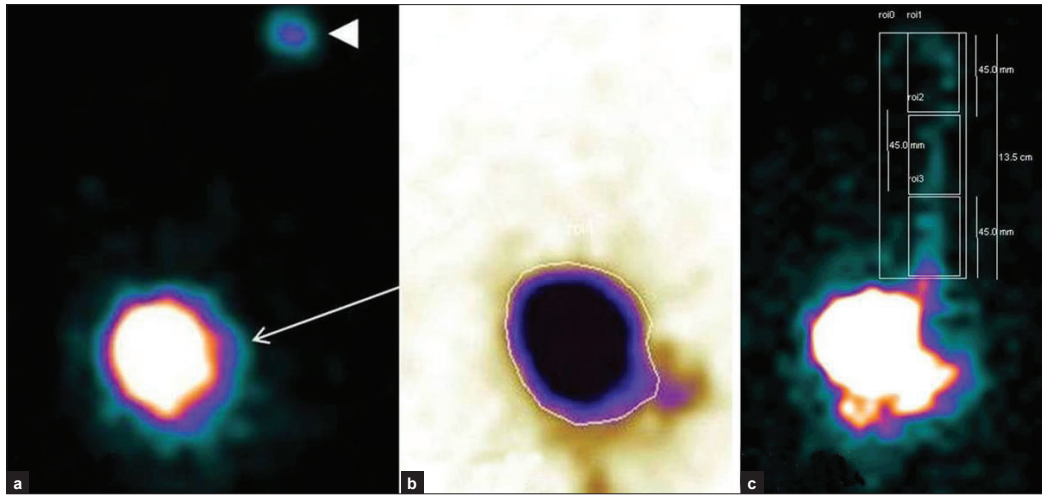
Table 1: Clinical scoring system

Parameters	Scoring system
Symptoms (recurrent cough, vomiting, refusal to feed)	Absence=0, Presence=1
Signs (tachypnea, wheezing, crackles, chest retraction)	Absence=0, Presence=1
Complications (failure to thrive, bronchopneumonia, apnea)	Absence=0, Presence=1
Total leucocyte count in cubic mm	Normal range (4,000-11,000)=0 Greater than 11,000=1
X-ray findings	Normal=0, Abnormal=1

Table 2: Image processing to create scintigraphic scoring parameters

Parameters	Image processing
Time of onset of reflux	Based on GE $t_{1/2}$ ROI drawn on all frames over the stomach and time activity curve was generated [Figure 1b]. GE $t_{1/2}$ calculated from the TAC
Level of reflux	Region between the cricoid marker and esophagogastric junction divided into three equal regions; [Figure 1c] upper, middle and lower third
Percentage of reflux	ROI drawn over the esophageal region, in the frame of reflux. esophageal counts (in the frame of reflux) divided by the gastric counts in the first frame is equal to percentage reflux
Frequency of reflux	Number of episodes of reflux in 60 min dynamic study ROI drawn over esophageal region [Figure 2a] on all frames and a TAC is generated [Figure 2b]
Duration of reflux	Based on the persistence of radioactivity in the esophagus; Persistent: Radioactivity present in 2 or more consecutive frames; non-persistent: radioactivity present in a single frame only [Figure 3]
Lung uptake	Visualized in the static image acquired at the end of dynamic imaging

TAC: Time activity curve, ROI: Region of interest, GE $t_{1/2}$: Gastric emptying half time

Figure 1: (a) Static image acquired with cricoid marker (arrow-head) for localizing the upper end of esophagus; radiolabelled milk visualized in stomach (arrow), (b) gastric region of interest over the first frame of dynamic study for initial counts, as a part of measurement of gastric emptying time, (c) region of interest over the entire esophageal region, and then division into three parts for grading level of reflux
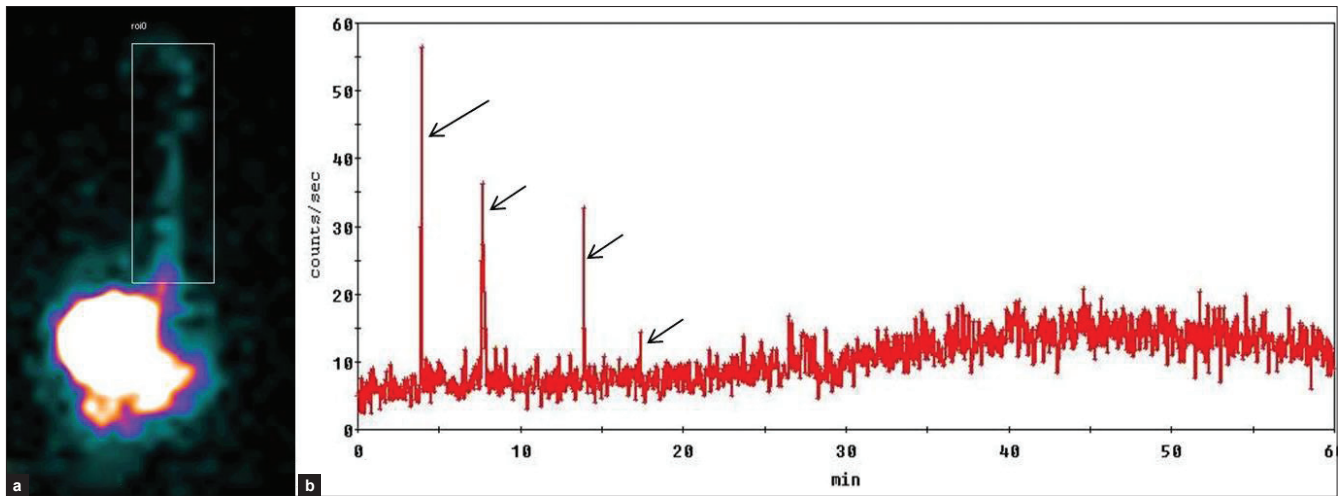

Figure 2: (a) Region of interest drawn over the entire esophageal region in all frames of dynamic study as shown, (b) time activity curve generated for these region of interests showing spikes of activity indicating reflux, which is used to calculate the number of episodes of reflux

Table 3: Scintigraphic scoring system

Parameters	Grades	Scores
Time of onset of reflux	Reflux within GE $t_{1/2}$	1
	Reflux beyond GE $t_{1/2}$	2
Level of reflux	Lower third	1
	Middle third	2
	Upper third	3
Percentage of reflux (%)*	4–6 %	1
	6.1–8 %	2
	Greater than 8%	3
Frequency of reflux (no. of episodes)	Less than 2	1
	2–4	2
	Greater than 4	3
Duration of reflux	Non-persistent	1
	Persistent	2
Lung uptake	Present	3
	Absent	0

*Reference percentages were derived from the range of values obtained from the results of pilot GER scintigraphic studies performed before the commencement of this study. Any spike of activity with percentage greater than 4 was considered as reflux.[2] GE$t_{1/2}$: Gastric emptying half time
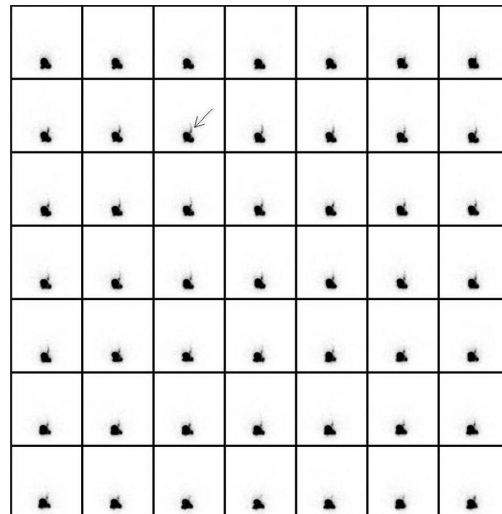

Figure 3: Dynamic study framed at 3 s/frame showing persistent episodes of reflux, occurring for more than 3 consecutive frames

Post-treatment study

Follow-up GES, similar to initial study, was done following treatment after 6-8 weeks. The processed data as described earlier was used to derive post-treatment scintigraphic scores, which were compared with pre-treatment scores to assess treatment response.

Statistical analysis

A total of 39 patients were included in the study between May 2007 and May 2009. A comparative analysis was performed between the pre- and post-treatment scintigraphic scores. A comparative analysis was also made between pre- and post-treatment clinical scores. Both these analysis was performed by applying paired *t*-test. Scintigraphic scores were also correlated with the clinical scores. Chi-square test was applied to test the statistical significance of results.

RESULTS

Demographic data

The distribution of age among the patients showed that 79.5% of patients were below the age of 12 months and it is well-known that this age group i.e., less than 12 months is highly susceptible to GERD and therefore to respiratory infections.

Scintigraphic scores

Analysis of pre Domperidone treatment scintigraphic scores had shown that most patients have a score of 8 or more, indicating that the majority of children (71.8%) had moderate to severe GERD. Analysis of post-treatment scintigraphic scores had shown that most patients had a score of 5 or less i.e., about 77%, indicating that domperidone indeed was effective in reducing the severity of GERD [Figure 4]. In fact in 56.4% of patients, score was 0, which meant that there was no detectable GER post domperidone treatment. The paired *t*-test on pre and post Domperidone treatment scintigraphic scores showed that the decline in post-treatment scores was highly significant, with *P* value < 0.001 [Table 4]. Analysis of pre-treatment clinical scores had shown that 24 of the 39 patients had scores of 4 and 5, indicating that the majority of the children (61.5%) had a clinically severe GERD. Analysis of post-treatment clinical scores showed that 84.6% of the children had clinical scores between 0 and 2, indicating a significant clinical improvement. In fact, 53.8% had a score of 0, indicating there was complete clinical recovery after treatment with domperidone. The paired *t*-test on pre and post domperidone treatment clinical scores showed that the decline in post-treatment scores was highly significant, with *P* value < 0.001 [Table 5].

Scintigraphic versus clinical scores

The scintigraphic scoring system was compared with the clinical scores using Chi-square test. In the absence of 24 h esophageal monitoring, clinical scores were considered as a gold standard and scintigraphic scores were compared with clinical scores. The scintigraphic scoring system had a sensitivity of

Table 4: Paired samples statistics for scintigraphic scores

Parameter	Mean	N	Standard deviation	Standard error mean
Scintigraphic score				
Pre-treatment	9.90	39	2.257	0.361
Post-treatment	3.03	39	3.766	0.603

Table 5: Paired samples test for scintigraphic pre and post treatment scores

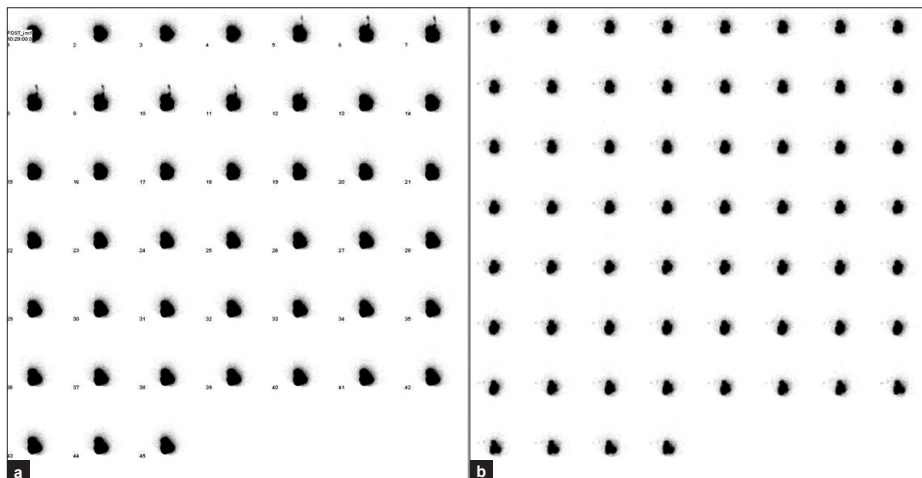| Parameter	Paired differences					t	df	Significant (2-tailed)
	Mean	Standard deviation	Standard error mean	95% confidence interval of the difference		Mean	Standard deviation	*P* value
Scintigraphic score Pre-treatment Post-treatment	6.872	4.996	0.800	5.252	8.491	8.590	38	0.000 (<0.001)

Figure 4: Baseline gastro-esophageal reflux scintigraphy (a) in a 2-month-old child showing multiple episodes of reflux, which on post-domperidone gastro-esophageal reflux scintigraphy, (b) show complete resolution of gastro-esophageal reflux

93.9% in assessing treatment response to domperidone, when compared with clinical scores, i.e., 93.9% of patients, who show scintigraphic improvement, and also show an improvement in clinical scores [Table 6]. The scintigraphic scoring system had specificity of 83.3% i.e., 83.3% of children with no decline in scintigraphic scores show no clinical response to domperidone. The scintigraphic scoring system had a positive predictive value of 96.9% and a negative predictive value of 71.4% [Table 7].

DISCUSSION

GERS has a definite role in the detection of reflux and assessment of the severity of reflux episodes and it has been established that 24 h esophageal pH monitoring is the gold standard for diagnosing GERD. However, after doing an extensive literature review [Table 8], it is evident that GERS has a sensitivity of 70-80% and specificity of 93% in detecting reflux episodes.[5] It scores over pH monitoring on account of its ease of performance, non-invasive and physiologic nature. This makes it an even better modality to assess treatment response since the main aim of any therapy is to correct the altered physiology.

The treatment response to domperidone has been assessed by Bines *et al*,[14] with 24 h esophageal probe monitoring and radionuclide GE study. This study sought to define the therapeutic efficacy of domperidone in infants and children with GERD. Our study compared pre and post domperidone scintigraphic scores in children clinically diagnosed with GERD at our center. It showed that there was a significant improvement in the GER as shown by the scintigraphic scores in 30 out of the 39 children, with a statistically significant reduction in scintigraphic scores, *P* value < 0.001. This indicates the effectiveness of domperidone in significantly reducing GER episodes, both its severity and frequency. This finding strongly justifies the use of domperidone, which is one of the most commonly used drugs in GERD. This study may be the first wherein a quantitative approach is used to objectively determine the response of domperidone in the treatment of GERD.

An attempt was made in the existing literature to add a quantitative dimension to GERS. However, it was only a single parameter of number of frames that was compared.[15,16] Shorter the framing time, more sensitive is the study in diagnosing reflux episodes with less volume of refluxate. Similarly, other studies used parameters such as number of reflux episodes and GER index i.e., the percentage of gastric activity refluxing into esophageal region as scintigraphic interpretation criteria,[9,17] but no scores were assigned to these parameters. In our study, a composite evaluation of all scintigraphic parameters could be performed, which was useful in objectively assessing the severity of reflux. This formed a baseline for post-treatment scintigraphic studies to follow, which were similarly scored in order to assess treatment response. In the present study, none of the children showed pulmonary uptake of radiotracer. Lung uptake of radiotracer is a very significant parameter, presence of which would indicate severe GERD. However, its absence even in children with high scintigraphic scores indicates that it is a very rare phenomenon to get the refluxed matter into the lower respiratory tract.

It was not ethically and logistically possible to subject the children to an invasive procedure like the 24 h esophageal probe monitoring. Hence, a comparison was made between scintigraphic score and clinical score, before and after treatment. It showed in 31 out of the 39 children, a good correlation in response pattern; thus, making quantitative GERS 93.9% sensitive. This clearly indicates that the scoring system is an extremely valuable tool to assess treatment response. The study shall be continued to generate a larger data, from a much bigger patient population, in order to establish the validity of scoring system to grade the severity of reflux episodes in GERD.

Furthermore, the existing literature, to our knowledge, does not show any standardized protocol or established guidelines for performing GERS or diagnosing GERD. We tried to standardize the imaging procedure and added a quantitative dimension as described in Table 9.

Table 6: Comparison between clinical and scintigraphic response

Scintigraphic response	Clinical response		Total
	Present	Absent	
Present	31	1	32
Absent	2	5	7
Total	33	6	39

Table 8: Studies with head-to-head comparison of GERS with other modalities

Author (reference)	Gold standard	Results %
Seibert *et al*.[6]	24 h esophageal pH monitoring	Sensitivity-79 Specificity-93
Kashyap *et al*.[7]	Histopathology	Sensitivity-78.54 Specificity-81.25
Blumhagen *et al*.[8]	Acid reflux test	Sensitivity-75
Orenstein *et al*.[9]	24 h esophageal pH monitoring	Sensitivity-92
Laudizi *et al*.[10]	24 h esophageal pH monitoring	Sensitivity-63
Le Luyer *et al*.[11]	Barium esophagography	Sensitivity-70 Specificity-100
Intarakhao *et al*.[12]	24 h esophageal pH monitoring	Sensitivity-76.92 Specificity-31.57
Shay *et al*.[13]	24 h esophageal pH monitoring	Sensitivity-36 Specificity-88

GERS: Gastro-esophageal reflux scintigraphy

Table 7: Chi-square test results for scintigraphic and clinical scores

Parameter	Sensitivity	Specificity	Positive predictive value	Negative predictive value	*P* value
Scintigraphic scoring system (compared against clinical scores)	93.9%	83.3%	96.9	71.4%	0.000 (<0.001)

Table 9: Standardization of imaging protocol for GERS

Imaging parameter	Modification	Advantage
Dynamic image acquisition	Posterior view	Reduces claustrophobia Ensures immobilisation
Marker image	Cricoid marker	Marks upper limit of esophagus for accurate division into three parts
Frame rate	3 s/frame	Detects smallest of refluxes
Acquisition duration	60 min	GER is an intermittent phenomenon and shorter imaging times can miss significant number of GER episodes
Static image	Lung delayed image (at 1 h)	To detect aspiration
Feeding volume	10-12 ml/kg body weight	Simulates the normal feeding and gastric emptying patterns
Gastric emptying	Measures number of episodes in first half and later	Episodes of reflux occurring beyond the first half of GE time were considered significant, since reflux occurred even with minimal amount of food in stomach, and has greater harming potential than GERD

GERS: Gastro-esophageal reflux scintigraphy, GER: Gastro-esophageal reflux, GE: Gastric emptying, GERD: Gastro-esophageal reflux disorder

CONCLUSION

Though 24 h esophageal pH monitoring is the established gold standard for diagnosis of GER, we did not correlate our results with it due to ethical and logistic reasons. Multiple other studies have compared their results and have found good correlation with scintigraphic GER studies. In our opinion, due to its invasive nature and strong correlation with scintigraphic GER study, we can obviate the need for esophageal pH monitoring procedure.

Moreover, addition of quantitative dimension and standardization of procedure has made GERS, a reliable procedure for diagnosing and follow-up of children with GER.

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