Original Article

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Risk factors for early surgical intervention in neonates with gastroesophageal reflux disease

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KEYWORDS

Gastroesophageal reflux,
Nissen Fundoplication,
Antireflux surgery,
Life-threatening complications

ABSTRACT

Background: Surgical intervention in neonates with Gastro-esophageal Reflux Disease (GERD) is usually reserved for failure of medical management or those having life-threatening complications of GERD. The optimal timing of intervention is still debatable. We aimed to identify the high-risk neonates with GERD requiring early surgical intervention.

Methods: This prospective cohort study was conducted at NICU and Pediatric Surgery Department, Ain Shams University, from June 2017 to June 2020, and enrolled the neonates and infants below 2 months with symptoms and signs suggestive of GERD. Demographic data, clinical history, medical management, need for antireflux surgery, and outcomes were recorded.

Results: In this study, 40 patients were enrolled and all were started on medical treatment. After the failure of medical management or life-threatening complications, 12 of these underwent anti-reflux surgery. In the medical group, six patients suffered from major complications (bronchopulmonary dysplasia and sepsis) and four mortalities. In the surgical group, three mortalities related to the development of bronchopulmonary dysplasia due to prolonged ventilation prior to surgery were recorded. The need for surgical intervention was significantly associated with younger gestational age ($p = 0.001$), younger age at presentation ($p = 0.006$), and lower weight at presentation ($p = 0.034$).

Conclusion: Medical treatment of more than 35 days with unsatisfactory response, low birth weight, gestational age (≤32 weeks), and NICU admission in the first 10 days of life are considered high-risk factors for early anti-reflux surgery in neonates.

INTRODUCTION

Gastroesophageal reflux (GER) is a frequently experienced physiological condition in neonates and infants that usually resolves spontaneously within the first year of age.[1] Gastroesophageal reflux disease (GERD) occurs when GER causes symptoms that affect the quality of life or causes pathological complications.[2] The treatment of neonatal GERD consists mainly of antireflux position, hypoallergenic formulas, and thickening of feed formula. Some medications, such as surface barrier agents, antacids, and proton pump inhibitors, may be used as a second line of management. Sometimes, nasogastric or 1asojejunal drip-feeding may be indicated.[3] Surgical intervention is usually reserved for patients who do not respond to conservative medical management or have life-threatening complications of GERD.[4] The optimal timing of surgical intervention in neonates and whether early interference would provide good postoperative outcomes are yet to be investigated further.[5] Moreover, no reported clear evidence for the accepted duration of medical treatment for GERD or an objective indicator for the proper timing of surgical intervention is available.[6,7] The decision for surgical intervention is usually dependent on the experience of neonatologists and pediatric surgeons. Therefore, the aim of the present study is to identify the high-risk neonates with GERD requiring early surgical intervention.

METHODS

Patient's selection

This was a prospective cohort study conducted at NICU and Pediatric Surgery Department, Ain Shams University, from June 2017 to June 2020. In this study, neonates and infants below 2 months,

admitted with symptoms and signs suggestive of GERD, were enrolled. The diagnosis of GERD was established when GER caused symptoms that affect the quality of life necessitating NICU admission or causing pathological complications. Patients with neurological conditions and patients suffering from secondary reflux due to other congenital GIT anomalies, as diagnosed by an upper GI contrast study, were excluded from the study. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Committee of the Pediatric Surgery Department, Ain Shams University (No. IRB 00006379). Informed consent was obtained from the parents of all enrolled individual participants.

Patient's evaluation

The demographic data and clinical history were recorded for all studied patients, including their gestational age in weeks, age at presentation in days, weight at birth in grams, weight at the time of presentation in grams, type of feeding, presenting symptoms, and history of any sibling with reflux. A contrast upper GI series was performed to confirm the presence of GER and to exclude secondary causes.

Management protocol

All patients started medical conservative management in the form of anti-Trendelenburg positioning, changing the feeding regimen into small frequent feeds with thickened formula, and nasogastric drip-feeding. Medical treatment was administered, which involved aluminum hydroxide and magnesium carbonate suspension in addition to proton pump inhibitors. Nasojejunal feeding was started after 2 weeks in case the previous regimen fails to control the symptoms. The surgical antireflux procedure was indicated in patients with failed medical treatment to control symptoms (persistent vomiting and regurgitation), and in patients with persistent complications, such as repeated respiratory tract infections, difficulties in weaning from artificial ventilation, or failure to thrive. The Nissen fundoplication with Stamm gastrostomy was the technique of choice (Fig. 1).

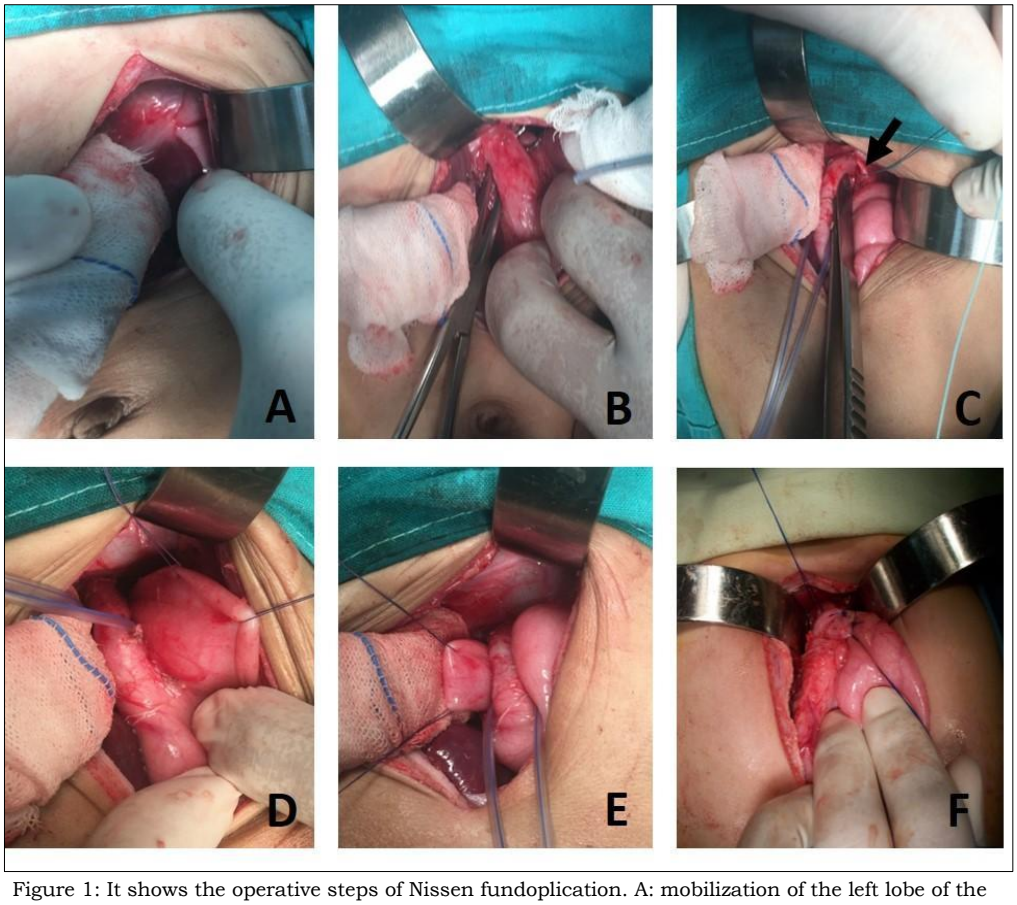


Figure 1: It shows the operative steps of Nissen fundoplication. A: mobilization of the left lobe of the liver to expose the esophageal hiatus; B: mobilization of the lower 2 cm of the esophagus; C: repair of esophageal hiatus if needed (arrow points to left crus; D: the released fundus after ligation and division of short gastric vessels; E: passing the gastric fundus through the retro-esophageal space; F: the creation of floppy 360° fundal wrap.

Postoperatively, we continued proton pump inhibitors for 2 weeks (as prophylaxis towards stress gastritis) to be stopped after that where mostly the baby reached his full oral intake. Surgery was performed by three

pediatric surgeons who have more than 10 years' experience in managing neonatal GERD.

Outcome assessment

The duration of medical treatment before being discharged or referred for surgery, evaluation of weight gain and tolerance of feeding, assessment of the respiratory status, and need for mechanical ventilation during medical treatment were recorded.

The collected data also included the timing of surgical intervention, any intraoperative complication, day of the start of postoperative feeding, time until full enteral intake was reached, early postoperative complications, and the need for postoperative ventilation. The patient's outcome was evaluated regarding the resolution of symptoms and signs of reflux, time elapsed for recovery, weight gain, respiratory status and development of chronic lung disease, period of NICU stay, NICU complications during admission including sepsis, central line insertion and its complications, and mortality.

The patients were divided into two groups: Group I included patients who had conservative medical management only, and Group II included patients who underwent surgical intervention after failure of medical treatment. Both groups were compared to determine the risk factors that are associated with the need for surgical intervention.

All patients were followed up for at least 6 months after discharge for the assessment of proper weight gain, recurrence of reflux symptoms, dysphagia, and respiratory condition.

Statistical analysis

Categorical data were presented as numbers and percentages, and between-group differences were compared using the Pearson chi-square test or the chi-square test for trends for nominal or ordinal data, respectively. Fisher's exact test was used in place of the chi-square test if >20% of the cells in any contingency table had an expected count of <5. Moreover, the quantitative data were presented as mean ± standard deviation, and Student's t-test was used for the comparison of both groups. P-values of <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 23 (IBM© Corp., Armonk, NY).

RESULTS

During the study period, 40 patients (35 neonates and 5 infants younger than 2 months of age) suffering from primary GERD were enrolled. Overall, 11 females and 29 males were followed up with a male-to-female ratio of 2.6:1. Their gestational age ranged from 30 to 39 weeks (mean = 34.15 ± 2.79). Age at presentation ranged from 1 to 59 days. Their weight at presentation ranged from 950 to 5500 g (mean= 2604.00 ± 1270.61). The type of feeding was breastfeeding in 9 patients (22.5%), formula feeding in 10 patients (25%), and both in 21 patients (52.5%). The cause of admission to NICU (presenting symptom) was respiratory distress in 15 patients (37.5%), prematurity and low birth weight in 15 patients (37.5%), jaundice in 8 patients (20%), and recurrent vomiting in 2 patients (5%). The diagnosis of GERD was established after admission in most of the cases.

The clinical manifestations of GERD were recurrent regurgitation with or without vomiting in 40 patients, respiratory symptoms associated with the start of oral or nasogastric tube feeding in 40 patients, poor weight gain in 22 patients, and weight loss in 6 patients; hematemesis or coffee-ground vomiting was not detected in this series. No significant antenatal history or a history of siblings with reflux was recorded.

A water-soluble contrast swallow and meal in the Trendelenburg position was performed for 35 patients, showing evidence of GER in 26 patients (74.3%). Overall, the diagnosis was confirmed by a contrast study in 65 % of the patients, whereas it was based on the clinical manifestation in the rest of 35% of the patients. The contrast study was not performed in five patients as these patients were mechanically ventilated and had a critical general condition to shift for the radiological tests. They were diagnosed clinically by the observation of milk getting out by suction from the endotracheal tube after a trial of nasogastric tube feeding on several occasions.

All patients were managed initially by conservative antireflux measures in addition to the medical treatment for a period of time ranging from 10 to 80 days [median (IQR) = 30 (19.5–56.5)]. Overall, 24 patients (60%) out of the 40 included in the study were improved by the conservative medical treatment. They had a median medical treatment duration of 21.5 days (IQR = 14.25–34.25). Four patients died while being medically managed, and 12 patients underwent antireflux surgery after failure of medical treatment. Failed medical treatment was considered when there was no improvement of clinical symptoms or development of GERD complications.

A significant correlation was observed between gestational age and age at presentation with the duration of medical treatment needed wherein younger gestational age (P-value < 0.001) and age at presentation (P-value < 0.001) were associated with a longer period needed for medical treatment (Fig. 2).

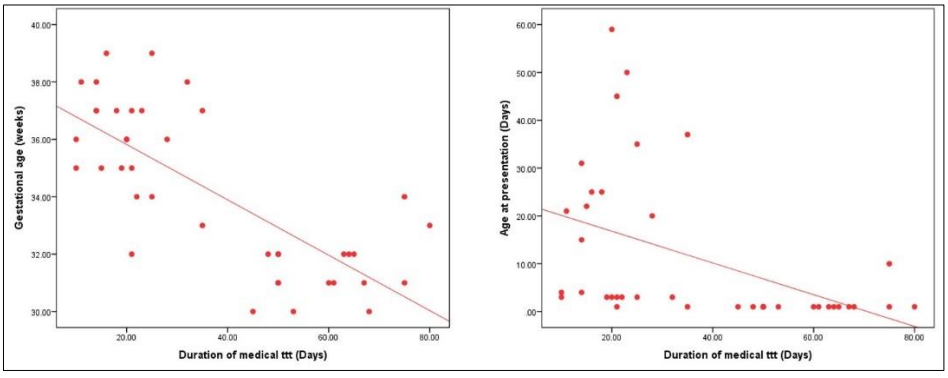
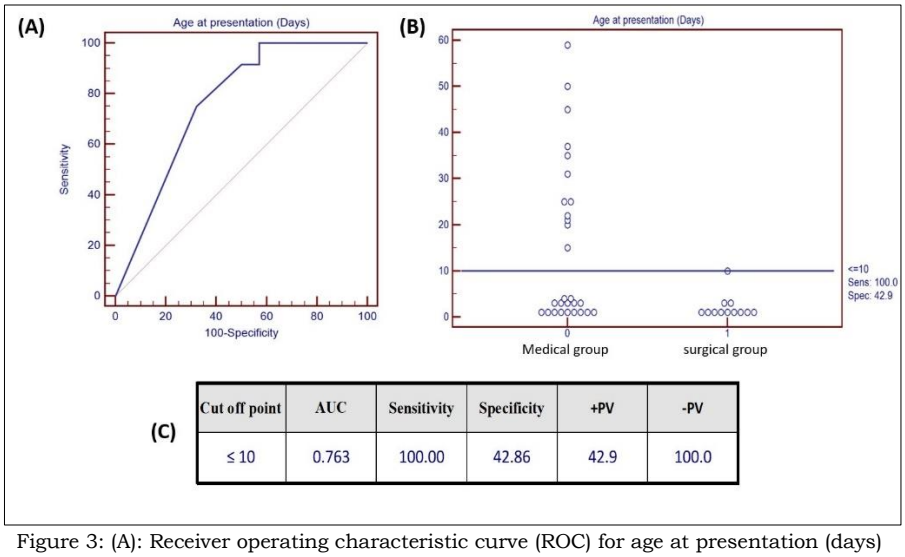


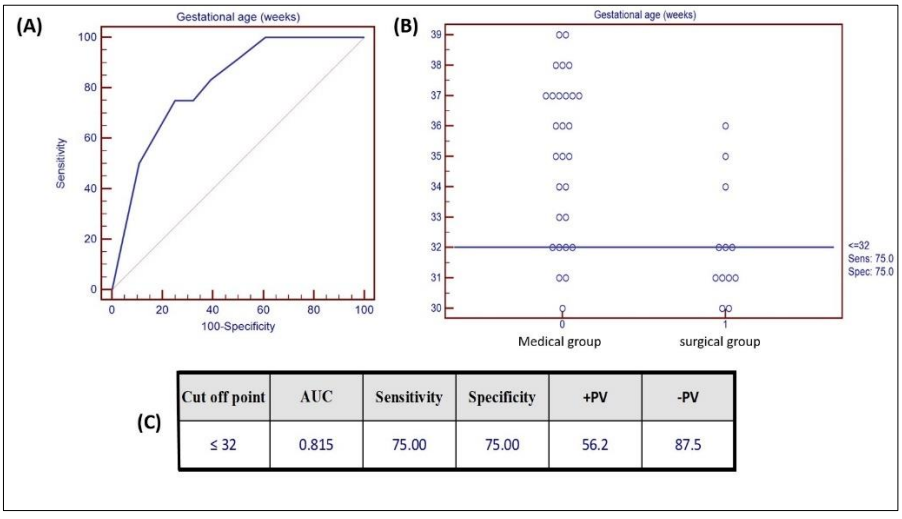
Figure 2: Graph showing the relation between gestational age and duration of medical treatment (Left image), and the relation between age at presentation and duration of medical treatment (Right image).



(C)

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
≤ 10	0.763	100.00	42.86	42.9	100.0

Figure 3: (A): Receiver operating characteristic curve (ROC) for age at presentation (days) as a predictor to differentiate between medical and surgical cases; (B): Patient's distribution according to the age at presentation (days) in both groups; (C): Area under the curve (AUC) and sensitivity and specificity of the cutoff point.



(C)

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
≤ 32	0.815	75.00	75.00	56.2	87.5

Figure 4: (A): Receiver operating characteristic curve (ROC) for gestational age (weeks) as a predictor to differentiate between medical and surgical cases; (B): Patient's distribution according to the gestational age (weeks) in both groups; (C): Area under the curve (AUC), sensitivity and specificity of the cutoff point.

In the surgical group; the age at the time of surgery ranged from 22 to 76 days (mean = 48.92 ± 17.77). Their weight ranged from 1400 to 4100 g (mean = 2287.50 ± 736.74) at the time of surgical intervention. Nissen fundoplication and gastrostomy feeding were performed for the 12 patients. No intraoperative complications were recorded, and the operative time ranged from 45 to 75 min. Ten of them were ventilated in the postoperative period where seven of these patients were weaned from the ventilator at Days 5–7 postoperatively. The other three cases died at days 3, 4, and 5 postoperatively. Gastrostomy feeding was started on day 2 postoperatively in one patient, day 3 in four patients, day 4 in three patients, and day 5 in two patients.

When comparing both groups with regard to the different risk factors, a statistically significant difference was observed in gestational age, age at presentation, and weight at presentation (Table 1). Younger gestational age, age at presentation, and lower weight at the time of presentation are associated with the need for surgical intervention.

All patients who underwent the surgical antireflux procedure were presented in the first 10 days of life (sensitivity 100% and specificity 43%) (Fig. 3), and the majority were preterm with a gestational age of <32 weeks (sensitivity 75% and specificity 75%) (Fig. 4).

Four patients died in the medical group because of respiratory complications and severe sepsis. Three mortalities occurred in the early postoperative period in the surgical group because of the deterioration of the respiratory condition, as they had already developed chronic lung disease from prolonged ventilation before the surgical intervention. They had medical treatment for 50, 53, and 61 days consecutively before being referred for surgery. Mortality was related statistically to younger gestational age and age at presentation, lower weight at presentation, and longer duration of medical treatment (Table 2) (Fig. 5).

Among the surviving patients, significant morbidities were reported in six patients in the medical group in the form of sepsis, central line complications, and the development of chronic lung disease. These morbidities were associated also with prolonged hospitalization ranging from 35 to 80 days. Moreover, wound infection and burst abdomen occurred in one surgical patient who was admitted for 61 days before surgical intervention. Incisional hernia developed in another patient who was operated on after failure of medical treatment for 76 days in the NICU.

Morbidity was statistically significantly associated with younger gestational age (P-value = 0.013) and age at presentation (P-value = 0.009), lower weight at presentation (P-value = 0.005), and longer duration of medical treatment (P-value = 0.015).

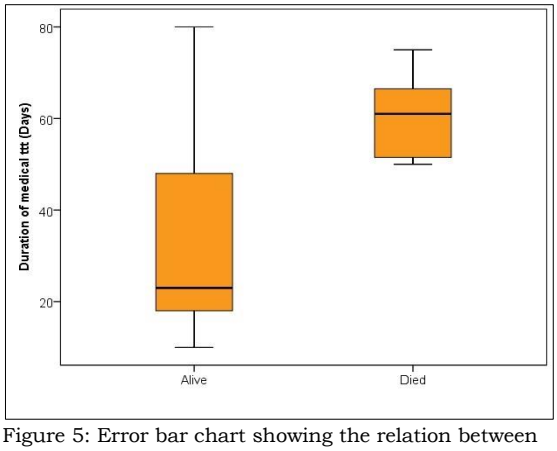


Figure 5: Error bar chart showing the relation between mortality and the duration of medical treatment during NICU admission.

Table 1: Comparison between the medical group and the surgical group regarding demographic data at the time of presentation

		Medical group	Surgical group	Test value	P-value	Sig.
		No. = 28	No. = 12			
Gestational age (weeks)	Mean ± SD	35.04 ± 2.65	32.08 ± 1.93	3.479•	0.001	S
	Range	30 – 39	30 – 36			
Age at presentation (Days)	Median (IQR)	3.5 (1 – 25)	1 (1 – 2)	-2.748≠	0.006	S
	Range	1 – 59	1 – 10			
Weight at presentation (grams)	Mean ± SD	2880.36 ± 1390.07	1959.17 ± 577.15	2.203•	0.034	S
	Range	950 – 5500	1100 – 2900			
Type of feeding	Breast	7 (25.0%)	2 (16.7%)	2.547*	0.280	NS
	Formula	5 (17.9%)	5 (41.7%)			
	Both	16 (57.1%)	5 (41.7%)			
Presenting symptom	Respiratory distress	12 (42.9%)	3 (25.0%)	7.262*	0.064	NS
	Preterm	9 (32.1%)	6 (50.0%)			
	Jaundice	7 (25.0%)	1 (8.3%)			
	Recurrent vomiting	0 (0.0%)	2 (16.7%)			

P-value > 0.05: Non significant (NS); P-value < 0.05: Significant (S). *: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

Among the studied patients; 30 patients needed mechanical ventilation at the time of admission, and another 6 needed ventilatory support while on medical management. In the surgical group, 9 patients were on mechanical ventilation at the time of surgery, out of which six could be weaned successfully from the ventilator postoperatively.

Table 2: The relation between mortality and gestational age, age and weight at presentation, duration of medical treatment

		Alive	Died	Test value	P-value	Sig.
		No. = 33	No. = 7			
Gestational age (weeks)	Mean ± SD	34.82 ± 2.59	31 ± 0.82	3.823•	0.000	S
	Range	30 – 39	30 – 32			
Age at presentation (Days)	Median (IQR)	3 (1 – 22)	1 (1 – 1)	-2.883≠	0.004	S
	Range	1 – 59	1 – 1			
Weight at presentation (grams)	Mean ± SD	2871.52 ± 1231.19	1342.86 ± 400.45	3.220•	0.003	S
	Range	1100 – 5500	950 – 2000			
Duration of medical ttt (Days)	Median (IQR)	23 (18 – 48)	61 (50 – 68)	-2.993≠	0.003	S
	Range	10 – 80	50 – 75			

P-value > 0.05: Non significant; P-value < 0.05: Significant •: Independent t-test; ≠: Mann-Whitney test

The living 33 patients were followed up for a period ranging from 6 to 18 months (median = 12 months). In the medical group, recurrence of symptoms occurred in six patients in the form of recurrent attacks of vomiting and regurgitation with a respiratory infection, whereas no recurrence in the surgical group. Recurrence was confirmed by a contrast study. These six recurrent cases continued their medical treatment. Two of them underwent an antireflux procedure at the age of 12 and 14 months, three patients improved on medical treatment around the age of 1 year, and one patient was lost to follow-up.

DISCUSSION

Gastro-esophageal reflux is a very common presentation in neonates. About 75–80% of infants have GER in the first 2 months of life, which usually resolves spontaneously before the age of 1 year.[2] Approximately 50% of infants seek medical attention for symptoms suggestive of GER.[8] The incidence is higher in preterm infants and may reach up to 85%.[9] It occurs slightly more frequently in males than in females.[2] Although GER and GERD are very common conditions, pediatricians are challenged to differentiate between physiological GER and pathological GERD, which usually require a more meticulous evaluation and management, especially in neonates and infants younger than 3 months old.[5,6]

The first line of management of GERD is conservative medical treatment. However, the indication and optimal timing of surgical intervention for neonates with GERD need to be investigated further. Hassal stated that antireflux surgery offered poor outcomes and adequate medical treatment can be an effective and safe alternative to surgery in many cases. However, he did not discuss the timing required for assessing the success of such medical treatment.[10] Jancelewicz and his colleagues also reported that further data are needed to establish the optimal timing of surgical intervention and determine whether early interference would provide good postoperative results or not and to which extent it would protect the patient from the ongoing pulmonary complications.[5] Mullassery and Jones stated that inadequate response to medical management and the presence of significant and recurrent respiratory complications are the indications for surgical intervention. However, they did not mention any guidelines for the timing of surgical intervention.[6]

In the present study, we evaluated the management of neonatal GERD. Several risk factors were studied trying to have objective parameters to determine which patient may need surgery and the appropriate time for an intervention.

The duration of medical treatment in our patients ranged from 10 to 80 days. The resolution of symptoms occurred in 24 patients with a percentage of 60% only, and unfortunately, four patients died from respiratory complications and sepsis. These four mortalities in addition to the other three mortalities in the surgical group could be attributed to the prolonged trial of medical treatment, which ranged from 50 to 75 days. Thus, the neonatologist and pediatrician should always weigh the benefits versus the risk of prolonged hospitalization for these babies considering the low satisfactory response to the conservative management. The three patients who died postoperatively had already developed chronic lung disease from prolonged ventilation, as they were medically managed for 50, 53, and 61 days consecutively before the referral for surgical intervention. The failure of medical treatment to

control the condition with persistent symptoms with or without the development of disease complications is an indication for surgical intervention as agreed in different centers.[9,11,12]

In the medical group, 14 patients were free from complications; all of them received medical treatment for a period of fewer than 35 days. Six patients in the medical group suffered from major complications related mainly to the prolonged hospitalization and mechanical ventilation period and poor nutritional state due to failure to achieve adequate enteral feeding. Those six patients received medical treatment for more than 35 days. Prolonged medical treatment and hospitalization predispose the patients to venous access complications, and the subsequent risk of hospital-acquired infection, sepsis, and death. A similar observation was reported in series from different centers.[13,14] Day and Ryan reported that patients with persistent reflux (resistant to medical treatment) with recurrent deterioration of the respiratory condition developed bronchopulmonary dysplasia after 28 days of being oxygen dependent.[15] In our series, medically resolved 24 cases needed a median of 21.5 days of medical treatment (IQR = 14.25–34.25). From these data, we suggest that 35 days is a reasonable period to provide medical management to improve the patient's condition and for the patient to be discharged without the development of acquired morbidities associated with prolonged hospitalization and mechanical ventilation. However, the neonatologist and the pediatric surgeon should be alert that if there is a life-threatening GERD complication, there will be no place for conservative management where surgical intervention should be offered immediately.

In the surgical group, the age at the time of operation ranged from 23 to 76 days (mean = 44.14). They were operated on after 20 to 75 days of medical treatment. The procedure was successful in all patients; only one patient suffered from a wound infection complicated by the burst abdomen, and an incisional hernia occurred in a second case. Mortalities and morbidities in the surgical group were reported in the patients who were managed medically for more than 50 days before being referred for surgery. All mortality cases may have already developed bronchopulmonary dysplasia before being referred for surgery. In literature, the reported high rate of mortality and morbidities in neonates who underwent antireflux surgery is mostly due to the prolonged medical management and the development of bronchopulmonary dysplasia from prolonged ventilation.[12,15] Antireflux surgery should not be postponed if the patient presents with intractable symptoms or risk of life-threatening GERD complications (e.g., apneic episodes).[9,16]

In the medical group, recurrence of symptoms occurred in six patients (25%) after 6 months, which decreased to 12.5% after continuing the medical treatment for another 6 months, whereas no recurrence was observed in the surgical group in our series.

In the surgical group, the patients were discharged shortly after the surgical intervention, thus decreasing the overall hospitalization time and its related complications in addition to minimizing the individual and governmental costs. Jadcherla and his colleagues stated similarly that interventions that rapidly deal with GERD can lower the length of hospital stay.[17]

In the present study, the duration needed for medical treatment and the referral for surgical intervention was significantly related to the younger gestational age and the younger age at presentation, indicating that the disease is usually more severe in preterm neonates. In agreement with this finding, Kimber and his colleagues reported that fundoplication is effective management of non-neurological GERD in preterm neonates when performed in the earlier stage of the disease.[18]

Our study is limited by the small number of patients as well as the unavailability of more precise diagnostic procedures in our hospital to confirm the relations between the acidic reflux and the symptoms and whether it was the actual cause or only an association. Further multicentric studies on a larger cohort of patients are needed to establish a set of guidelines for the treatment of GERD in neonates and infants younger than 2 months.

CONCLUSION

Medical and conservative antireflux measures are the initial management for all cases of GERD. A low threshold for surgical intervention should be maintained if the patient shows no adequate response to the medical treatment for more than 35 days, especially in low-birth-weight, preterm neonates with a gestational age of ≤32 weeks or in neonates admitted to the NICU in the first 10 days of life.

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Abbreviation: GER: gastroesophageal reflux, GERD: gastroesophageal reflux disease, NICU: neonatal intensive care unit.

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