Predictive score for positive upper endoscopies outcomes in children with upper gastrointestinal bleeding.

Score prédictif de la présence de lésions endoscopiques dans l'hémorragie digestive haute de l'enfant

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RÉSUMÉ

Prérequis: L'hémorragie digestive haute (HDH) est une urgence fréquente en pédiatrie. L'endoscopie digestive haute (EDH) est l'examen de choix pour identifier l'origine du saignement. Néanmoins l'étiologie demeure inconnue dans 20% des cas. En outre, l'endoscopie d'urgence n'est pas disponible dans de nombreux hôpitaux dans notre pays .

Objectifs: Décrire les lésions endoscopiques retrouvées chez l'enfant dans l'HDH, identifier les facteurs prédictifs de la présence de ces lésions et élaborer un score clinique à partir de ces paramètres.

Méthodes: Etude rétrospective des EDH réalisées chez les enfants présentant un premier épisode d'HDH, à l'unité d'endoscopie digestive de l'hôpital d'enfants de Tunis, au cours d'une période de 6 ans. Une analyse univariée et une étude multivariée en régression logistique ont été réalisées pour établir un score clinique.

Résultats: Nous avons colligé 655 endoscopies (23.2% normales, 76.8% pathologiques). Nous avons identifié comme facteurs prédictifs de la, présence de lésions endoscopiques: le délai de réalisation de l'endoscopie, inférieur à 24 H à partir du début du saignement (p = 0.027;ORaj: 3.30 [1.14-9.53]), la récidive hémorragique dans les premières 24 H (p = 0.009;ORaj: 6.01 [1.57-23.02]), le lavage gastrique positif (p = 0.001;ORaj: 4.79 [1.95-11.79]) et la prise d'anti-inflammatoires non stéroïdiens (p = 0.035;ORaj: 5.66 [1.13-28.31]). En attribuant à chaque facteur, l'Odds ratio ajusté (ORaj), nous avons développé un score de quatre items, allant de 4 à 20. En utilisant la courbe ROC, nous avons trouvé une valeur seuil: score ? 9 (sensibilité 88.2%, spécificité 60.6%, valeur prédictive positive de 92.7% et une valeur prédictive négative de 47.6%). Le score avait un bon pouvoir prédictif puisque l'aire sous la courbe ROC était de 0.837 (IC à 95% [0.769-0.905]).

Conclusion: Ce score clinique est un outil simple permettant d'identifier les enfants qui ont besoin d'EDH en urgence. Une étude prospective est nécessaire pour valider ce score et identifier d'autres facteurs prédictifs pour améliorer le score.

Mots-clés
Score prédictif, lésion endoscopique,hémorragie digestive haute enfant.

SUMMARY

Background: Upper gastrointestinal bleeding (UGIB) is a common pediatric emergency. Esophago-gastro-duodenoscopy (EGD) is the first line diagnostic procedure to identify the source of bleeding. However etiology of UGIB remains unknown in 20% of cases. Furthermore, emergency endoscopy is unavailable in many hospitals in our country.

Aims: Identify clinical predictors of positive upper endoscopy outcomes and develop a clinical prediction rule from these parameters.

Methods: Retrospective study of EGDs performed in children with first episode of UGIB, in the endoscopic unit of Children's Hospital of Tunis, during a period of six years. Statistical analysis used SPSS20. Univariate analysis was performed and multivariate logistic regression was then modelled to derive a clinical prediction rule.

Results: We collected 655 endoscopies (23.2% normal, 76.8% pathological). We found that time to EGD within 24 hours from the onset of bleeding (p=0.027; Adj OR: 3.30 [1.14 – 9.53]), rebleeding (p=0.009; Adj OR: 6.01 [1.57 – 23.02]), positive gastric lavage outcome (p=0.001; Adj OR: 4.79 [1.95 – 11.79]) and non steroidal anti-inflammatory drugs intake (p=0.035; Adj OR: 5.66 [1.13 – 28.31]) were predictors of positive upper endoscopy outcomes. By assigning each factor, the adjusted odds ratio (Adj OR), we developed a score with four items, ranging from 4 to 20. Using the receiver operating characteristic (ROC) curve the best cut off ≥ 9 was defined (sensitivity 88.2%, specificity 60.6%, positive predictive value 92.7% and negative predictive value 47.6%). The score discriminated well with a ROC curve area of 0.837 (95% confidence interval [0.769 - 0.905]).

Conclusions: This clinical prediction rule is a simple measure that may identify children who needed emergency endoscopy. A prospective study is required to validate our results and evaluate other clinical features that were insufficient for this analysis.

Key-words
Upper gastrointestinal bleeding – children – Upper gastrointestinal endoscopy – Predictive factors – Clinical Prediction Rule.

The upper gastrointestinal bleeding (UGIB) is a common pediatric emergency, it varies greatly in presentations and it may be potentially life-threatening in some cases. There is a paucity of data available from studies of UGIB in the pediatric population throughout the world. The etiologies of acute UGIB are multiple and vary with age and geographical origin. The esophago-gastro-duodenoscopy (EGD) is the first line diagnostic procedure to identify the source of bleeding, establish a prognosis and suggest appropriate treatment. However, the causes of bleeding are not identified in 20% of cases, this may be due to time to endoscopy greater than 24 hours, and the existence of lesions in which bleeding stops spontaneously and that heal rapidly (1). Furthermore, emergency endoscopy is unavailable in many hospitals in our country.

The aim of this study was to describe the endoscopic findings in a Tunisian pediatric population with UGIB, to identify clinical predictors of positive upper endoscopy outcomes and to derive a clinical prediction rule (score) from these predictive factors, able to identify children with positive endoscopy outcomes which will require admission for urgent endoscopy.

METHODS

This retrospective study was carried out in the pediatric gastroenterology department of Tunis Children's Hospital, between January 2007 and December 2012. Children aged less than 16-year-old, with a first episode of UGIB, were included. Children with gingival bleeding or swallowed nosebleed, and UGIB caused by swallowing caustic agents, were excluded. We used PENTAX and FUJINON endoscopes. EGD was performed without sedation. Conscious sedation was available (Kalinox®) for children over six-year-old,

A retrospective chart review of all EGD performed during this period, was done. Data collected from records included: age, gender, personal and family history, presentation of UGIB (coffee-ground striated with blood, haematemesis, melena and red blood stools), associated symptoms, hemodynamic parameters, hemoglobin level, taking non steroidal anti-inflammatory drugs (NSAID), time to EGD from the onset of bleeding recorded in hours, need for transfusion, outcome of gastric suction or stomach pumping, treatment received before EGD, rebleeding in the first 24 hours, endoscopic findings, and histological diagnoses.

Patients were divided into three groups according to age: Group A: neonates (from birth to 28 days), group B: infants (from 29 days to 3 years) and group C: children older than three years. The importance of bleeding was considered low, if UGIB was coffee ground emesis or vomiting striated with blood; was moderate, if there was no decreasing of hemoglobin level and without an impact on the hemodynamic status, and was severe if there was severe anemia or an impact on the hemodynamic status. The outcome of gastric lavage was considered positive when we found coffee grounds or bright red blood. The decreasing of hemoglobin level was defined by a drop of hemoglobin by 2g/dL in the first 24 hours, compared to hemoglobin on admission. The description of mucosal lesions in the gastrointestinal tract has been made according to international classifications.

Statistical analysis: Statistical analysis was performed by using SPSS Program version 20. The calculations of means, medians, standard deviations and percentages were used to characterize the population studied. We compared averages of two independent groups by using the Student t test and percentages of independent series by the chi-square test of Pearson and the bilateral Fisher exact test whenever necessary. Univariate analysis for the associations between clinical parameters and positive endoscopy outcome was carried out. All variables with $p<0.05$ at the univariate analysis were included in the multivariate analysis. Multivariate logistic regression analysis (method: Wald) was conducted to identify the independent variables associated with positive endoscopy outcome. Calibration of the model was assessed using Hosmer and Lemeshow goodness of fit test. Predictive score was developed from the parameters derived from the multivariate analysis. The best cutoff point of the resulting clinical prediction rule to differentiate children with and without positive endoscopy outcome was determined from the receiver operating characteristic (ROC) curve. The sensitivity and specificity rates, positive predictive value (PPV) and negative predictive value (NPV), of the cutoff point were calculated. The study was approved by the ethics committee of Tunis Children's Hospital.

RESULTS

Epidemiological results:

During the period of the study, 4144 diagnostic procedures were performed in our unit. We included in this study 655 endoscopies performed for UGIB (328 girls and 327 boys). The mean age was 4.18 ± 4.14 years (range 1 day - 16 years). Group A included 86 neonates (13%), group B included 284 infants (43%) and group C included 285 children (44%). Among the 655 endoscopies studied, EGD did not identify the source of bleeding in 152 cases (23.2%). A NSAID history intake was recorded in 115 cases (17.5%): 69 were Aspirin (Acetylsalicylic Acid), 20 Ibuprofen, 19 Mefenamic Acid (INFLAMYL®) and 7 Niflumic Acid (NIFLURIL®). Omeprazole was administered intravenously at 2mg/Kg/day, before EGD in 617 cases (94.2%). The main clinical, biological and endoscopic features of our population are summarized in table 1. The presentations of UGIB were haematemesis (N= 586; 89.4%); melena (N=13; 2%); haematemesis and melena (N=39; 6%) and red blood stool (N=17; 2.6%).

Rebleeding (p=0.002; OR (IC 95%): 2.76 [1.41–5.38]), need for transfusion before performing EGD (p<0.001; OR 6.30 [2.73–14.53]) and decreasing of hemoglobin level (p=0.001; 3.88 [1.70–8.82], were significantly more found in patients presenting with haematemesis and melena than those with other presentations of UGIB (Table 2).

Endoscopic findings in Tunisian children with upper gastrointestinal bleeding:

In group A, EGD was normal in nine cases (10.4%). We found 69 cases of neonatal esogastroduodenitis (NNEGD) (80.2%), six cases of peptic esophagitis, one case of gastric angioma and one case of gastric tumor (teratoma).

Esophageal lesions were found in 132 cases (23.2%), in groups B and C. The distribution of these lesions according to etiologies is summarized in table 3. The mean age of patients with peptic esophagitis was 4.3 ± 3.92 years and the sex ratio was 1.07 (44 boys/41 girls). This lesion was significantly more common in group B than in group C (p = 0.024). Gastroesophageal reflux disease was reported in 18 cases (21%). Chronic vomiting, dyspepsia, chronic

abdominal pain were recorded respectively in 49 (58%), 24 (28%) and four (5%) cases. Peptic esophagitis was classified in 35 cases (41%) as grade I, in 26 cases (31%) as grade II, in 19 cases (22%) as grade III, in four cases (5%) as grade IV and in one case (1%) as grade V. The mean age of patients with Mallory Weiss tears (MWT) was 6.6 ± 3.84 years and the sex ratio was 4.5 (9 boys/ 2 girls). MWT was significantly more common in group C than in group B (p=0.034, OR: 4.5 [1 – 21.4]). Acute and repeated vomiting preceded the bleeding in 10 cases. A single linear longitudinal ulceration in the lower third of the esophagus, surrounded with congestive mucosa, was found in nine cases. Multiple ulcerations were found in two cases, associated with active bleeding in one case. The mean age of patients with esophageal varices (EV) was 6.4 ± 4.57 years and the sex ratio was 0.9 (9 boys/ 10 girls). EV were classified as grade I in six patients, grade II in 12 cases and grade III in one case. Pathological history was reported in 17 cases: nine cases of cirrhosis, four cases of portal vein cavernoma, three cases of congenital hepatic fibrosis and one case of arteriovenous malformation of the liver. Signs of portal hypertension were found in 15 cases (79%). Sandostatin® was administered intravenously before performing endoscopy in three cases (15.8%). Rubber band ligation was performed in ten cases to prevent rebleeding.

Gastric lesions were found in 332 cases (58.3%), in groups B and C. The distribution of these lesions according to etiologies is summarized in table 3. Gastric biopsies were undertaken in 115 cases. They were normal in 20 cases and they showed chronic gastritis, chronic atrophic gastritis, chemical reactive gastritis and eosinophilic gastritis respectively in 87, two, four and two cases. Helicobacter Pylori was isolated in 87 biopsy samples. The mean age of patients with chronic gastritis due to H.Pylori infection was 8 ± 3.62 years and the sex ratio was 0.89 (41 boys/ 46 girls). This lesion was significantly more common in group C than in group B (p<0.001). Family history of peptic ulcer disease was recorded in 22 cases (25.3%). Nodular gastritis was found in 63 cases (72.4%), it was associated with erosive lesions in 11 cases, ulcerated lesions in three cases and hemorrhagic gastritis in eight cases. Acute gastritis due to NSAID intake was reported in 78 cases, the mean age was 3.9 ± 3.2 years and the sex ratio was 1.16 (42 boys/ 36 girls). The endoscopic features were as following: 17 cases (22%) of hemorrhagic gastritis, eight of them were associated with active bleeding; 32 (41%) erosive or ulcerated lesions; six cases (8%) of ulcer and 23 (29%) congestive lesions. Gastric ulcer was recorded in six cases; the mean age was 3.8 ± 3.66 years and the sex ratio was 0.5 (2 boys/ 4 girls). NSAID intake was reported in all cases of gastric ulcer. The ulcer was prepyloric in three cases and antrofundic in three cases.

Bulbous lesions were recorded in 27 cases (4.7%) in groups B and C. They were congestive (N=10), petechial (N=6), hemorrhagic (N=5), erosive (N=4) and ulcerated (N=2). Bulbous ulcer was recorded in six cases, aged respectively 8 months, 9 months, 14 months, 18 months, 30 months and 14 years. It was associated to chronic gastritis in two cases. NSAID intake was reported in two cases and hemorrhagic stress ulcer in two cases. Duodenal lesions were recorded in 24 cases (4.2%), in groups B and C. They were congestive (N=3), petechial (N=11), erosive (N=5) and ulcerated (N=2). Nodular lymphoid hyperplasia was observed in three cases. An ulcerated duodenal polyp was reported in a 9-year-old boy with a family history of adenomatous polyposis. An ulcerated duodenal parietal hematoma was reported in a 9-year-old girl with Henoch–Schönlein purpura.

Predictive score for positive outcome of upper Gastrointestinal Endoscopies:

Univariate statistical analysis found that positive endoscopy outcome was significantly associated with rebleeding (p<0.001), positive gastric lavage outcome (p<0.001), NSAID's intake (p=0.002), transfusion before EGD (p=0.008) and decreasing of hemoglobin level (p=0.016). A bleeding source was significantly more found in patients having EGD within 24 hours from the onset of bleeding (p<0.001) (table 4). Among NSAID, Aspirin intake was significantly associated with positive endoscopy outcome (p=0.035; OR: 2.15 [1.04 – 4.44]).

Multivariate logistic regression analysis was conducted to identify predictive factors of positive endoscopy outcomes. We introduced in the first step the six factors identified in univariate analysis and we stopped on the third step because the Hosmer test was satisfactory since the probability of Chi-square with 5 df was 70.5% which means that the model fit was good.

Thus, the predictors of positive endoscopy outcome were time to EGD within 24 hours from the onset of bleeding (p=0.027; Adj OR: 3.30 [1.14 – 9.53]), rebleeding (p=0.009; Adj OR: 6.01 [1.57 – 23.02]), positive gastric lavage outcome (p=0.001; Adj OR: 4.79 [1.95 – 11.79]) and NSAID's intake (p=0.035; Adj OR: 5.66 [1.13 – 28.31]).

To derive a clinical prediction rule, the coefficients obtained from the logistic regression were used to produce a scoring system that required the addition of integer values, which were associated with specific risk factors identified. Each factor identified in multivariate analysis was assigned to its adjusted odds ratio rounded to the nearest integer if present, and it was scored 1 if absent (table 5). We studied patients for whom we have complete data of considered factors (N=220). The best cutoff point of the resulting clinical prediction rule was determined from the receiver operating characteristic (ROC) curve (figure 1). Using the ROC curve, a cutoff ≥ 9 was chosen as the best cutoff for predicting positive outcome. The sensitivity, specificity, PPV and NPV for positive outcome with this cutoff were 88.2%, 60.6%, 92.7% and 47.6% respectively. Other cutoffs were also explored to maximize sensitivity or specificity. Area under the ROC curve of this clinical prediction rule was 0.837 (95% CI [0·769 - 0·905]), implying good discriminant ability.

DISCUSSION

Endoscopic findings

EGD is the first line diagnostic procedure to identify the source of bleeding. In our study, the bleeding source was not found in 23.2% of cases. This may be due to EGDs performed at greater than 24 hours from the onset of bleeding, or lesions that healed spontaneously before being confirmed by endoscopy or early administration of proton pump inhibitors before performing endoscopy. In the literature, the proportion of normal endoscopies ranged from 9.8% to 28.2% (figure 2). In our study, the main etiology of UGIB in neonates was esogastroduodenitis. These lesions have been widely reported in the literature (1). Esophagitis represented 17.2% of UGIB etiologies in infants and children. Peptic esophagitis was significantly more common in infants. In our study, EV represented 3.3% of UGIB etiologies in infants and children. In the literature, this prevalence

ranges from 2% to 16% (table 6). Rubber band ligation is the best haemostatic treatment to prevent rebleeding; it was made in ten children in our study. This interventional endoscopic procedure is commonly performed in our department; it is the main purpose for interventional endoscopy in children older than 10 years (9). Acute gastritis due to NSAID intake represented 13.7% of the etiologies of UGIB in infants and children, in this study. In two previous studies conducted in our department, this prevalence was respectively 28% (1) and 29.8% (10), it was 27.4% (6) in a sfaxian pediatric study, between 15% and 46.9% (11, 12) in French studies and in a Turkish study NSAID intake was recorded in 56% of infants with UGIB (7). Endoscopic features are mainly congestive and erosive lesions, ulcerations are less common (15% of cases) and ulcers are possible. The lesions are most often in the duodenum than in the stomach (13). In our study 15.3% of children and infants, had chronic gastritis due to H.Pylori infection diagnosed by gastric biopsy. This prevalence is probably underestimated because the biopsy was not done in all children. In two studies conducted in our department in 2007 and 2009, the prevalence was respectively 48% (14) and 48.8% (10). In our study, chronic H.Pylori gastritis was significantly more frequent in children than in infants. The most endoscopic feature found in chronic H.Pylori gastritis was nodular gastritis. In our study, the prevalence of gastro-duodenal ulcer was 2.1%, in infants and children. In the literature this prevalence varied from 3% to 25% (table 6). Most ulcers are secondary and occur in a particular pathological context such as toxic drug intake as it was shown in our study.

Predictive score for positive upper endoscopies outcomes

The proportion of normal endoscopies was significant. Furthermore, emergency endoscopy is unavailable in many hospitals in our country. This prompted us to identify clinical predictors of positive endoscopy outcomes. Our results are promising and indicate that clinical utility of predictive models for positive endoscopy outcomes, merits further studies. However, we recognize the limitations of our retrospective study. The sample size was insufficient. Furthermore the NPV of our clinical prediction rule was moderate (47.6%) and the risk of false negatives was significant. Given these limitations, a prospective study is required to improve and validate our results and evaluate other clinical features that were insufficient for this analysis.

Predictive factors for positive upper endoscopies outcomes:

Time to EGD within 24 hours from the onset of bleeding was found as a predictive factor of positive endoscopy outcomes (Adj OR: 3.30 [1.14 – 9.53]). Several Tunisian studies have established that time to endoscopy from the onset of bleeding had an effect on the ability to identify a bleeding source. Maherzi, showed that bleeding source was identified in 90% of cases if EGD was performed within 24 hours, and in 57% of cases if EGD was postponed more than 24 hours ($p<0.001$) (8). Another predictor of positive endoscopy outcomes was NSAID's intake (Adj OR: 5.66 [1.13 – 28.31]). A French study showed that one third of UGIB cases were attributable to exposure to NSAID (Adj OR: 8.2 [2.6 - 26.0]) at doses used for analgesic or antipyretic purposes, which may be attained with alternative therapy. The findings from this study call for more caution in prescribing NSAIDS to children (12). Positive gastric lavage outcome was found as a predictor of positive endoscopy outcome (Adj OR: 4.79 [1.95 – 11.79]). Nasogastric aspiration with saline lavage is beneficial to detect the presence of intragastric blood and to clear the gastric field for endoscopic visualization with an efficiency of about 60% (15). Bright red blood suggests currently active bleeding, whereas coffee grounds suggest recently active bleeding. Gastric lavage allows monitoring bleeding activity (16, 17). Nasogastric aspiration of red blood is associated with a significantly higher rate of endoscopic stigmata of recent hemorrhage (18).

We found very few pediatric studies that developed models to accurately determine the outcomes of diagnostic endoscopies performed in children with UGIB. Cleveland (USA) found that presentation of UGIB with melena, time to endoscopy within 48 hours before the onset of bleeding and transfusion before performing endoscopy, were significantly associated with positive endoscopy outcomes (7), which join our results.

However, a Canadian study, in which upper endoscopies performed in children with different clinical symptoms (UGIB, dysphagia, poor growth, weight loss …) and biological signs (anemia, hypoalbuminemia, eosinophilia …), found that age above 13 years, vomiting, and hypoalbuminemia were significant predictors of positive endoscopy outcomes (19). The results of this study cannot be compared with our results because our study included only upper endoscopies performed for UGIB.

Derivation of clinical prediction rule:

We report the derivation of a predictive model that has a high sensitivity (88.2%) and moderate negative predictive value (47.6%) for the identification of children with positive endoscopy outcomes. This score is easily calculated and is based on available clinical data. The model was well calibrated as evident from the Hosmer and Lemeshow goodness-of-fit test. Our score discriminated well between patients who needed emergency endoscopy and those for whom endoscopy may be delayed because the area under the ROC curve of this clinical rule was 0.837. The area under ROC curve is a measure of the validity of a scoring system. These areas can range from 0.5 when a score performs no better than chance to 1 for a score that perfectly discriminates between outcomes (20, 21).

In the literature, no clinical score was developed in children to assess the severity of UGIB and the risk of rebleeding or to predict need for treatment to manage bleeding. A clinical prediction rule was developed to identify children with liver disease or portal hypertension, at high risk for esophageal varices by using noninvasive test (22). However several risk assessment and scoring systems for UGIB have been developed in adults, in an attempt to stratify risk for poor outcome. However, most, including the widely used Rockall score, include endoscopic findings. An abbreviated pre-endoscopy admission Rockall score, using only clinical criteria is able to predict the evolution without endoscopy, but this score has not been fully validated (23, 24). The Glasgow-Blatchford bleeding score (GBS) based on simple clinical and laboratory variables, identifies low-risk patients with UGIB who can be managed safely as outpatients. This score is easily calculated, unlike many previous risk scores, it does not rely on endoscopic findings and could be easily used for acute admissions. This score reduces admissions for this condition, allowing more appropriate use of in-patient resources (23, 25).

CONCLUSION

UGIB is a common, potentially life threatening pediatric condition, which remains the first indication for EGD in our department. We found that UGIB etiologies in Tunisian children do not differ much from those in developed countries. Time to EGD within 24 hours from the onset of bleeding, rebleeding, positive nasogastric aspiration outcome and NSAID's intake, were predictors of positive endoscopy outcomes. Then a clinical prediction rule of positive upper endoscopy outcomes was derived from these parameters, to identify children who need urgent endoscopy. Our score was the first pediatric clinical score to predict positive endoscopy outcomes. It had a high sensitivity and a good specificity, but it should be validated in a prospective study. Several prognostic scores have been developed, in adults, to identify patients at high risk requiring urgent endoscopy and intensive care, and those at low-risk for whom endoscopy may be delayed. An ideal prognostic score should be accurate, simple, reproducible and validated prospectively to stratify the risk to optimize care. No score has reached a sufficient evidence level to allow its application to emergencies safely

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