Les facteurs cliniques prédictifs de lésions endoscopiques à haut risque de saignement chez un enfant présentant une hématémèse.

Clinical predictors of high risk bleeding endoscopic lesions in children with haematemesis

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RÉSUMÉ

Prérequis : L'hématémèse est un symptôme alarmant chez l'enfant, même si l'endoscopie digestive est normale dans 10 à 21% des cas et les causes sont souvent bénignes. Le but de l'étude était d'identifier les paramètres cliniques prédictifs de lésions endoscopiques à haut risque de saignement et d'établir un score qui en prédirait l'existence.

Méthodes : Une étude rétrospective menée entre 1997 et 2006 à l'Hôpital d'Enfants de Tunis a concerné des enfants ayant eu une endoscopie digestive pour hématémèse. Plusieurs paramètres cliniques ont été analysés. Une étude uni variée puis multi variée en régression logistique a été menée pour identifier les paramètres associés de façon indépendante avec le risque de développer des lésions à haut risque de saignement. Un score de réalisation d'une endoscopie digestive devant une hématémèse a été calculé ainsi que sa sensibilité et sa spécificité.

Résultats : Sur 2814 fibroscopies, 814 ont été réalisées pour hématémèse et 489 ont été retenues pour l'étude dont 140 avaient des lésions à haut risque de saignement. L'analyse multi variée en régression logistique a identifié six facteurs indépendants : l'endoscopie réalisée dans les 48 heures (OR=2,2 ; IC95% 0,7-6,9),premier épisode d'hématémèse (OR=1,4 ; IC95% 0,7-2,5),l'importance du saignement (OR=1,8 ; IC95% 1-1,3), une hématémèse faite de sang clair (OR=1 ; IC95% 0,2-5,8), des antécédents de maladie digestive ou hépatique (0R=1,6; IC95% 1,1-3) et la prise de médicaments gastro toxiques (OR=1,3 ; IC95% 0,8-2,3). Ces paramètres ont permis d'établir un score dont la sensibilité, la spécificité, la valeur prédictive positive et la valeur prédictive négative étaient respectivement de 79,6%, 32,9%, 34,9% et 78% pour une valeur seuil > 0,22.

Conclusion : Ces paramètres cliniques prédictifs de lésions à haut risque de saignement, n'ont pas permis d'obtenir un score à sensibilité et spécificité élevé. Une étude prospective doit être menée pour améliorer ce modèle.

Mots-clés

Enfant, hématémèse, endoscopie digestive, score, facteurs prédictifs

SUMMARY

Background: Haematemesis is an alarming symptom in children, even if the proportion of normal endoscopies ranges from 10 to 21% and the causes are often benign.

The purpose of the study was to identify clinical predictors of endoscopic lesions with high risk of bleeding and to establish a score that predict the presence of these lesions.

Methods: Retrospective study carried in Children's Hospital of Tunis between 1997 and 2006 involved children with haematemesis who underwent Upper gastrointestinal endoscopy. Several clinical parameters were analyzed. Univariate analysis and multivariate logistic regression were performed to identify predictive parameters of endoscopic lesions with high risk of bleeding. A score was developed from the parameters derived from the multivariate analysis. The sensitivity and specificity of the score were determined.

Results: Among 2814 endoscopies, 814 were conducted for haematemesis and 489 were selected for the study. 140/489 had lesions with high risk of bleeding. Multivariate logistic regression analysis identified six factors independently associated with high risk bleeding lesions: endoscopy performed within 48 hours (OR=2.2; 95% CI 0.7-6.9), re-bleeding (OR=1.4; 95% CI 0.7-2.5), the importance of the bleeding, mild to severe (OR=1.8; 95% CI 1.1- 3), bright red haematemesis (OR=1; 95% CI 0.2-5.8), history of gastrointestinal and liver disease (OR=1.6; 95% CI 1.1-3) and intake of gastro toxic drugs (OR=1.3; 95% CI 0.8-2.3). Then, we established a score. The sensitivity, specificity, positive predictive value and negative predictive value of this score were respectively 79.6%, 32.9%, 34.9% and 78% for a cut off value> 0.22.

Conclusion: The clinical predictive parameters of high risk bleeding lesions identified have not yielded a score with significant sensitivity and specificity. A prospective study should be performed to improve the score.

Key-words

Children, haematemesis, gastrointestinal endoscopy, score, predictive factors

Hematemesis is an alarming symptom for patients of all ages [1]. It can cause children and their caretakers to panic. Early diagnosis and treatment of Hematemesis is essential. The aetiologies of Hematemesis in infants and children include numerous causes ranging from benign disorders, which require in main cases little or no treatment, to severe diseases which require immediate intervention [2]. The causes of bleeding could not be ascertained in 11.8 % [3] to 20.5% [2] of the cases because of the delay in performing endoscopy or because causes were frequently benign and got healed up rapidly before being confirmed by endoscopy. Furthermore, even when there is aetiology, the bleeding stopped spontaneously without any need to endoscopic or surgical intervention. Given the above discussion, and since that these procedures are invasive, we conclude that they require intravenous sedation or general aesthesia. It is necessary to mention that they are also associated with significant anxiety for the patient and his family. Since these procedures are not always available in the different hospitals of our country, it is worth asking if the endoscopy is always mandatory when a child presents an Hematemesis.

The present study aimed : 1) to identify clinical parameters that predict the presence of high risk bleeding lesion in children with Hematemesis before they undergo GIE and; 2) to develop a GIE predictive score of high risk bleeding lesions, based on clinical findings in patients.

METHOD

Setting and eligibility

A retrospective cohort study, of 489 children aged between 30 days and less than 18 years, who had undergone GIE, between 1998 and 2006 at the tertiary care hospital of children of Tunis for Hematemesis, was undertaken. To maintain the independence of the endoscopy outcome, it is necessary to mention that in the case of a child had two or more endoscopies performed during the period of the study; only the first endoscopy was considered in the analysis.

Non inclusion criteria

Newborns and patients with hematemesis caused by swallowing caustic agents and foreign bodies were excluded. Children with epistaxis and hemorrhagic bleeding disease were also excluded. Endoscopies were performed by one of the three paediatric gastroenterologists of the children's hospital.

The following variables were investigated and data was retrieved from each patient's hospital chart: age, sex, type of bleeding (hematemesis, melena or both), history of gastro toxic drug intake, underlying disease, rebleeding during the hospitalisation. GIE (Olympus = GIF SP20 and Olympus GIF P30) was performed at different times. We consider emergency cases all GIE that were done within the first 48 hours after the bleeding episode. All patients underwent GIE, after receiving a written consent from their parents.

Definitions

The endoscopy outcomes were classified according to the findings of a high risk bleeding lesions that need treatment, such as: peptic ulcer, erosive gastroduodenitis, peptic oesophagitis upper than grade two and oesophageal or gastric varices. Upper gastrointestinal haemorrhage was defined as hematemesis, and/or melena. The loss of blood was considered low, if the child had vomiting striated with blood; it was considered average if the child vomited blood without consequences, this is to say neither on the level of the haemoglobin nor in the hemodynamic status; and it was considered important, if the child needed blood transfusion or if he had substantial fall in haemoglobin concentration after his admission.

Statistical analysis

First, univariate analysis was performed on variables that were determined subjectively by the investigator to be potentially associated with high risk bleeding lesions. The parameters were age, gender, delay between the onset of bleeding and endoscopy (in hours), emergency (less than 48hours), first bleeding episode, average or important bleeding, type of bleeding (hematemesis alone), history of gastric disease, gastro toxic drug intake and helicobacter pylori infection. All variables with $p<0.2$ at the univariate analysis were included in the multivariate analysis. Age and the delay of realisation of the endoscopy, two continuous variables, were modelled as a dichotomous variable to allow easier interpretation of the model. Categorical variables were presented as proportions and compared using the X2 test or Fischer's exact test. $P<0.05$ was considered statistically significant. Continuous variables were presented as standard deviation mean (SD) or median interquartile range and compared using unpaired Student t -test or the Fisher- Snedecor analysis of parametric variance (ANOVA with one factor). Univariate logistic regression was used to obtain the corresponding odd ratio (OR) and 95% confidence interval (CI) for each predictive variable. Multivariate logistic regression analysis was used to identify independent parameters and was presented with odd ratio and 95% confidential interval. The adequacy of the regression model was tested by the Hosmer- Lemeshow test at a $P<0.05$[4].

The score of the endoscopy realisation was developed from the parameters derived from the multivariate analysis. The final score provided the logit (p) of an endoscopy with high risk bleeding lesions where p represented the probability of a high risk bleeding lesions in the endoscopy. We calculated the risk of high risk bleeding lesions in a child with an UGIB using $P = 1/1+ e - (\text{alpha} +\beta E +\beta 1X1+\beta 2X2+ \ldots +\beta nXn)$. For each predictive model, a scoring system was devised using the regression coefficients of each variable that contributed to the model.

The sensitivity and specificity of each score were determined and expressed in ROC including an estimation of the area (AUC). AUC ≥0.5 indicated that the model predicts a high risk bleeding endoscopic lesions greater than chance alone. Then we chose the cut off value using the receiver operating curve (ROC). Statistical analysis was performed by using SPSS program 11.5.The present study was approved by the ethic committee of Children's Hospital of Tunis.

RESULTS

Epidemiological results

2814 endoscopies were performed during this period: 614 for UGIB, among which 125 were excluded because they were newborns. Finally, 489 were included: 205 infants and 284 children older than three years. The mean age was 54.53 months±50.7 (51.5–216 months).

Endoscopic results

The endoscopy was observed normal in 101 patients. 109 cases of peptic oesophagitis were collected and classified in 52 cases of oesophagitis stage I, and 57cases of oesophagitis up to stage II (34 cases stage II, 20 cases stage III, three cases stage IV). Mallory Weiss tears were reported in 11 patients and oesophageal varices were reported in 10 patients: five girls and five boys with mean age 8.25±54.59 [6–13 years]. The signs of portal hypertension were present in four cases. Two of them had cirrhosis and, three had portal vein thrombosis. Sandostatine® was used to stop bleeding. Band ligation was done in five patients with a delay of one or two months after the episode of bleeding. We identified 250 cases of gastritis, 63 had high risk bleeding lesion (45 erosive and 18 ulcerative gastritis). These lesions were isolated or associated to another one on the digestive tract. We recorded ten cases of peptic ulcer (six gastric, one duodenal and three bulbous). Finally, 140 patients (28.6%) had high risk bleeding lesions.

In the univariate analysis, the risk factors associated to high risk bleeding lesions that attained statistical significance (re-bleeding, mild to important bleeding, bright red hematemesis, history of gastro duodenal and liver disease) were summarized in table 1.

In order to identify the predictive factors linked directly to the event, we had to conduct a multivariable logistic regression analysis with factors having p<0.22 and with the parameters that attained statistical significance in the univariate analysis. Six factors were noticed to be independently associated with high risk bleeding lesions mucosal lesion outcome: emergency endoscopy within 48 hours (EE) (OR=2.2; 95% CI 0.7-6.9), re-bleeding (RB) (OR=1.4; 95% CI 0.7-2.5), the importance of the bleeding, mild to severe (IB) (OR=1.8; 95% CI 1.1-3), bright red hematemesis (BRH) (OR=1; 95% CI 0.2-5.8), history of gastrointestinal and liver disease (HGLD) (OR=1.6; 95% CI 1.1-3) and intake of gastro toxic drugs (IGTD) (OR=1.3; 95% CI 0.8-2.3). Then, we calculated the probability of having a high risk bleeding lesions using the logistic regression equation in presence of some factors (x1, x2 ..., xm) according to this formula

$$P = 1/1+e^{-(\text{alpha} + \beta_1 x_1 + \beta_2 x_2 \ldots + \beta_n x_n)}$$

The variables in this equation are presented in table 3. In this formula: Alpha =0.005-2.108= -2.058. If one of the parameters was present, it was scored 1; if the parameter was absent, it was scored 0. The UGIB high risk bleeding lesions score using the six independent factors was as follow:

$$P = 1/1+e^{-(-2.058 + 0.799\ EE + 0.315\ (RB) + 0.076\ (BRH) + 0.510\ HGLD + 0.303\ (IGTD) + 0.606\ (IB).}$$

Using the receiver operating curve (ROC) (figure 1), a cut off > 0.22 was chosen as the best one for predicting high risk bleeding mucosal lesions P = 0.024 [OR 1.91; 95% CI 1.08 – 3.37]. It corresponded to a sensitivity of 79.6%, a specificity of 32.9% a PPV of 34.9% and a NPV of 78 %. As a conclusion, a patient with a score of 0.22 or more exhibits a high risk of having bleeding lesions.

DISCUSSION

In the population of this investigation, several clinical characteristics were found to be independently predictive of high risk bleeding mucosal lesions for upper gastrointestinal bleeding, such as: re-bleeding, the importance of bleeding, bright red hematemesis, background of gastric and liver diseases, and intake of gastro toxic drugs. These characteristics were retained in the model because of their clinically correlation with significant high risk bleeding mucosal lesions.

The limitations of the study included firstly, its retrospective design. The researcher defined the endpoint after analysing the data. Secondly, the definition of high risk bleeding mucosal lesions is not standardised as it is in adult case; in which high risk of endoscopic stigmata of bleeding were defined to be an adherent clot after irrigation, or a bleeding (oozing or spurting) or non bleeding visible vessel pigmented protuberance [5]. Thirdly, it is believed that laboratory investigations should have been included (anemia, hypoalbuminemia) as it was currently done in previous investigations of adults'cases. The conclusions of this study are limited by the fact that the researcher lacks the information concerning an eventual previous treatment of these children by proton pump inhibitors. An eventual treatment might have confounded the association between the parameters and the high risk bleeding lesions.

We didn't attempt to define a statistically significant model because the sensitivity and specificity were respectively of 79.6 % and 32%. In practice, models with sensitivity of approximately 90% would have been more useful clinically. Nevertheless, it is the first predictive model of endoscopic diagnosis for UGIB in children. It is believed that this model is strong enough as it does not require the near perfect sensitivity needed in adult population, because the risk of missing a gastrointestinal carcinoma or severe complication of GRD is small. Such a model could be used to help determine the necessity of upper endoscopy, avoid unnecessary admission of such patients, and reduce the cost and decrease hospitalisation in areas where endoscopy is unavailable. This score, needs to be evaluated prospectively to assess its effectiveness.

Clinical prediction rules for hematemesis are sparse in children. A predictive model for positive outcomes of upper gastrointestinal endoscopies in children without gastrointestinal disease was proposed by Noble [6]. The parameters that were retained as significant were an older age of 13 years, vomiting and hypoalbuminemia. Two other studies [7, 8] derived a clinical prediction rule that used simple noninvasive tests and showed accuracy for the identification of children who required GIE to characterize their esophageal varices. On the contrary, various scoring systems have been developed in adults (Rockall, Blatchford, Baylor)[9-16], because upper gastrointestinal hemorrhage in adults remains a significant cause of hospital admission with a mortality rate, up to 14%. This list is certainly incomplete because there is a lack of standard nomenclature in articles describing clinical prediction rules [17].

CONCLUSION

Several clinical predictive variables were found positive for high risk bleeding lesions in children who underwent gastrointestinal endoscopy for hematemesis. A score was then calculated from these predictive variables. This predictive model containing these variables was not statistically significant and it has to be improved. It will help to prevent unnecessary admission of such patients and it will reduce cost and exposure of patients to hospital associated hazards.

Références

1. Kalyoncu D, Urganci1 N, Cetinkaya F. Etiology of Upper Gastrointestinal Bleeding in Young Children. Indian J Pediatr 2009; 76): 899-901.
2. Dehghani SM, Haghighat M, Imanieh M H, Tabebordbar MR.Upper Gastrointestinal Bleeding in Children in Southern Iran. Indian J Pediatr 2009; 76 :635-38.
3. Cleveland K, Ahmad N, Bishop P, Nowicki M. Upper gastrointestinal bleeding in children: an 11-year retrospective endoscopic investigation. World J Pediatr 2012; 8: 123-28.
4. Ananth CV, Kleinbaum DG. Regression models for ordinal responses: a review of methods and applications. Int J Epidemiol 1997; 26:1323-33.
5. Romagnuolo J, Barkun AN, Enns R, Armstrong D, Gregor J. Simple clinical predictors may obviate urgent endoscopy in selected patients with nonvariceal upper gastrointestinal tract bleeding. Arch Intern Med 2007; 167:265-70.
6. Noble AJ, Drouin E, Tamblyn R. Design of predictive models for positive outcomes of upper and lower gastrointestinal endoscopies in children and adolescents. J Pediatr Gastroenterol Nutr 2008 ; 46:409-13.
7. Fagundes ED, Ferreira AR, Roquete ML, Penna FJ, Andrade EM , Pimenta Paulo et all Clinical and Laboratory Predictors of Esophageal Varices in Children and Adolescents With Portal Hypertension Syndrome. J Pediatr Gastroenterol Nutr 2008;46:178–83.
8. Gana JC, Turner D, Roberts E A, Ling SC.Derivation of a Clinical Prediction Rule for the Noninvasive Diagnosis of Varices in Children. J Pediatr Gastroenterol Nutr 2010; 50: 188-193.
9. Blatchford O, Murray W, Blatchford M.A risk score to predict need for treatment for uppergastrointestinal Haemorrhage. Lancet 2000; 356: 1318-21.
10. Pongprasobchai S, Nimitvilai S, Chasawat J, Manatsathit S.Upper gastrointestinal bleeding etiology score for predicting variceal and non-variceal bleeding.World J Gastroenterol 2009 ; 15: 1099-104.
11. Tammaro L, Di Paolo MC, Zullo A, et all. Endoscopic findings in patients with upper gastrointestinal bleeding clinically classified into three risk groups prior to endoscopy.World J Gastroenterol 2008 ; 14: 5046-50.
12. Stanley A J, Ashley D, Dalton H R, et al. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation . Lancet 2009; 373: 42–7.
13. Subramanian V, Hawkey CJ.Assessing bleeds clinically:what's the score? Lancet 2009; 373:5-7.
14. Tham T C K, James C, Kelly M. Predicting outcome of acute non-variceal upper gastrointestinal haemorrhage without endoscopy using the clinical Rockall Score. Postgrad Med J 2006; 82:757–59.
15. Chiu PW , Enders KW. Predicting Poor Outcome from Acute Upper Gastrointestinal Hemorrhage.Gastroenterology Clinics of North America 2009; 38: 215-30.
18. 16.Atkinson RJ, Hurlstone DP. Usefulness of prognostic indices in upper gastrointestinal bleeding. Best Pract Res Clin Gastroenterol. 2008; 2:233-42.
19. Ingui BJ, M. Rogers M A. Searching for Clinical Prediction Rules in MEDLINE. Am Med Inform Assoc 2001; 8:391–7.