

高雄醫學大學附設醫院實證醫學臨床問題分析

科別: 小港肝膽內	Chart No: 01389241	入院日期: 97.04.23
報告者: 劉丁元 u9200003	職級: <input type="checkbox"/> Resident <input type="checkbox"/> PGY1 <input checked="" type="checkbox"/> Intern <input type="checkbox"/> Clerk	完成日: 97.05.12
個案病歷摘要		
<p>This 66-year-old woman has been a patient of:</p> <ol style="list-style-type: none"> 1. Liver cirrhosis, hepatitis C related 2. Esophageal varices bleeding episodes, multiple post ligation <i>Multiple episodes of variceal bleedings, 8x ligation</i> 3. Gastric ulcer 4. diabetes mellitus <p>She followed in our HB OPD with medical control regularly. She had history of esophageal varices bleeding several times. Her last hospitalization was during 2007/12/31 to 2008/1/11 due to esophageal varices bleeding. This time, she was brought to our emergency department this afternoon(4/23) due to tarry stool. According to her family, intermittent tarry stool found about 3 days prior to admission. Associated symptoms included mild epigastric abdominal pain (+), dizziness(+), fever(-), chills(-), coffee ground(-), hematemesis(-), hunger pain(-), post-prandial pain(-), nausea(-) vomiting(-), body weight loss(-). In our ER, her consciousness was alert and oriented. On physical examination, her vital sign was within normal limits. NG irrigation showed fresh blood. Emergent EGD was performed and EV bleeding was noted, then ligation was done. However, conscious loss was noted during EGD process. Blood pressure dropped gradually. Central venous catheter insertion and blood transfusion were done. Due to above problems, she was admitted for further treatment.</p>		
提出可回答的臨床問題(Asking)		
<p>本病人已經有三次因為 esophageal varices bleeding 而入院緊急處理治療，目前要完全治癒 EV bleeding，Liver transplantation 是唯一的方法。但病人年紀已經 66 歲並且有糖尿病多年，liver transplantation 似乎並不適合本病人。所以如何防止 recurrent bleeding 對她而言是最重要的課題。</p> <p>目前計劃每隔 1~2 星期就住院做 endoscopic ligation therapy 來 prevention esophageal varices bleeding。這個方法和其他方法(sclerotherapy, beta blockers, oral nitrates, TIPS)比較起來，在降低 recurrent bleeding 方面而言是否是目前最佳的方法?實證醫學方面的證據為何?</p>		
Patient : recurrent esophageal varices bleeding、Liver cirrhosis Child A		
Intervention : endoscopic variceal ligation		
Comparison : endoscopic sclerotherapy, beta blockers and oral nitrates, transjugular intrahepatic portosystemic shunt(TIPS) or combination therapy		
Outcome : <u>reduction</u> rebleeding <i>rate</i>		
搜尋最有用的資料(Acquire)		
關鍵字(Key word) : recurrent variceal bleeding, variceal rebleeding, prevention, liver cirrhosis <i>Variceal</i>		
資料來源(Database) : 1. 經過整理的文獻: Cochrane Library 、 ACP Journal club 、 EBMR 、 UptoDate		

2. Guideline : National Guideline Clearinghouse

主要內容：

謹慎的文獻評讀 (Appraisal)

文獻等級：

Worksheet：

Databases	Return	level
ACP Journal Club	1	Level I Randomized controlled trial
Cochrane Library	1	Level I Randomised clinical trials
Cochrane Central Register of Controlled Trials	3	Level I Randomised clinical trials
National Guideline Clearinghouse	1	

National Guideline Clearinghouse

Patients with Cirrhosis Who Have Recovered from Acute Variceal Hemorrhage

1. Patients with cirrhosis who survive an episode of active variceal hemorrhage should receive therapy to prevent recurrence of variceal hemorrhage
2. Combination of nonselective beta-blockers plus EVL is the best option for secondary prophylaxis of variceal Hemorrhage
3. TIPS should be considered in patients who are Child A or B who experience recurrent variceal hemorrhage despite combination pharmacological and endoscopic therapy

ACP Journal Club

Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. N Engl J Med. 2001 Aug 30;345:647-55 , Villanueva C, Miñana J, Ortiz J, et al.

Design

Randomized controlled trial with mean follow-up of 24 months.

Patients

144 patients (mean age 59 y, 63% men) who had cirrhosis, were hospitalized for esophageal variceal bleeding, and had emergency endoscopy. Exclusion criteria included < 18 years of age, poor hepatic function, advanced hepatocellular carcinoma, and life expectancy ≤6 months. All patients were included in the analysis with 9 patients censored at the time of the last visit.

Intervention

72 patients were allocated to combined medication with nadolol, 80 mg orally once daily, adjusted over 5 days to reduce the resting heart rate by 25% (but not lower than 55 beats/min), and oral isosorbide mononitrate, progressively increased over 1 week from 20 mg once daily at bedtime to 40 mg twice/d or to the maximal tolerated dose. 72 patients were allocated to endoscopic ligation with a single band with an overtube or a multiband device done after randomization, on day 7, and

every 2 to 3 weeks until the varices were eradicated. Follow-up endoscopy was done at 3 months after eradication and every 6 months thereafter, and additional sessions of ligation were done, if required. In both groups, sclerotherapy or somatostatin, or both, were used for endoscopic control of acute hemorrhage during the index or recurrent bleeds.

Main results

Analysis was by intention to treat and used Kaplan-Meier survival curves. The cumulative risk for recurrent bleeding was of borderline statistical significance between groups ($P = 0.04$). The cumulative risk for recurrent variceal bleeding was lower in the combined medication group than in the ligation group. Fewer severe treatment-related complications occurred in the combined medication group than in the ligation group (3% vs 12%, $P = 0.05$), but groups did not differ for occurrence of overall complications ($P = 0.71$). Groups did not differ for cumulative risk for death.

Conclusion

In patients with cirrhosis hospitalized for esophageal variceal bleeding, treatment with nadolol and isosorbide mononitrate prevented recurrent variceal bleeding more effectively than did endoscopic ligation.

可取数据做meta分析 MNT
 别说是发表在 NEJM, 仍应对其 validity 做判断, 可取数据做 meta-analysis
 的 Guide 选项判断. (RAAMBO)

Cochrane Library

Portosystemic shunts versus endoscopic therapy for variceal rebleeding in patients with cirrhosis

S Khan, C Tudur Smith, P Williamson, R Sutton; *Cochrane Database of Systematic Reviews* 2008 Issue

Selection criteria

Randomised clinical trials comparing TS, DSRS or TIPS with ET in patients who had recovered from a variceal haemorrhage and were known to be cirrhotic

Main results

Twenty-two trials evaluating 1409 patients were included. All trials had problems of method. Shunt therapy compared with ET demonstrated significantly less rebleeding (OR 0.24, 95% CI 0.18 to 0.30) at the cost of significantly increased acute hepatic encephalopathy (OR 2.07, 95% CI 1.59 to 2.69) and chronic encephalopathy (OR 2.09, 95% CI 1.20 to 3.62). There were no significant differences regarding mortality (hazard ratio 1.00, 95% CI 0.82 to 1.21) and duration of in-patient stay (weighed mean difference 0.78 day, 95% CI -1.48 to 3.05). The proportion of patients with shunt occlusion or dysfunction was 3.1% (95% CI 0.4 to 10.7%) following TS (two trials), 7.8% (95% CI 3.8 to 13.9%) following DSRS (four trials), and 59% (range 18% to 72%) following TIPS (14 trials).

Authors' conclusions

All shunts resulted in a significantly lower rebleeding rate at the expense of a higher incidence of encephalopathy. TIPS was complicated by a high incidence of shunt dysfunction. No survival advantage was demonstrated with any shunt.

Cochrane Central Register of Controlled Trials

Variceal band ligation and variceal band ligation plus sclerotherapy in the prevention of recurrent variceal bleeding in cirrhotic patients: a randomized, prospective and controlled trial.

Gastrointestinal Endoscopy. 51(2):157-63, 2000 Feb. Argonz J, Kravetz D, Suarez A, Romero G, Bildoza M,

METHODS: Eighty cirrhotic patients were randomized to group I (band ligation) with 41 patients or to group II (band ligation plus sclerotherapy) with 39 patients in whom polidocanol (2%) was injected 1 to 2 cm proximal to each band.

RESULTS: At baseline, both groups were similar with regard to clinical, demographic and laboratory data. Mean follow-up time (standard error) for group I was 336.5 +/- 43.4 days and for group II 386.1 +/- 40.1 days ($p = 0.4$). No statistical differences were observed between group I and group II in relation to recurrence of bleeding (31.7% vs. 23%, $p = 0.38$), treatment failure (24.4% vs. 12.8%, $p = 0.18$), death (39% vs. 30.8%, $p = 0.44$) and variceal eradication (65.8% vs. 74.4%, $p = 0.40$). Group II had a significantly higher number of complications than group I, 30.8% versus 7.3%, respectively ($p = 0.05$). The number of bleeding related deaths was higher in group I than in group II (22% vs. 10.3%, respectively; $p = 0.15$).

CONCLUSIONS: No significant difference was observed between band ligation and band ligation plus sclerotherapy in prevention of recurrent variceal bleeding. Furthermore, there was a higher incidence of complications in the latter group

Randomised trial of transjugular-intrahepatic-portosystemic shunt versus endoscopy plus propranolol for prevention of variceal rebleeding. [Clinical Trial. Journal Article. Randomized Controlled Trial] *Lancet*. 349(9058):1043-9, 1997 Apr 12.

METHODS: Between March, 1993, and March, 1996, 126 patients with variceal bleeding were randomly assigned either transjugular shunt ($n = 61$) or endoscopic treatment ($n = 65$). Patients were followed up for a median of 14 (IQR 8-25) months and 13 (8-25) months, respectively. In 31 (51%) of the shunted patients, simultaneous transjugular-variceal embolisation was done at the time of shunt placement. Endoscopic treatment consisted of sclerotherapy and/or banding ligation and was combined with propranolol medication

FINDINGS: Technical success was achieved in all patients assigned to the shunt group. During follow-up, the cumulative 1-year variceal rebleeding rates in the shunted and endoscopically treated patients were 15% and 41% and the 2-year rates were 21% and 52% ($p = 0.001$), respectively. In nine (12%) patients from the endoscopic group treatment failed and the patients received the transjugular-shunt treatment. A total of 19 bleeding episodes from any source occurred in 15 patients in the shunt group compared with 100 episodes in 33 patients in the endoscopic group. There was no difference in survival with estimated 1-year survival rates for shunted and endoscopically treated patients of 90% and 89%, and 2-year survival rates of 79% and 82%, respectively. The incidence of clinically significant hepatic encephalopathy after 1 year was higher in the shunt group (36% vs 18%, $p = 0.011$).

INTERPRETATION: These results suggest, that the transjugular shunt is more effective than endoscopic treatment in prevention of variceal rebleeding but has a considerable risk of hepatic encephalopathy. Survival is similar in the two groups.

Isosorbide mononitrate and propranolol compared with propranolol alone for the prevention of variceal rebleeding. *Hepatology*. 31(6):1239-45, 2000 Jun.

Abstract :

The aim of this study was to test the effectiveness of isosorbide-5-mononitrate (IM) as an adjunct to propranolol (PR) in the prevention of variceal rebleeding. Ninety-five cirrhotic patients with variceal bleeding were randomly assigned to treatment with PR + IM (46 patients) or PR alone (49 patients). Eighteen patients in the PR + IM group and 28 in the PR group had rebleeding during the 2 years after randomization. The actuarial probability of rebleeding 2 years after randomization was lower in the PR + IM group (40.4% vs. 57.4%) but the difference was not significant ($P = .09$). However, the decrease in the risk of rebleeding reached statistical significance after stratification according to age, i.e. less than 50 versus ≥ 50 years old, ($P = .03$) or by adding an additional year of follow-up ($P = .05$). No significant difference was found in rebleeding index and survival. The multivariate Cox analysis indicated first, that both treatment ($P = .03$) and age ($P = .001$) were factors predictive of rebleeding and second, that PR + MI reduced the risk of rebleeding by half (relative risk: 0.51, 95% confidence interval: 0.28-0.95). Seven patients in the PR + MI group and 1 patient in the PR group had to discontinue one of the drugs because of adverse events ($P = .03$). These results suggest that the addition of IM improves the efficacy of PR alone in the prevention of variceal rebleeding in cirrhotic patients. However no beneficial effects were observed on other parameters reflecting the efficacy of treatment.

original article 還是看你 RAAMBO 傳新做
譯譯

是否可應用到此臨床個案上 (Apply)

文獻評讀結論

1. 作 transjugular-intrahepatic-portosystemic shunt (TIPS) 比 endoscopic ligation 在預防 EV rebleeding 更有效，但容易造成 hepatic encephalopathy 而對 survival 也沒有幫助。所以似乎不是第一選擇的方法。
2. 使用 endoscopic ligation 併用 beta blocker (nadolol) 和 nitrate (isosorbide mononitrate) 比單獨使用 endoscopic ligation 更能有效預防 rebleeding，而加上 nitrate 更可以增加 beta blocker 的效果。
3. Band ligation + sclerotherapy 和單獨使用 band ligation 在 prevention of rebleeding 兩者是差不多的，但 Band ligation + sclerotherapy 的方法更容易發生 esophageal stricture 等的 complication。
4. 由目前找的 paper 和 guideline 來看，除非有對於使用 nonselective beta-blockers 和 nitrate 的 contraindication (例如 hemodynamic unstable 病人)，對於防止 esophageal varices 再次出血，Combination of nonselective beta-blockers +/- nitrate and endoscopic ligation 是目前最佳的預防方法，當這個治療方法沒有效時再考慮作 Transjugular-intrahepatic-portosystemic shunt (TIPS)。
5. 除此之外我們也應該教育病人日常生活注意事項以預防 EV bleeding：
 - (1) 採軟質飲食，勿食用過硬、粗糙、過熱及刺激性食物，以免刺激曲張之靜脈而破裂出血。
 - (2) 保持規律的生活及情緒穩定。
 - (3) 勿用力排便，避免咳嗽及舉重物。
 - (4) 注意出血徵兆如：臉色蒼白、呼吸急促、心跳加快、解黑便及嘔血，應立即到醫院求治
 - (5) 依醫囑按時服藥，定期門診追蹤。

自我評估改善 (Audit)

- 經過文獻評讀之後得到對本臨床問題的解答，並提供臨床處置的證據基礎。
- 目前仍有一些 review 的 papers 仍是在 protocol 階段而尚未有相關的結論例如 “Beta-blocker plus nitrates for secondary prevention of variceal bleeding”

“Beta-blockers alone or with endoscopic therapy for prevention of variceal rebleeding in portal hypertension”

“Beta-blockers for prevention of oesophageal variceal rebleeding in cirrhotic patients”

所以未來仍必須追蹤後續的比較結果。

- 在搜尋過程中亦出現其他相關議題，包括如尚未發生 gastroesophageal varices 的 Liver cirrhosis 病人如何避免 EV、GV 或 portal hypertension 的發生之文獻，未來同樣可利用 EBM 模式進行這些重要議題的研讀。

教師(各科窗口)批註及簽名:

- ① 治療效果的文獻以 RCT 及 systematic review of RCT 為最佳證據，但仍需做嚴格的評讀，以確定證據的品質
- ② 治療效果應以 NNT 呈現。

李智雄



可諮詢之人員或單位：實證醫學中心(5380)及其各委員(委員名單詳見 EBM 中心網頁)
實證醫學中心網址：<http://www.kmuh.org.tw/www/ebm/index.htm>