Review Article

Critical Care Management for Upper Gastrointestinal Bleeding

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INTRODUCTION

Despite massive revolution in medical technology and decreasing in the incidence, upper gastrointestinal bleeding (UGIB) is still the leading cause of mortality in emergency patients[1,2]. This may be accounted to an increasing age of patients with UGIB and the presence of severe life-threatening co-morbidity[2]. Prompt resuscitation and endoscopic therapy are the main armamentariums to safe these patients. It has been shown that an early intensive resuscitation of patients with UGIB significantly decreases mortality and myocardial infarction rates[3]. Team approach is the mainstay for a successful management of UGIB. Therefore, apart from the role of endoscopist this review will focus on the role of other physicians in the team regarding early intensive resuscitation and medical management during pre and post endoscopy.

Objectives in UGIB management

To minimize the rate of recurrent bleeding is the primary goal for UGIB management. In standard practice the rebleeding rate is reported to be around 10-20%[2,4,5]. Therefore, after primary hemostasis is achieved, maintaining coagulum to prevent rebleeding is important. Currently, pharmacologic agents have become a standard of care and are recommended in many guidelines[6,7]. Standard agents for non variceal bleeders are intravenous proton pump inhibitors whereas somatostatin, vasopressin and their derivatives are the key to control acute and recurrent bleeding in portal hypertensive patients. Another factor to be considered in limited resources unit is cost effective bleeding treatment strategy. Lastly, treatment related complications can be minimized by using less invasive method especially in the management of elderly patient with high risk.

Risk stratification

Not all patients with UGIB require intensive care admission and even some can wait for elective endoscopy (especially the next day). In contrast, early endoscopy in high risk patients is mandatory. In has been shown that early endoscopy in selected patient is associated with reduction in length of hospital stay, risk of recurrent bleeding and possibly surgery[8]. Earlier, we reported the results of emergency gastroscopy in UGIB as; initial hemostasis was achieved in 91.2 percent of the patients; recurrent bleeding within 72 hours developed in 9.1 percent of patients; 2.0 percent of patients (2/99) had to go for emergency surgery after failed therapeutic endoscopy; and overall mortality was 15.2 percent[5]. Theoretically, intensive care monitoring is usually required in all high risk patients and high risk endoscopic findings. However, for practical purpose, clinical criteria are preferred over endoscopic criteria to categorize patients into high risk group since patients must often be triaged before endoscopy. Increased risks of rebleeding and death have been reported to be associated with age older than 60 years; shock; blood per rectum; bright red blood hematemesis or blood via nasogastric tube; poor over all health status; multiple co-morbid illnesses; bleeding during hospitalization; low initial hemoglobin level; sepsis; liver or kidney failure; unstable hemodynamic status and portal hypertension[9,10]. To date, there are many helpful scoring systems to be used for UGIB risk stratification including Rockall and Blatchford score[11,12]. In

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Thailand, a group from Chulalongkorn University constructed a risk scoring system in UGIB patients and found that concurrent illnesses, heart rate above 110 beat/min and blood transfusion over 6 units were associated with poor outcome including major rebleeding, the need for emergency surgery to control bleeding and hospital death. The accuracy of the test was 82.5 percent. The positive and negative predictive values were 46.3 percent and 92.7 percent respectively with the likelihood ratio of 4.5[13].

Initial work-up and management

Insufficient early resuscitation is believed to be the main factor for a persistently high mortality rate in UGIB patients. Baradarian *et al*. reported that with adequate fluid and blood replacement to maintain stable hemodynamic status and correction of coagulopathy, the risk for myocardial infarction and mortality rate can be reduced significantly[14]. Generally, the basic requirements for clotting mechanism are platelet count and prothrombin time. The American Society of Gastrointestinal Endoscopy (ASGE) advised to have prothrombin time with international ratio (INR) to be less than 1.4 and over 50,000 /cc of platelet count, before therapeutic endoscopy can be started[15]. Wolf et al. demonstrated that the optimal INR that yield the lowest probability of rebleeding after therapeutic endoscopy in UGIB was an INR less than 1.4 (Figure 1)[16]. Hui *et al*. reported that the risk of bleeding in poorly coagulated patient who underwent colonoscopic polypectomy was significantly increased with an Odd ratio of 13.37[17]. The recommended timing for discontinuation of drugs in patients with anti-platelet or anti-coagulant before elective endoscopy are; 1) two hours for intravenous standard heparin 2) eight hours for low molecular weight heparin 3) at least seven to ten days of clopidogreal and ticlopidine and 4) no need for discontinuation of aspirin, non-steroidal agents and dipyridamole. However, it is advisable to discontinue these drugs in every patient who has no strong indication to use and usually this can be checked by weighing between the risk of an acute cardiovascular event against the risk of continued bleeding[18]. Practically, UGIB patient who required urgent endoscopy may not have enough time to wait until the effect of anti-platelet or anticoagulant disappearing from the system. Therefore, prompt correction with concentrated platelet or protamine sulfate or vitamin K or fresh frozen is necessary in the emergency setting.

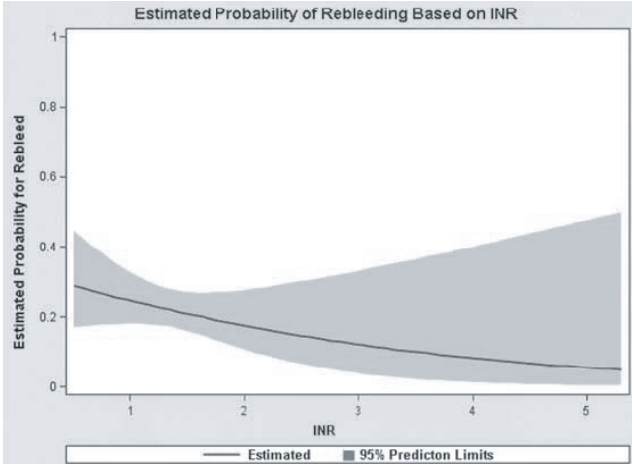

Figure 1. Demonstrating the optimal prothrombin time (INR) for therapeutic endoscopy in UGIB. *(Copied from Wolf et al. Am J Gastroenterol 2007;102:290-96)*

Pre-endoscopic medications

It has been well accepted to provide agent that reduced portal pressure prior to endoscopic therapy in patient with acute variceal bleeding. Randomised clinical trials comparing sclerotherapy with vasoactive treatments including vasopressin (plus minus nitroglycerin), terlipressin, somatostatin, and octreotide showed no difference in the rates of failure to control bleeding; five-day failure rate; rebleeding; rebleeding before other elective treatments; mortality; mortality before other elective treatments; and volume of blood replacement[19]. In contrast, there were more serious adverse events in the sclerotherapy group[19]. In standard practice, these agents can control bleeding in 80% of the patients with variceal bleeding[20]. In addition to control bleeding, terlipressin has been shown to protect kidney from impending hepatorenal syndrome as well[21]. However, due to limited number of patients in many recent studies, there was no statistically significant different in efficacy was demonstrated among terlipressin and other agents including somatostatin and its analogue[22]. In a standard practice, giving agents to reduce portal pressure is recommended in variceal bleeding especially when therapeutic endoscopy is not promptly available.

Apart from prevent the risk of bacterial infection in cirrhosis with UGIB, more recent studies have shown the reduction in recurrent bleeding rate can be facilitate by giving antibiotic in cirrhotic patient who presened with UGIB[23,24]. Hou et al showed that the ac-

tuarial probability of rebleeding was significantly higher in patients without prophylactic antibiotics[23]. The difference of rebleeding was mostly due to early rebleeding within 7 days (4/12 vs 21/27, $p = 0.0221$)[23]. Moreover, units of blood transfusion for rebleeding was also lower in the patients who received antibiotics (1.40 ± 0.89 vs 2.81 ± 2.29 units, $p < 0.05$)[23]. Bacterial endotoxin and infection induced impairment of hemostasis may have played role for the risk of variceal rupture. Until recently, there was no role of pre-endoscopic pharmacologic agents in non variceal bleeding. There has been very little evidence in the recent past in the setting of randomised, controlled, clinical trials for somatostatin and its analoques for non variceal bleeding[24-27]. However, results were discordant. At this moment it is difficult to conclude on the benefit of these agents for non variceal bleeders. Many anecdotal series reported on the benefit of oral and intravenous proton pump inhibitors in term of decreasing transfusion requirement, reducing the rate of rebleeding and possible less number of re-endoscopy[27-29]. However, the database systemic review showed only the benefit in reduction of the proportion of patients with stigmata of recent hemorrhage at index endoscopy. However, there is no evidence that PPI treatment affects clinically important outcomes, namely mortality, rebleeding or need for surgery[30]. Moreover, only one trial in this systemic review used high dose proton pump inhibitor whereas the other four trials use either oral or around the clock dose of intravenous proton pump inhibitors. Recently, a large trial from Hong Kong reported on the success of high-dose omeprazole infusion before endoscopy to accelerate the resolution of signs of bleeding in ulcers and to reduce the need for endoscopic therapy. They found that the bleeding stigmata that requiring endoscopic treatment including active bleeding, non bleeding visible vessel, and clot with visible vessel were less in the omeprazole group than control (19% vs 28%, $p < 0.007$) (Figure 2). In addition, they demonstrated that the hospital stay was less than 3 days in 60.5% of patients in the omeprazole group, as compared with 49.2% in the placebo group ($p = 0.005$)[31]. The neutral gastric pH may have played role for the stability of clots over bleeding arteries. Bruuner et al., demonstrated that continuous infusion of pantoprazole (8 mg/h) after 80 mg bolus was the only dose that can maintain neutral gastric pH (Figure 3).[32]

To apply this concept for all UGIB patients is still controversial due to the high cost of medication that given in high dose. Therefore, it is recommended to use only in patient who may have a high chance of stigmata that requiring endotherapy such as patient with frank hematemesis or heavy melena. However, in the setting of prompt endoscopy is available, an early endoscopy may be the best option since intravenous proton pump inhibitors may not have enough time to take full effect. In addition, if the key to success for UGIB treatment is "the lowest rate of rebleeding", the Hong Kong study did not demonstrate the difference in recurrent bleeding rate between patients in placebo group who underwent endoscopic therapy and patients in omeprazole group.[31]

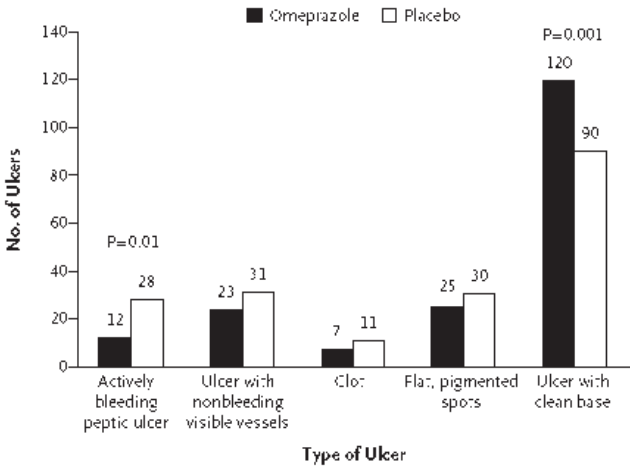

Figure 2. Demonstrating the stigmata of bleeding in patients with high dose omeprazole and placebo. *(Copied from Lau JY et al. N Engl J Med 2007;356:1631-40)*

Airway management, gastric lavage, and sedation in UGIB endoscopy

Blood aspiration may cause pneumonia that lead

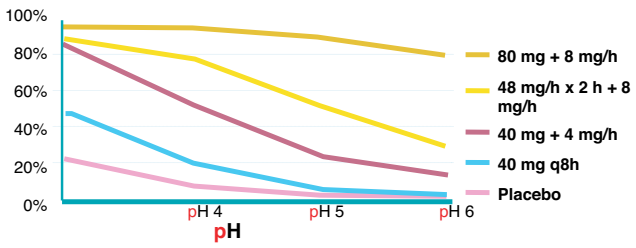

Figure 3. Median time for neutral gastric pH at different dose of intravenous pantoprazole. *(Modified from Brunner et al. Yale J Biol Med 1996;69:225)*

to significant morbidity during emergency endoscopy for severe UGIB. A group from Minneapolis reported on their results of routine endotracheal intubation in UGIB patients with hematemesis, altered mentation, unstable cardiopulmonary status, or large amounts of blood in the proximal GI tract, or before endoscopic treatment of lesions at high risk for bleeding. Surprisingly, endotracheal intubation did not significantly change the relatively high frequency of acquired pneumonia or cardiopulmonary events. However, it may prevent the rare fatal episode of massive aspiration. Another study from Bermingham and Alabama, they performed elective intubation in variceal bleeding patients who were encephalopathic and found that pulmonary infiltrates developed in 7 of 42 electively intubated aptients (17%), with an overall mortality rate of 9 of 42 (21%) whereas 20 patients without intubation did not develop pulmonary infiltrates, and the overall mortality rate was 1 in 20 (5%)[34]. We may conclude that intubation is not a routine procedure but may be of benefit in massive bleeder.

Currently, the real benefit of gastric lavage has been challenged by modern endoscope with good irrigation system. However, many experts still prefer to perform nasogastric intubation for gastric lavage because of many reasons such as for improving visualization at endoscopy, for optimal timing of endoscopy (urgent versus semielective), for prioritizing the order of endoscopy (upper endoscopy versus colonoscopy), and for avoiding or deferring endoscopy in low-yield situations (e.g., colonoscopy when the NG aspirate is bloody). In patients with increased risk for endoscopy including patient after recent myocardial infarction (MI) prioritizing timing for endoscopy is very important. A study in recent MI patients who presented with UGIB reported that the stigmata of recent bleeding from upper endoscopy were found more in MI patients with positive for blood via NG tube. Also colonoscopy yielded a significant number of positive lesions in patients with clear NG tube content[35]. In addition to gastric lavage to clear the visual field during endoscopy, giving prokinetic agent especially intravenous erythromycin may improve the quality of endoscopy. Coffin B *et al*., from France reported on their success of the use of intravenous erythromycin (3 mg/kg). They demonstrated that patients who received erythromycin had a better quality picture from upper endoscopy ($p = 0.02$) and required less number of second endoscopy significantly ($p = 0.089$)[36].

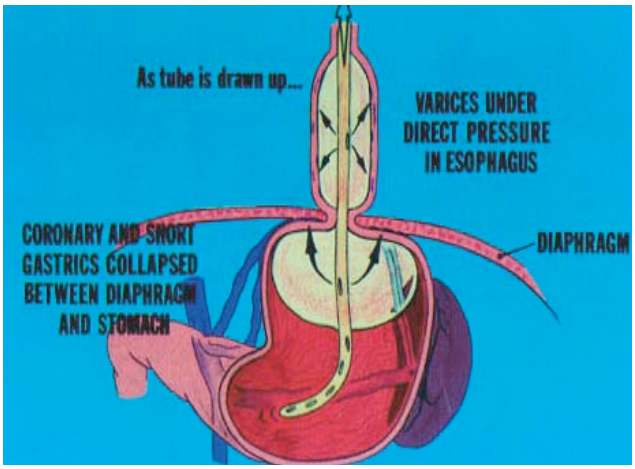

Figure 4. Sengstaken-Blakemore tube placement and its balloons. *(Modified from the American Gastroenterological Association teaching slide)*

Many patients with UGIB are still alert and awake and sedation is needed before performing endoscopy. Practically, the standard conventional agents like combination of midazolam and meperidine or fentanyl can still be given with good safety profile. However, dose reduction may be required in patients who are hypotensive or subject to desaturtion. Recently, propofol has been used widely for general endoscopy due to its short action and quick recovery period. It may be possible that propofol can be given to UIGB patients. In a study from Japan, even though the reported rates of hypotension (systolic blood pressure < 90 mmHg) and hypoxemia (peripheral oxygen saturation < 90%) in patients with gastrointestinal bleeding who had propofol sedation was higher than those in the patients who had elective endoscopy under propofol (8.3% vs 6.7%). However, neither mask ventilation nor endotracheal intubation was required[37].

In the setting where endoscopy is not promptly available for variceal bleeding or post endoscopy failure, the balloon tamponade (Sengstaken-Blakemore tube) plays an important part in the management of this problem along with pharmacologic agents (Figure 4). However, careful attention must be used while placing the balloon since esophageal perforation which is a severe disaster may occur if misplacing of the balloon occurs[38,39]. It has to be noted that this balloon is used as only a temporary measure to control bleeding before a definitive treatment. Prolonged placement of the balloon more than 48 hours may increase the chance of esophageal ulcer and ischemia.

Post endoscopic care

Triage of patients with UGIB for possible intensive care unit admission is recommended in high risk individual and high risk bleeding stigmata. However in the real life practice, only patient with high chance of rebleeding with co-morbid illness is eligible for the ICU admission. Patient with low risk after optimal endotherapy and patient with low risk of rebleeding stigmata can be admitted in general floor or in some certain cases, patients can be discharged home. A study from the University of Florida showed that patients with high APACHE II score, active bleeding, end-organ dysfunction, and hepatic cirrhosis are independent predictors of poor outcome. These patients should be admitted in ICU or at least requiring intensive monitoring[40].

Post endoscopic intravenous proton pump inhibitor has been established in a standard UGIB management protocol for many years. In a large systemic review[41] included 24 RCTs and 4,373 patients with

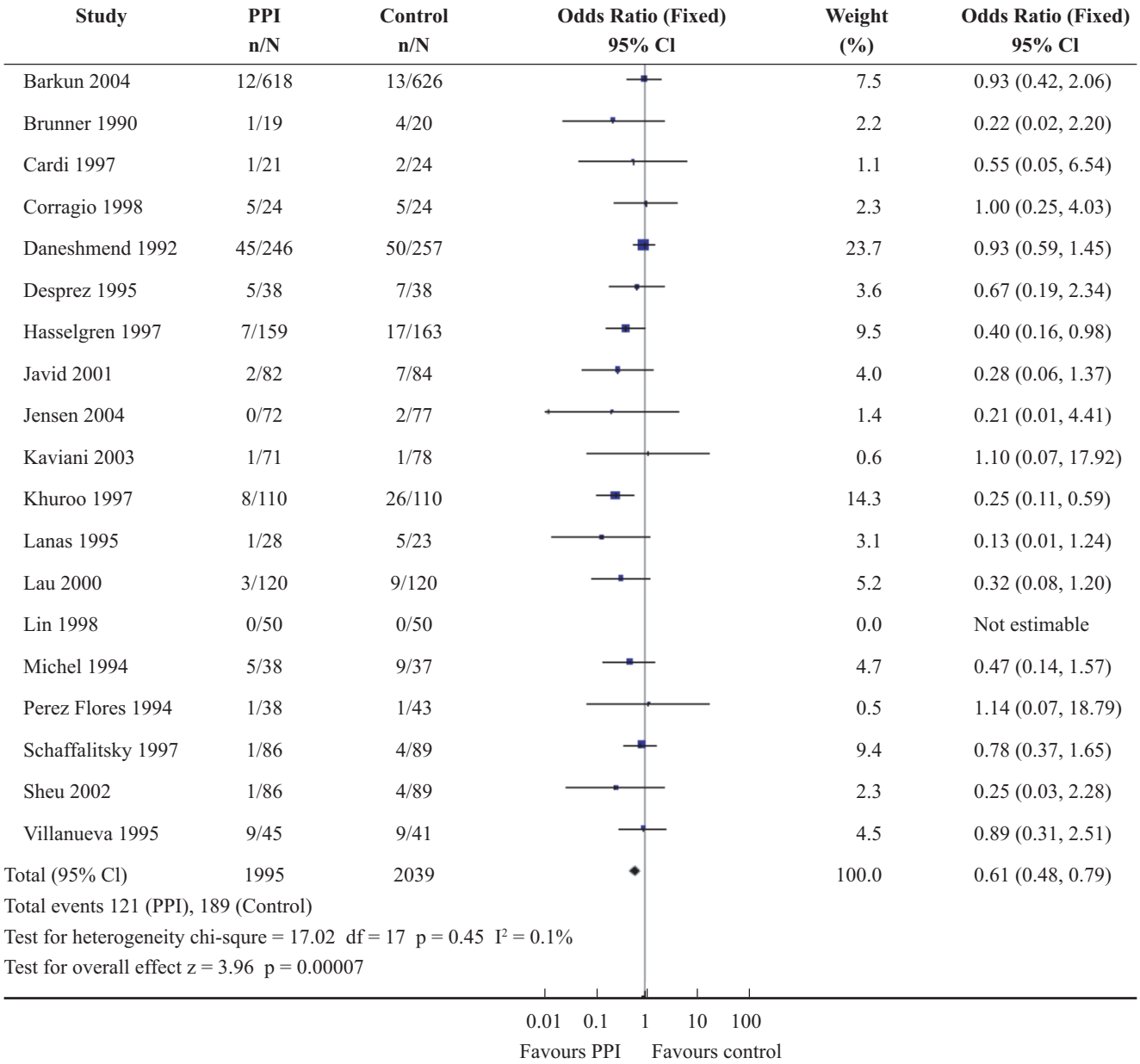

Figure 5. Analysis of rebleeding rates in patients with and without proton pump inhibitors. *(Copied from Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. Cochrane Database Syst Rev 2006:25;(1):CD002094.)*

UGIB, they analyzed and found that proton pump inhibitors significantly reduced rebleeding compared to control; pooled rates were 10.6% with proton pump inhibitors versus 17.3% with control treatment (OR 0.49; 95% CI 0.37 to 0.65) (Figure 5). In addition, proton pump inhibitors treatment significantly reduced surgery compared with control; pooled rates were 6.1% on proton pump inhibitors versus 9.3% on control (OR 0.61; 95% CI 0.48 to 0.78) (Figure 6). However, the mortality rates were not different. Of note, the routes and dosages of proton pump inhibitors were different and only 6 RCTs used a high dose regimen (80 mg intravenous bolus of either omeprazole or pantoprazole then followed by 8 mg per hour for 3 days). It is advisable that high dose regimen is preferred over others. Interestingly, this review also showed that proton pump inhibitors seem to be more effective in Asian population. Perhaps, majority of Asians contain high

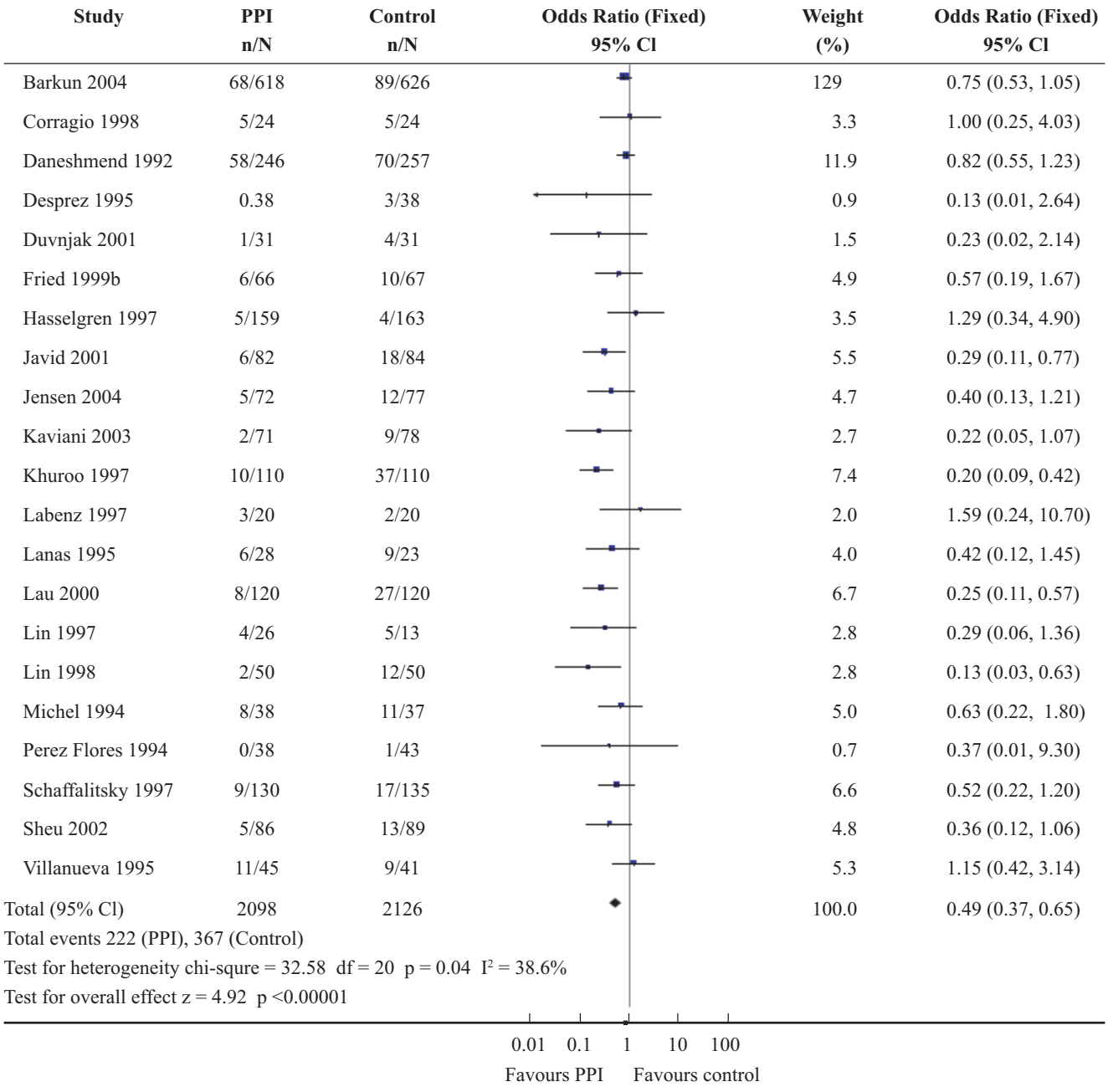

Figure 6. Analysis of surgery rates in patients with and without proton pump inhibitors. *(Copied from Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. Cochrane Database Syst Rev 2006 :25;(1):CD002094.)*

frequency of CYP2C19 polymorphisms which is the cause for slow proton pump inhibitors metabolism[42].

CONCLUSION

Management of UGIB is a team approach. Even endoscopy and endotherapy play a major role in diagnosing and treating this condition. However, pre-endoscopic and post-endoscopic cares are very important. Triage patients according to their risk and predictive stigmata of bleeding help to identify individual in which urgent endoscopy will provide the most benefit. Pre-endoscopic resuscitation, gastric lavage and airway management have to be in consideration in massive bleeders. Pharmacologic agents including portal pressure reducing agents and proton pump inhibitors to be given before and after endoscopy can reduce the number of patients in whom endotherapy is required. In addition, these agents are also important factors for minimizing the rate of rebleeding.

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