Prevalence of Re-bleeding after Initial Endoscopic Management in Peptic Ulcer: A Systematic Review and Meta-Analysis


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Abstract

Peptic ulcer disease has been the most common source of bleeding diagnosed among patients admitted to a hospital for acute upper gastrointestinal bleeding. Patients presenting with a perforated peptic ulcer is another severe complication of peptic ulcer requiring hospitalization. For that, we performed an extensive literature search in 11 databases for all relevant original publications assessing the risk of re-bleeding following endoscopic hemostasis of bleeding peptic ulcer during the last ten years. There were no restrictions on study design, country or language. After extensive screening, three independent reviewers evaluated the risk of bias in included studies. For observational studies, methodological quality assessment was done using National Institutes of Health (NIH) quality assessment tool, while Cochran’s tool was used for randomized controlled trials. R software version 3.6.1 was used to conduct the analyses. Six studies with 3043 patients were included in the analysis. The overall re-bleeding was 8.94% with 95% CI = 5.46 to 14.64; nevertheless, a significant heterogeneity among results $I^2 = 92\%$ and P-value < 0.001 was detected. On sensitivity analysis with removal, the heterogenous studies, the heterogeneity has disappeared ($I^2 = 4\%$ and P-value = 0.372) and the prevalence rate changed to be 6.84% with 95% CI = 5.97 to 7.85. The endoscopic management of bleeding peptic ulcers sounds to be a very effective method with low re-bleeding rates.

Keywords: Peptic Ulcer; Re-Bleeding; Endoscopy; Hemostasis

Introduction

A peptic ulcer usually defined as a mucosal break in the stomach or duodenum and has a diameter of more than 3 mm (some argue for a 5 mm) and a noticeable width [1]. Histologically, the concept of an ulcer is a breach through the mucosa muscularis [2]. If it splits only through the lamina propria mucosae, or if it is wider than 3-5 mm, it is considered erosion instead [2]. Peptic ulcer risks include leakage, perforation, entry (to another organ) and obstruction (from strictures) [3]. Bleeding from peptic ulcer occurs when an underlying vessel

is eroded by an ulcer [4]. A peptic ulcer’s perforation or invasion means the entire stomach and duodenum wall is damaged [4]. Fibrotic strictures, complicated by an obstruction, would mainly affect the pyloric region; caused by chronic inflammation and ulceration [5].

Over recent years, the average prevalence of uncomplicated peptic ulcer has declined [6]. An annual incidence of 0.10 - 0.19 percent could be expected to decrease in the upcoming years [7]. A corresponding decline in the incidence of complicated peptic ulcer disease, as well as mortality, but these outcomes do not appear to be decreasing at the same rate [7]. There are contradictory results in publications on the incidence and mortality of complicated peptic ulcer diseases and there are significant variations among the various countries [8]. Bleeding is the most common complication in peptic ulcers, followed by perforation [9]. In a 2011 longitudinal study, the estimated annual peptic ulcer bleeding incidence rate in the general population ranged from 19 to 57 cases per 100,000 populations (0.02 to 0.06%) mainly based on European studies [10].

The endoscopic dual treatment with the infusion and epinephrine in conjunction with either a clip or a thermal system or an implant approach [11,12]. New methods exist, for instance, hemostatic dust, but further testing is required [13]. Second-view endoscopy is not advised after initial hemostasis unless the patient has clinical signs of re-bleeding [14]. Continuous proton pump inhibitors (PPIs) infusion will take 72 hours, both in the Forrest Class Ia-Ila and in the IIb ulcers that did not get treatment [15,16]. A second endoscopic attempt is advised if the patient re-bleeds again [17]. In this study, we provide a comprehensive overview of re-bleeding rates following endoscopic treatment of peptic ulcers.

Methods
Search strategy and study selection
We performed an extensive literature search in 11 databases including Popline, WHO health library (GHL), System for Information on Grey Literature in Europe (SIGLE), Scopus, Web of Science (ISI), PubMed, Virtual Health Library (VHL), The New York Academy of Medicine (NYAM), Medline, Cochrane, and EMBASE databases on 20 November 2019. Whenever supported, medical subject headings (MeSH) terms “peptic ulcer [MeSH Terms]” AND “bleeding [MeSH Terms]” AND “endoscopic hemostasis [MeSH Terms]”. In databases where Mesh terms were not supported, combinations of different possible synonyms have been used. An additional manual search of references across relevant studies has been performed.

Three independent reviewers scanned the titles and abstracts against our inclusion and exclusion criteria to select potential articles. We included all relevant original publications assessing the risk of re-bleeding following endoscopic hemostasis of bleeding peptic ulcer, during the last ten years. There were no restrictions on study design, country or language. Papers were excluded if any of the following exclusion criteria were met: i) in vitro or animal studies; ii) data duplication, overlapping or unreliably extracted or incomplete data; iii) abstract only articles, reviews, thesis, books, conference papers or articles without available full texts (editorials, author response, letters, and comments) along with any previous systematic reviews, meta-analyses and literature reviews on our topic of interest. Full texts of initially eligible articles were then retrieved and reviewed for final inclusion. In both steps of the screening, a decision made by all three reviewers was considered conclusive. Controversies during the process were resolved by discussion and consensus. When necessary, disagreements and discrepancies were resolved by consensus with senior reviewers.

Data extraction
Based on a pilot review and extraction, a data extraction form was developed by two authors, using Microsoft Excel file. Three reviewers independently extracted data from included studies using the excel sheet. Whenever the re-bleeding rate was assessed at multiple points, the last and most complete data set was used. Data rechecking was carried out by at least two different authors and re-checked by a third reviewer for accuracy. All the disagreements and discrepancies were resolved by discussion and consensus. Papers published by the same research group were checked for potential duplicate data with reference to the year of patients’ recruitment and the hospital where the patients were recruited.

Quality assessment
Three independent reviewers evaluated the risk of bias in included studies. For observational studies, methodological quality assessment was done using the National Institutes of Health (NIH) quality assessment tool [18]. Quality assessment of each study was obtained

through a scoring system including 14 questions. The criterion was judged as following; a score of 13 to 14 was good, 9 to 12 was fair, and studies scoring below 9 are considered of poor quality for cohort studies [19]. For randomized controlled trials (RCTs), methodological quality assessment was done using Cochran’s tool for risk of bias [20].

Statistical analysis

R software version 3.6.1 was used to conduct the analyses [21]. To calculate the re-bleeding rate, a random-effects model was chosen due to the presence of heterogeneity between studies. Heterogeneity was evaluated using the Q statistic and I² test [22,23]. Publication bias testing, using Egger’s regression test, was not performed because of the small number of studies per analysis (less than 10) [24,25].

Results

Search results

Database search yielded 1904 reports and no additional reports were found with the manual search of references. Following the removal of 832 duplicates via Endnote software, the total number passed to the title and abstract screening was 1,072; of which, 167 were relevant to our inclusion criteria. Following the extensive full-text screening, only six studies were included in the meta-analysis (Figure 1).

Quality assessment and characteristics of included studies

Six studies with 248,517 total patients were included in this study with variable overall sample sizes ranging between 20 to 247,119. The total number of peptic ulcer patients assessed for re-bleeding risk was 3043. Moreover, the overall survival rate of FDPs ranged from

Figure 1: Extensive full-text screening, six studies were included in the meta-analysis.
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3.3% up to 30.6%. The mean age of the included patients was variable; ranging from 57.8 to 72.1 years old and male percentage ranged from 49% to 90% (Table 1).

Two studies have retrospectively screened patients’ data and the other four were randomized controlled trials. The methodological quality of the included studies ranged from good to fair with moderate to low risk of biases (Table 1).

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Case Group Definition</th>
<th>N</th>
<th>Case Group Age; Mean (SD/range)</th>
<th>Male (%)</th>
<th>Control Group Definition</th>
<th>N</th>
<th>Control Group Age; Mean (SD/range)</th>
<th>Male (%)</th>
<th>Overall Re-bleeding Rate (%)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enestvedt/2010/</td>
<td>Observational (Retrospective)</td>
<td>All adult patients who underwent esophagogastroduodenoscopy (EGD) performed for peptic ulcer hemostasis</td>
<td>3,692</td>
<td>65.2</td>
<td>70%</td>
<td>All adult patients who underwent esophagogastroduodenoscopy (EGD) performed for any other cause</td>
<td>243,427</td>
<td>57.8</td>
<td>49%</td>
<td>7.3%</td>
<td>Fair (moderate risk of bias)</td>
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<td>USA [26]</td>
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<tr>
<td>Kuipers/2011/</td>
<td>Randomized controlled trial</td>
<td>Adults who had undergone successful hemostatic treatment of a bleeding peptic ulcer by endoscopy with intravenous esomeprazole followed by oral esomeprazole</td>
<td>375</td>
<td>62.1 (18-95)</td>
<td>68%</td>
<td>Adults who had undergone successful hemostatic treatment of a bleeding peptic ulcer by endoscopy with intravenous placebo followed by oral esomeprazole</td>
<td>389</td>
<td>60.2 (18-98)</td>
<td>69%</td>
<td>4.8%</td>
<td>Good (low risk of bias)</td>
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<td>Canada [27]</td>
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<td>Chen/2012/</td>
<td>Randomized controlled trial</td>
<td>patients with active spurring (Forrest Ia), active oozing (Forrest Ib) ulcers or those with the non-bleeding visible vessel (NBVV, Forrest Ila) followed by high-dose pantoprazole regimen</td>
<td>100</td>
<td>65.5 (15.1)</td>
<td>79%</td>
<td>patients with active spurring (Forrest Ia), active oozing (Forrest Ib) ulcers or those with the non-bleeding visible vessel (NBVV, Forrest Ila) followed by standard-dose pantoprazole regimen</td>
<td>101</td>
<td>64.9 (12.2)</td>
<td>70%</td>
<td>7%</td>
<td>Good (low risk of bias)</td>
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<td>Taiwan [28]</td>
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</table>
Re-bleeding rate following endoscopic hemostasis

Six studies with 3043 patients were included in the analysis. The overall re-bleeding was 8.94% with 95% CI = 5.46 to 14.64. However, there was significant heterogeneity among results $I^2 = 92\%$ and $P$-value $< 0.001$ (Figure 2). Two studies [29,30] were the main sources of this heterogeneity for the highest rates; one [30] was a pilot RCT (33.3% re-bleeding rate) and the other [29] did not use any re-bleeding prevention medication in the control group (30.6% re-bleeding rate). A sensitivity analysis with removing those two studies has been performed. The heterogeneity has disappeared ($I^2 = 4\%$ and $P$-value $= 0.372$) and the prevalence rate changed to be 6.84% with 95% CI $= 5.97$ to 7.85 (Figure 3).

One study [26] has compared different endoscopy techniques where injection monotherapy has the highest re-bleeding rate (12.2%) followed by a combination of thermal/injection therapy (7.1%) and thermal monotherapy (6.1%), respectively. The studies that used proton pump inhibitors (PPIs) have reported the lowest re-bleeding rates with 3.3% [31] using the oral pantoprazole, 4.5% using the intravenous pantoprazole [31] and 4.8% using esomeprazole [27].

**Table 1: Characteristics of the included studies.**

*Table 1: Characteristics of the included studies.*

*N: Number; SD: Standard Deviation.*
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Discussion

Peptic ulcer bleeding is the most common complication in peptic ulcer patients [10,32] with decreasing incidence [33-35]. The incidence of bleeding peptic ulcers varies from 19 per 100,000 in the UK [36] to 80 per 100,000 in Spain [32]. Bleeding peptic ulcers are usually categorized according to the Forrest classification with differences in re-bleeding and mortality rates [37]. The reported re-bleeding rates and mortality were based on older publications when patients did not receive endoscopic therapy [38]. Based on the Forrest classification, ulcers can nowadays be categorized based on their need for endoscopic therapy as major stigmata of ulcer bleeding (Forrest Ia-IIb), or minor stigmata of ulcer bleeding (Forrest IIc or III) [37].

The current study has shown a pooled re-bleeding rate of 8.94% with individual studies ranging between 3.93% to 21.05%, which is consistent with the previous literature. The re-bleeding rates of peptic ulcers by Forrest classification after successful endoscopic hemostasis but with no PPIs therapy were 23% in Ia ulcers, 5% in Ib, 11% in Ia, and 18% in IIb, respectively, suggesting that Ib ulcers after initial endoscopic management should not be categorized as major stigmata of hemorrhage [39]. In another study from the Netherlands during 2009 - 2012, the overall re-bleeding rate was quite high (19%) varying from 59% among Forrest Ia ulcers to 7% in Forrest III ulcers [40]. In that study, only 70 - 74% of patients were treated with dual therapy in endoscopy. Based on a systemic review of 28 studies, the recurrent rate of all bleeding ulcers after successful initial endoscopic hemostasis has varied from 0-38%, being on average at 10%

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[10]. In a recently published study from Finland, 4.4% of bleeding peptic ulcer patients hospitalized during 2000 - 2015 needed a secondary procedure for bleeding, and 1.0% were admitted to prophylactic transcatheter arterial embolization [41].

The endoscopic therapy is recommended for ulcers with active bleeding or with a non-bleeding visible vessel or an adherent clot (Forrest Ia-IIb) for their risk of recurrent bleeding [42]. The removal of an adherent clot (IIb) in search of an artery is suggested in some studies, and only when it is present the endoscopic therapy should be given [43,44]. Among patients with haematin on ulcer base (IIc) or a clean base ulcer (III) endoscopic therapy is not needed. According to the international guidelines, dual therapy with epinephrine injection is recommended for reducing the risk of rebleeding, surgery and mortality [17,45]. The endoscopic treatment can be traditionally divided into injection, thermal and mechanical methods. Recently, novel endoscopic topical hemostatic powders have come onto market [44]. However, the proportion of patients receiving dual therapy for major stigmata of hemorrhages has been reported in some national audits to be as low as 34% in Canada, 35% in Italy and 38% in the UK [46-48].

The current study has some limitations; including the small number of studies included and heterogeneity of treatments used along with endoscopic treatment. Although the heterogeneity could be resolved with sensitivity analysis, it is a limitation to be considered. Studies have good methodological quality; nevertheless, two studies were retrospective with the associated flaws of this study design.

Conclusion

The endoscopic treatment of bleeding peptic ulcers has shown to be effective with low risk of re-bleeding. Adjuvant treatment with PPIs has shown to reduce the re-bleeding rates even more. Large scale studies are needed for a better assessment and more concrete conclusions.

Funding

None.

Conflicts of Interest

No conflicts related to this work.

Bibliography


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