Effectiveness of oral and intravenous PPI for peptic ulcer re-bleeding and management after endoscopic therapy

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**ABSTRACT**

To explain the effectiveness of different oral and intravenous (IV) Proton Pump Inhibitors (PPI) used in the management of peptic ulcer re-bleeding after successful endoscopic intervention. This article offers the summarization of various articles on PPI which are published in a well-known journals. All the articles used the same method in the management of peptic ulcer re-bleeding. Rockall risk scoring system were used for grading the rate of the bleeding. Pubmed and Embase was used to identify the related articles that assessed the efficacy of PPI and found Six articles matched our criteria. All the results where P <0.05 where considered significant for writing this review article. Neither any alterations or modifications nor any softwares were used in this article. All the results and conclusions were briefed and summarized carefully after a through discussion of the articles included in our review.

**Keywords:** Proton Pump Inhibitors (PPI), endoscopic therapy, rebleeding, peptic ulcer, hemostasis, mortality rate, surgical rate

**Introduction**

Peptic ulcer bleeding represents the substantial clinical and economic burden with reported incidence ranging from 48-160 cases/100,000 adults per year. Despite advance in the management of this serious medical condition, morbidity and mortality rate still remains significantly high. Endoscopic therapy is now recommended as the first hemostatic modality for the management of these conditions. But the above mentioned intervention is not an adequate procedure to prevent further bleeding, in order to prevent such further bleeding, proton pump inhibitors (PPIs) must be used either IV or oral to elevate the intra-gastric PH>6 and to prevent the disaggregation of platelet plugs, which otherwise will be the cause of future bleeding after successful endoscopic
therapy if no PPI was administered. [1, 2] Most patients who died from peptic ulcer bleeding have at least one co-morbid illness, this co-morbid illness is exacerbated by peptic ulcer bleeding. [3] The therapeutic efficacy of PPI is related to its potent inhibition of gastric acid because gastric acid inhibits clot formation and promotes the breakdown of the clot which results in bleeding. [4] The main objective of this article is to provide a brief review of various PPIs efficacy most widely used in the clinical settings to prevent and/or in the management of peptic ulcer bleeding. This article also illustrates the use of histamine receptor antagonists (H2RAs) versus PPIs for the prevention of peptic ulcer re-bleeding as far as the therapeutic efficacy is concerned. In this article, a comprehensive review is provided to highlighten the efficacy of PPIs in the management of peptic ulcer re-bleeding after successful endoscopic hemostatic therapy. Table 1 illustrates the studies included for this review and the respective methods used in the prevention of peptic ulcer rebleeding.

<table>
<thead>
<tr>
<th>Name of the study</th>
<th>Study design</th>
<th>Method</th>
<th>Significancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin HJ et al , 2010</td>
<td>Editorial</td>
<td>Large IV dose of PPI for 3 days is recommended as compared with H2RAs</td>
<td>P&lt;0.01*</td>
</tr>
<tr>
<td>Cheng HC et al , 2011</td>
<td>Editorial</td>
<td>Increased intra-gastric pH by IV PPI</td>
<td>P&lt;0.001*</td>
</tr>
<tr>
<td>M.Bardou et al , 2004</td>
<td>Meta-analysis</td>
<td>High dose IV PPI tested on 1855 patients (18 studies) rebleeding and hospital stay LAN group: Shorter hospital stay, Re-bleeding</td>
<td>-20.6% ;95% CI: -24.7 to -16.6* P&lt;0.01*, P=1</td>
</tr>
<tr>
<td>Liang et al, 2012</td>
<td>Research article</td>
<td>High dose Vs Non-High dose PAN for bleeding ulcers</td>
<td>P=1</td>
</tr>
<tr>
<td>Mostaghni et al , 2011</td>
<td>RCT</td>
<td>Oral OME Vs IV PAN followed by OME</td>
<td>P=0.8</td>
</tr>
</tbody>
</table>

IV-Intravenous, PPI-Proton Pump Inhibitor, H2RAs-Histamine 2 Receptor Anagnotons, LAN-Lansoprazole, ESO-Esomeprazale, PAN-Pantoprazole, OME-Omeprazale, *significant

Role and mechanism of PPI in the management of peptic bleeding

Due to the acidic environment of the stomach, the clinical course of peptic ulcer healing and bleeding is much more complicated than the skin wound healing. The main concern for the clinicians is not the treatment of peptic ulcer (gastric and/or duodenal ulcer) but the occurrence of re-bleeding after successful endoscopic hemostasis. The re-bleeding rate for the peptic ulcers varies widely from 5% to 100%. [5] In order to prevent the recurrent bleeding after successful endoscopic hemostasis, inhibition of gastric acid secretion will be the mainstay of therapy. This inhibition of gastric acid secretion can be achieved by using PPI either through IV or orally and also can be attained by H2RAs. PPI accumulate in the secretory canaliculi of parietal cells where they are protonated by acid which converts into the active form sulfenamide. The activated sulfenamide undergoes series of reactions with cysteine sulfhydryl group, this ultimately results in the inactivation of the pump and thus
inhibits gastric acid secretion. In an acidic environment of the stomach, the formation of platelet plug will be arrested that is the coagulation cascade and platelet aggregation, therefore it is of very important to raise the intra-gastric PH above 5.4 where below this PH the platelet aggregation and plasma coagulation are both abolished.\[6\]

With the worldwide aging population and the increasing usage of anti-platelets and anti-coagulants for the treatment of vascular diseases and malignancy, the proportion of patients with GI bleeding are expanding. Anti-platelets cause ulcers and erosions at different levels of the digestive tract and anti-coagulants might precipitate bleeding from pre-existing lesions. Both of these medications make the control of GI bleeding more difficult and failure of successful hemostatic achievement after endoscopic therapy for the actively bleeding peptic ulcers. So inhibition of the gastric acid secretion and careful prescription of anti-platelets and anti-coagulants is very crucially important in the management of actively bleeding peptic ulcer. In clinical practices, PPI whether orally or IV are most widely used for the management of peptic ulcer treatment and bleeding.

**Efficacy of different PPIs on peptic ulcer re-bleeding**

Peptic ulcer bleeding management is one of the great medical problem with significant morbidity and mortality. Endoscopic therapy significantly reduces further bleeding, surgery and mortality in these group of patients and this intervention should be considered as the first hemostatic mordality.\[7, 8\] PPIs plays a great role in the prevention of re-bleeding but the question remains controversial on the usage of appropriate PPI whether orally or IV in the management of peptic ulcer bleeding. In this review article, efficacy of Omeprazole (OME), Lansaprazole (LAN), Esomeparzole (ESO) and Pantaprazole (PAN) will be discussed. The summary of above mentioned PPIs are listed in Table 2 with the dose, route of administration, duration and significancy.

**Table: 2 Different Proton Pump Inhibitor with its efficacy**

<table>
<thead>
<tr>
<th>PPI</th>
<th>DOSAGE</th>
<th>ROUTE</th>
<th>DURATION</th>
<th>EFFICACY</th>
</tr>
</thead>
<tbody>
<tr>
<td>OME</td>
<td>40 mg followed by 160 mg/d</td>
<td>IV</td>
<td>3 Days</td>
<td>Re-bleeding rate Reduced</td>
</tr>
<tr>
<td>OME</td>
<td>80 mg followed by 8 mg/h</td>
<td>IV</td>
<td>3 Days</td>
<td>Re-bleeding rate Reduced</td>
</tr>
<tr>
<td>OME</td>
<td>3.3 mg/h</td>
<td>IV</td>
<td>7 Days</td>
<td>Re-bleeding rate Reduced</td>
</tr>
<tr>
<td>OME</td>
<td>8 mg/h</td>
<td>IV</td>
<td>3 Days</td>
<td>Re-bleeding rate reduced</td>
</tr>
<tr>
<td>LAN</td>
<td>90 mg followed by 9 mg/h</td>
<td>IV</td>
<td>1 Day</td>
<td>pH &gt;6 after 2-3 hours</td>
</tr>
<tr>
<td>LAN</td>
<td>120 mg bolus followed by</td>
<td>IV</td>
<td>1 Day</td>
<td>pH &gt;6 after 3-4 hours</td>
</tr>
<tr>
<td>LAN</td>
<td>30 mg four times daily for 3 days</td>
<td>ORAL</td>
<td>3-60 Days</td>
<td>Normal to mild effect on re-bleeding and pH</td>
</tr>
<tr>
<td>ESO</td>
<td>40 mg IV every 6 hours followed by oral 40 mg once daily for 60 days</td>
<td>I/V</td>
<td>3-60 Days</td>
<td>Normal to mild effect on re-bleeding and pH</td>
</tr>
<tr>
<td>PAN</td>
<td>40 mg followed by 4 mg/h</td>
<td>IV</td>
<td>1 Day</td>
<td>pH&gt;6</td>
</tr>
<tr>
<td>PAN</td>
<td>80 mg followed by 8 mg/h</td>
<td>IV</td>
<td>1 Day</td>
<td>pH&gt;6</td>
</tr>
</tbody>
</table>

OME ( Omerprazole), LAN ( Lansoprazole), ESO ( Esomeperzole), PAN ( Pantoprazole), pH( Intragastric pH)
The optimal dosage, the duration of PPIs for peptic ulcer bleeding is of very crucial importance. PPI is not activated in the body anywhere else other than stomach, so clinicians must be very sure of the appropriate selection, route of administration and indication of PPIs in the management of recurrent peptic ulcer bleeding.

In a study, Lin HJ et al, 50 patients were tested on PPI versus H2 blockers and showed that PPI were better than H2 blockers (P<0.01). Lin HJ et al in their study used 40mg omeprazole IV bolus followed by 160 mg/day continuous infusion and the result was intra-gastric PH rose to >6.\(^9, 26\) They also conducted a study on 78 patients each on IV omeprazole and oral rabeprazole where the conclusion was no significant difference in preventing re-bleeding in high risk bleeding peptic ulcer even given through different routes (equal effective, P>0.1).\(^10, 11\) Cheng et al, concluded that low dose of omeprazole (3.3mg/hr) followed by high dose of omeprazole (8mg/hr) through IV reduces re-bleeding rate in the first 28 days.\(^12\) In a similar study, Lau et al, concluded that re-bleeding rates are lower in patients given omeprazole 80mg IV bolus followed by 8 mg/hr(P<0.001).\(^13\)

Several studies are conducted to evaluate the prevention of re-bleeding by increasing gastric pH above 6 and the results of those studies showed that the re-bleeding rate decreased. High dose omeprazole given either by infusion or injection for the first three days rises the intra-gastric PH≥6.\(^14\) This study was supported by conducting another study in India where they also used high dose infusion of PPI and the result was increase in intra-gastric≥6.\(^10, 16\) High dose of Omeprazole, Rabeprazole, Pantaprazole and Lansaprazole infusions keeps intra-gastric PH>6. Interestingly in a study conducted by Hung’s et al\(^17\) showed that intra-gastric pH was above 6 maintained in a group who received high dose PPI versus in a group who received non high dose PPI (P=0.182). This remained a topic of controversy in the clinical practice and raised a question as to what is the most appropriate dosage among the PPIs which is able to achieve the required therapeutic efficacy. However the high dose PPI delivered through IV as the evidence with the relationship with the use of low dose PPIs is limited.\(^18, 19\) Additionally a study conducted by Kiilerich et al showed that low dose omeprazole (4mg/hr) continuous infusion after a bolus of 80 mg is a effective as the high dose in maintaining the intra-gastric PH around 4-6.\(^20, 21, 22\)

Two studies were conducted in Taiwan which showed that a favourable intra-gastric pH can be obtained with initially starting with a low dosage of omeprazole ( IV 80 mg omeprazole bolus followed with 40 mg bolus twice daily for 3 days or omeprazole 3.3 mg/hr infusion or 40 mg injected every 12hr for 3 days) could significantly decrease the rates of recurrent bleeding because of adequate maintainence of the intra-gastric pH, thereby preventing the platelet disaggregation and clot-lysis.\(^11, 23, 24\)

**Proton Pump Inhibitor association with the mortality rate and surgery rate**

High dose oral PPI reduces re-bleeding rates but not the surgery and mortality rate [-20.6%; 95% CI: -24.7 to -16.6 (significant)].\(^25\) This finding is also supported by studies performed by Lau et al and Hasselgren et al where both compared omeprazole versus
placebo in reduction of mortality rate where as studies performed by Lin et al and Goletti et al compared high dose omeprazole versus H2RA in reduction of mortality rate.\textsuperscript{[9, 13, 26]}

Regarding forest classification for the peptic ulcer lesions endoscopic treatment combined with the administration of high dose IV PPI was significantly better than the administration of high dose IV PPI alone for the re-bleeding management (0% and 9%, respectively, \(P=0.01\)) but in not terms of mortality rate (2.6% and 5.1%, respectively, \(P>0.20\)).\textsuperscript{[27]} Gisbert et al,\textsuperscript{[28]} studied that the comparison of high dose IV PPIs and non high dose PPIs versus H2RAs for the re-bleeding, mortality and surgery rates. Their results concluded that the former way of management was superior to latter in terms of re-bleeding but not for mortality or surgery. We also, as a result assume that high dose PPI administration [IV or ORAL] should be administered after successful endoscopic treatment for a patient with a bleeding peptic ulcer and with high risk sigmata and in this way can reduce both the re-bleeding and mortality.\textsuperscript{[29]}

In a research article, Yen et al,\textsuperscript{[29]} performed a comparison of IV esomeprazole followed by orally versus oral lansaprazole for three days on 100 patients (esomeprazole 40 mg IV every 6hr for 3days followed by esomeprazole 40 mg orally once daily for 2 months), (lansaprazole 30 mg four times a day for 3 days followed by once daily for 2 months).Their primary outcome was re-bleeding rate whereas surgery, mortality and hospital stay was secondary outcome. The result of their study showed that re-bleeding occurred in both the groups (4%, \(P=1\)) but the hospital stay was statistically significant with the shorter stay in the oral lansaprazole group compared with IV esomeprazole group (P<0.01). Their study did not encounter any patient with mortality or surgical intervention. A similar study have been also conducted for the re-bleeding rate with the PPIs (IV omeprazole versus oral rabeprazole) which showed no significant difference re-bleeding rates.\textsuperscript{[11]}

Conclusion
It is hereby, we can conclude that, PPIs were superior to H2 blockers and the result was intra-gastric PH rose to >6 in the management of peptic ulcer re-bleeding, low dose PPIs followed by high dose PPI can also reduce the risk of the re-bleeding rate which plays a great role in preventing the platelet disaggregation and clot-lysis. High dose oral PPI reduces re-bleeding rates but not the surgery and mortality rate.

References


