

# Efficacy Comparison of Divided and Infusion Intravenous Pantoprazole Methods after Endoscopic Therapy in Patients with Acute Gastrointestinal Bleeding

## Abstract

**Background:** Intravenous pantoprazole administration in patients with severe bleeding under urgent endoscopic therapy is effective. Furthermore, its infusion dose is useful to control bleeding; however, it is not economical. In this study, clinical outcomes and intravenous infusion of pantoprazole after endoscopic therapy plus efficacy of infusion dosage and divided doses are compared. **Materials and Methods:** This prospective, comparative study conducted on 18 adult (>18 years) patients referred to Al Zahra Hospital for hematemesis and melena bleeding who underwent endoscopic treatment with pantoprazole which divided into two groups of forty patients. First group received intravenous infusion for 80 mg and 8 mg/h. The second group received intravenous infusion with divided doses as 40 mg twice daily for 3 days. Clinical outcomes such as rebleeding, duration of hospitalization, amount of blood transfused, and mortality within 3 days after endoscopic treatment were collected and analyzed by SPSS software (version 20) using independent *t*-test, Chi-square test, and Fisher's exact test. **Results:** Duration of hospitalization in the pantoprazole infusion group was  $5.42 \pm 4.62$  days, with three patients (7.5%) having rebleeding, and in the divided pantoprazole group was  $5.90 \pm 3.08$  days, with four patients (10%) having rebleeding, and overall, only one person died in the divided pantoprazole group (2.5%) out of eighty patients. No significant difference was observed between two groups in terms of clinical outcomes ( $P > 0.05$ ). **Conclusion:** Regarding to results, it can be stated that both methods with specified dosage had significant impact on improvement of hematemesis and melena. Furthermore, due to lower costs, low dose of pantoprazole in divided approach as 40 mg/12 h is proposed.

**Keywords:** Acute gastrointestinal bleeding, divided, infusions, pantoprazole

## Introduction

Peptic ulcer bleeding is one of the most common causes of upper gastrointestinal (GI) bleeding.<sup>[1,2]</sup> About 48–160 per 100,000 people are dealing with the disease annually.<sup>[2–4]</sup> In addition, 25%–30% of patients with peptic ulcer have bleeding lesion that has a high risk of rebleeding after drug treatment.<sup>[5,6]</sup> Excessive bleeding caused by blood clots in the acidic environment of the GI tract may lead to death of 14% of patients with severe bleeding. It could happen three times more in patients with a history of rebleeding.<sup>[7,8]</sup> Therefore, rebleeding is an important predictive factor of mortality after bleeding in the upper digestive tract.<sup>[9]</sup> Reestablishing hemostasis is recommended for patients with high risk of peptic ulcer bleeding.<sup>[10,11]</sup> Even with this treatment, there is the possibility of rebleeding

in 15%–25% of patients.<sup>[9,12,13]</sup> Despite simultaneous pharmaceutical and endoscopy treatment, still 6%–8% of the causes of hospitalization and death exist in patients with upper GI bleeding.<sup>[6,13]</sup> Endoscopic treatment decreases bleeding, surgery, and mortality in patients with upper GI bleeding significantly, and 24 h endoscopic treatment has been recommended in the majority of patients with the disease. However, due to the high rate of bleeding stop, rebleeding with increased mortality may occur in approximately 10%–30% of cases.<sup>[6,14–16]</sup> On the other hand, stomach acid in patients with hemorrhagic lesions prevents clot formation and accelerates clot lysis, which as a result, hemostasis of wound in the stomach and duodenum is impaired; hence, this process can be prevented by reducing acid secretion.<sup>[17]</sup> Increase of gastric pH >6 can reduce the

**Amin Motiei,  
Vahid Sebghatollahi**

*From the Department of  
Internal Medicine,  
Isfahan University of Medical  
Sciences, Isfahan, Iran*

*Address for correspondence:  
Dr. Vahid Sebghatollahi,  
Department of Internal  
Medicine, Isfahan University of  
Medical Sciences, Isfahan, Iran.  
E-mail: sebghatollahi@gmail.  
com*

### Access this article online

**Website:** www.advbiores.net

**DOI:** 10.4103/abr.abr\_59\_16

**Quick Response Code:**



**How to cite this article:** Motiei A, Sebghatollahi V. Efficacy Comparison of Divided and Infusion Intravenous Pantoprazole Methods after Endoscopic Therapy in Patients with Acute Gastrointestinal Bleeding. *Adv Biomed Res* 2017;6:120.

**Received:** March, 2016. **Accepted:** October, 2016.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

risk of bleeding. This process can be completely accessible using pantoprazole.<sup>[18,19]</sup> Several studies have noted that use of intravenous pantoprazole increases the pH and reduces rebleeding well.<sup>[18,19]</sup>

Recent researches have shown that use of intravenous pantoprazole in patients with severe bleeding under urgent endoscopic therapy is effective.<sup>[20]</sup> Intravenous pantoprazole (80 mg, 8 mg every 3 days) has higher efficacy (reduction of rebleeding by 17%) and lower cost (<\$67 in hospital) compared to abandonment of the treatment. In Iran, cost of treating patients with intravenous infusion of pantoprazole is dramatically high (4,920,000 Rial) and imposes heavy burden on the country health system although it can be reduced with intravenous divided doses (1,800,000 Rial). In addition, studies in Canada and the USA suggest that pantoprazole administered intravenously for 3 days is more effective in stopping bleeding compared to the abandonment of treatment in patients with peptic ulcers after successful endoscopic therapy.<sup>[21]</sup> On the other hand, several studies have demonstrated that infusion of pantoprazole (80 mg initially and then 8 mg/h) was not different for controlling of GI bleeding in comparison with divided doses of pantoprazole (40 mg every 12 h) for 72 h after treatment.<sup>[22-24]</sup> Moreover, meta-analysis study in 2009 has noted that pantoprazole with infusion dose is useful to control bleeding in patients with recurrent bleeding. In another study, it was observed that even low dose has not significant difference to high-dose pantoprazole.<sup>[25,26]</sup>

In the current study, clinical outcomes of patients such as rate of rebleeding, mortality, number of days of hospitalization, and the need for blood injection after endoscopic therapy in intravenous infusion of pantoprazole and divided doses groups were compared. Our aim was to evaluate both approaches and figure out if divided method is effective and has similar effect to intravenous infusion and if there is possible to management the health-care costs.

## Materials and Methods

This prospective clinical trial study was done on the patients referred to Al Zahra Hospital for hematemesis and melena bleeding. A total of 88 patients underwent GI endoscopy and the source of bleeding was specified. Sample size was obtained as 44 per group using formula of comparing two means with 95% confidence coefficient and 80% power and error level equal to least difference mean between two groups (0.6S).

Inclusion criteria were patients with upper GI bleeding (active bleeding, visible vessel or adherent clot [Forrest Ia, Ib, IIa, IIb]), age older than 18, endoscopic treatment involving argon plasma coagulation (APC) and injection, and consent to participate in research project. In cases of lack of consent, with low risk for

rebleeding (Forrest IIc, III), observed abnormal bleeding of peptic and having diseases predisposing to bleeding (such as end-stage renal disease and congenital or acquired coagulation disorders) have been excluded from the study. Eight patients in both groups with some exclusion criteria were excluded from the study, and finally, the study was conducted in two groups of forty people.

Consent of patients was obtained according to the approval of Ethics Council of Isfahan University of Medical to enter into this study, and they underwent endoscopic treatment (APC) along with injection. According to the GI guidelines, these patients needed to get intravenous infusion or intravenous divided dose of pantoprazole after endoscopic treatment. First group received proton-pump inhibitor intravenously with divided dose and the second group received intravenous infusion dose. The first group received divided pantoprazole as 40 mg twice daily for 3 days, and the second group received pantoprazole as 80 mg, then 8 mg/h for 3 days. Medical outcomes and comparison of two groups were done considering investigation of rebleeding within 7 days after successful endoscopic treatment (re-hematemesis or abnormal vital signs), the number of required days for hospitalization, required blood transfusion, mortality, and recurrent hemorrhage in patients within 3 days after endoscopic treatment.

Analysis of data was done by Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, Illinois, USA) using independent *t*-test, Chi-square test, and Fisher's exact test, and significance level was considered as <0.05.

## Results

Eight patients in both groups with some exclusion criteria were excluded from the study, and the study was conducted in two groups of forty patients with stomach bleeding receiving endoscopic therapy with intravenous infusions of pantoprazole (80 mg blues and then 8 mg/h) and divided doses (40 mg twice daily).

In the group receiving infusions of pantoprazole, there were 32 (80%) males and 8 (20%) females, with average age of  $58.53 \pm 11.70$  years, and in the group receiving divided dose of pantoprazole, there were 31 (77.5%) males and 9 (22.5%) females, with average age of  $59.03 \pm 12.13$  years.

Thirty-eight patients had a comorbid disease of the heart, lung, kidney, or liver. A total of 61 patients were using drugs associated with increased risk for bleeding (nonsteroidal anti-inflammatory drug [NSAID]/aspirin or clopidogrel: 50 patients; steroid: 3 patients; warfarin: 3 patients; NSAID + warfarin: 5 patients). During the admission endoscopy, Forrest I lesion was detected in 25 patients (infusions pantoprazole group: Forrest Ia = 2 [5%] and Forrest Ib = 14 [35%], and divided pantoprazole group: Forrest Ia = 0 [0%] and Forrest Ib = 9 [22.5%]) and Forrest II lesion was detected

in 55 patients (infusions pantoprazole group: 31 patients and divided pantoprazole group: 24 patients). There were no significant differences between the two treatment groups in age, sex, reason for admission, comorbid diseases, drug use, smoking, alcohol use, and Forrest classification ( $P > 0.05$ ) [Table 1].

Comparison of clinical outcomes such as duration of hospital stay, amount of blood transfused, rebleeding, and mortality in two groups showed that duration of hospitalization in the pantoprazole infusion group was  $4.62 \pm 5.24$  days receiving  $3.58 \pm 3.54$  units of blood and in pantoprazole divided group was  $5.09 \pm 3.08$  days receiving  $3.07 \pm 4.09$  units of blood ( $P > 0.05$ ). Further, rebleeding frequency percentage was three cases (7.5%) in pantoprazole infusion group and was four cases (10%) in pantoprazole divided dose group ( $P = 0.692$ ). Four of the seven rebleeding patients had a second endoscopy. One of these four patients had an active spurting bleeding ulcer (Forrest Ia) that could not be stopped by endoscopic intervention, so surgery was performed; one patient with a Forrest Ib ulcer and two patients with Forrest IIa ulcers were given the second endoscopic treatments [Table 2].

Finally, overall, only one person in the divided pantoprazole group (2.5%) out of eighty patients died. No significant difference was observed between the two groups in terms of clinical outcomes ( $P > 0.05$ ) [Table 2].

### Discussion

Endoscopic treatment is one of the most effective methods to stop the bleeding of peptic ulcers, decrease the probability of rebleeding, and reduce morbidity and mortality rates. Pharmacological treatment in combination with endoscopic treatment provides even better outcomes. The effect of pantoprazole in the treatment of GI bleeding and prevention of rebleeding in several medicine and comparative studies has been proven. It also seems that intravenous pantoprazole is effective for the prevention of acute gastric ulcers in intensive care patients. Its common side effects were reported as headache and diarrhea, and complications such as blood clots in injection location and other GI disorders have been less reported.<sup>[10,27]</sup>

In the current study, the relationship between pantoprazole approaches and clinical outcomes was evaluated. We

**Table 1: Demographic, clinical, and endoscopic characteristics of the patients in the two study groups**

Characteristics	Divided method (n=40)	Infusion method (n=40)	Significance level
Age	59.03±12.13	58.53±11.70	0.852
Sex (%)			
Male	31 (77.5)	32 (80)	0.785
Female	9 (22.5)	8 (20)	
Drug use associated with risk (%)	32 (80)	29 (72.5)	0.600
Smoking (%)	16 (40)	21 (52.5)	0.370
Alcohol use (%)	4 (10)	3 (7.5)	0.999
Comorbid disease (%)	15 (37.5)	23 (57.5)	0.117
Type of admission (%)			
Hematemesis	29 (72.5)	20 (50)	0.091
Melena	11 (27.5)	19 (47.5)	
Shock	0	1 (2.5)	
Forrest classification (%)			
Ia	0	2 (5)	0.204
Ib	9 (22.5)	14 (35)	
IIa	27 (67.5)	19 (47.5)	
IIb	4 (10)	5 (12.5)	
Epinephrine amount (%)			
≤15 cc	27 (67.5)	24 (60)	0.642
>15 cc	13 (32.5)	16 (40)	

Drug use associated with risk was NSAID, clopidogrel, aspirin, steroid, warfarin. Comorbid diseases include disease of the heart, lung, kidney, or liver. NSIAD: Nonsteroidal anti-inflammatory drug

**Table 2: Comparative study of treatment factors in the two study groups**

Factor	Divided method (n=40)	Infusion method (n=40)	Significance level
Duration of hospitalization (day)	3.08±5.90	4.62±5.42	0.590
Receiving blood (unit)	4.09±3.70	3.54±3.85	0.861
Rebleeding (%)	4 (10)	3 (7.5)	0.692
Mortality (%)	1 (2.5)	0	0.314

did not find any change in both groups regarding clinical outcomes and both groups had equal response to pantoprazole treatment methods ( $P > 0.05$ ). In agreement with our findings, other investigations have not found any change in laboratory parameters with pantoprazole treatment.<sup>[28]</sup> The body is able to resist taking pantoprazole in high doses; however, according to research results, the use of pantoprazole intravenous infusion of 8 mg/h for 3 days in patients with severe bleeding under endoscopic therapy is effective, which brings lower cost and higher effectiveness.<sup>[21]</sup> Furthermore, the recommended intravenous pantoprazole in patients who are not able to have oral therapy is 40 mg daily injection.<sup>[29]</sup>

The results of the incidence of rebleeding, mortality, length of hospital stay, and received blood transfusions with pantoprazole injection as 80 mg and then 8 mg/h were similar to injection of 40 mg pantoprazole every 12 h ( $P > 0.05$ ). In this regard, the findings of many studies suggest that suitable doses of pantoprazole are not necessarily high.<sup>[3,29]</sup> Based on our findings, intravenous administration of pantoprazole (in both ways) has positive impact on GI bleeding. Lau *et al.* identified that the initial injection of 80 mg within 72 h as 8 mg pantoprazole per hour was good value for peptic ulcers after successful endoscopic treatment,<sup>[6]</sup> while some evidence suggests the preference of 8 mg/h over other methods prescribed a lower dose.<sup>[10,11,30]</sup>

Some studies have also investigated the role of other factors such as stomach acid in a randomized controlled trial and compared the use of pantoprazole with high and low doses and found that the clinical efficiency and control of stomach acid had no beneficial effect among two groups.<sup>[9]</sup> In addition, the duration and the amount of acid secreted after endoscopic therapy are still unclear.<sup>[16,30,31]</sup> Although it is obvious that receiving high doses of pantoprazole as continuously way controls stomach acid to a greater extent, more research with detailed and standard statistical power seems to be necessary on endoscopic therapy to achieve more accurate information.

While in the methods of pantoprazole, there is not any specific dose being established, many studies and trials suggested 80 mg single dose after 40 mg/h for patients with peptic ulcer disease in Asia.<sup>[32,33]</sup>

On the other hand, execution path is another uncertain issue about the dose of pantoprazole in patients with stomach bleeding. Randomized controlled trials suggest that oral administration of pantoprazole is more effective in patients with gastric bleeding for reducing rebleeding, blood transfusion need, and surgery than placebo.<sup>[18,34]</sup> Likewise, our study proved this issue as well. Furthermore, according to the indirect comparisons in meta-analysis studies, there is no evidence that intravenous method is preferred over oral administration.<sup>[25,26]</sup> Recent consensus on the amounts of intravenous pantoprazole in patients with gastric bleeding under successful endoscopic therapy showed that consumption

of intravenous pantoprazole along with its continuous injection is effective for reducing bleeding.<sup>[29]</sup> In this regard, van Rensburg and Cheer stated that the amount of intravenous pantoprazole in patients with peptic ulcers that are not able to have oral therapy is recommended as 40 mg daily injection,<sup>[29]</sup> that is in conflict with the current study, as in this study it was found no difference between the two methods.

One of the strengths of this study is that appropriate therapeutic interventions including APC and epinephrine and sclerosis injection were conducted for bleeding ulcers including visible, active bleeding before the actions are taken. One of the limitations of this study is that it was not able to investigate the pharmacogenetics. According to other studies, the efficacy of pantoprazole in the Asian patients is more than Western ones.<sup>[32,33]</sup> In addition, pH of the stomach was not measured; hence, it cannot be concluded that both methods are identical in reducing and controlling acid. However, it should be noted that whether both methods have any effect on acid control, it does not change the conclusion of the investigation because the effect of the drug was being investigated.

## Conclusion

Our study showed that continuous infusion of pantoprazole and divided doses as 40 mg once every 12 h were identical so that clinical outcomes including rebleeding, blood transfusion, duration of hospitalization, and mortality in both methods were the same. Therefore, the current study challenged current routine doses and stated that use of low-dose divided can have a similar effect which economically has great importance on its cost-effectiveness.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

1. Rockall TA, Logan RF, Devlin HB, Northfield TC. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Steering Committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. *BMJ* 1995;311:222-6.
2. Lewis JD, Bilker WB, Brensinger C, Farrar JT, Strom BL. Hospitalization and mortality rates from peptic ulcer disease and GI bleeding in the 1990s: Relationship to sales of nonsteroidal anti-inflammatory drugs and acid suppression medications. *Am J Gastroenterol* 2002;97:2540-9.
3. Lassen A, Hallas J, Schaffalitzky de Muckadell OB. Complicated and uncomplicated peptic ulcers in a Danish county 1993-2002: A population-based cohort study. *Am J Gastroenterol* 2006;101:945-53.
4. Targownik LE, Nabalamba A. Trends in management and outcomes of acute nonvariceal upper gastrointestinal bleeding: 1993-2003. *Clin Gastroenterol Hepatol* 2006;4:1459-66.
5. Laine L, Peterson WL. Bleeding peptic ulcer. *N Engl J Med* 1994;331:717-27.

6. Lau JY, Sung JJ, Lee KK, Yung MY, Wong SK, Wu JC, *et al.* Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med* 2000;343:310-6.
7. Kang JY, Elders A, Majeed A, Maxwell JD, Bardhan KD. Recent trends in hospital admissions and mortality rates for peptic ulcer in Scotland 1982-2002. *Aliment Pharmacol Ther* 2006;24:65-79.
8. Mose H, Larsen M, Riis A, Johnsen SP, Thomsen RW, Sørensen HT. Thirty-day mortality after peptic ulcer bleeding in hospitalized patients receiving low-dose aspirin at time of admission. *Am J Geriatr Pharmacother* 2006;4:244-50.
9. Hung WK, Li VK, Chung CK, Ying MW, Loo CK, Liu CK, *et al.* Randomized trial comparing pantoprazole infusion, bolus and no treatment on gastric pH and recurrent bleeding in peptic ulcers. *ANZ J Surg* 2007;77:677-81.
10. British Society of Gastroenterology Endoscopy Committee. Non-variceal upper gastrointestinal haemorrhage: Guidelines. *Gut* 2002;51 Suppl 4:iv1-6.
11. Barkun A, Bardou M, Marshall JK; Nonvariceal Upper GI Bleeding Consensus Conference Group. Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2003;139:843-57.
12. Llach J, Bordas JM, Salmerón JM, Panés J, García-Pagán JC, Feu F, *et al.* A prospective randomized trial of heater probe thermocoagulation versus injection therapy in peptic ulcer hemorrhage. *Gastrointest Endosc* 1996;43(2 Pt 1):117-20.
13. Chung SC, Leung JW, Steele RJ, Crofts TJ, Li AK. Endoscopic injection of adrenaline for actively bleeding ulcers: A randomised trial. *Br Med J (Clin Res Ed)* 1988;296:1631-3.
14. Kovacs TO, Jensen DM. The short-term medical management of non-variceal upper gastrointestinal bleeding. *Drugs* 2008;68:2105-11.
15. Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. *N Engl J Med* 2008;359:928-37.
16. Elmunzer BJ, Young SD, Inadomi JM, Schoenfeld P, Laine L. Systematic review of the predictors of recurrent hemorrhage after endoscopic hemostatic therapy for bleeding peptic ulcers. *Am J Gastroenterol* 2008;103:2625-32.
17. Green FW Jr., Kaplan MM, Curtis LE, Levine PH. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. *Gastroenterology* 1978;74:38-43.
18. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database Syst Rev* 2006;3:CD002094.
19. Leontiadis GI, Howden CW. The role of proton pump inhibitors in the management of upper gastrointestinal bleeding. *Gastroenterol Clin North Am* 2009;38:199-213.
20. Herba K, Kennedy W, Barkun A, Fallone C. Cost effectiveness of IV PPI's in the treatment of non-variceal upper GI bleeding following urgent endoscopy. *Gut* 2002;51 Suppl III: A105.
21. Barkun AN, Herba K, Adam V, Kennedy W, Fallone CA, Bardou M. High-dose intravenous proton pump inhibition following endoscopic therapy in the acute management of patients with bleeding peptic ulcers in the USA and Canada: A cost-effectiveness analysis. *Aliment Pharmacol Ther* 2004;19:591-600.
22. Andriulli A, Loperfido S, Focareta R, Leo P, Fornari F, Garripoli A, *et al.* High-versus low-dose proton pump inhibitors after endoscopic hemostasis in patients with peptic ulcer bleeding: A multicentre, randomized study. *Am J Gastroenterol* 2008;103:3011-8.
23. Cheng HC, Kao AW, Chuang CH, Sheu BS. The efficacy of high- and low-dose intravenous omeprazole in preventing rebleeding for patients with bleeding peptic ulcers and comorbid illnesses. *Dig Dis Sci* 2005;50:1194-201.
24. Simon-Rudler M, Massard J, Bernard-Chabert B, DI Martino V, Ratziu V, Poynard T, *et al.* Continuous infusion of high-dose omeprazole is more effective than standard-dose omeprazole in patients with high-risk peptic ulcer bleeding: A retrospective study. *Aliment Pharmacol Ther* 2007;25:949-54.
25. Laine L, McQuaid KR. Endoscopic therapy for bleeding ulcers: An evidence-based approach based on meta-analyses of randomized controlled trials. *Clin Gastroenterol Hepatol* 2009;7:33-47.
26. Lam SK, Hasan M, Sircus W, Wong J, Ong GB, Prescott RJ. Comparison of maximal acid output and gastrin response to meals in Chinese and Scottish normal and duodenal ulcer subjects. *Gut* 1980;21:324-8.
27. van Rensburg CJ, Hartmann M, Thorpe A, Venter L, Theron I, Lühmann R, *et al.* Intra-gastric pH during continuous infusion with pantoprazole in patients with bleeding peptic ulcer. *Am J Gastroenterol* 2003;98:2635-41.
28. Cook DJ, Guyatt GH, Salena BJ, Laine LA. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: A meta-analysis. *Gastroenterology* 1992;102:139-48.
29. van Rensburg CJ, Cheer S. Pantoprazole for the treatment of peptic ulcer bleeding and prevention of rebleeding. *Clin Med Insights Gastroenterol* 2012;5:51-60.
30. Lin HJ, Lo WC, Lee FY, Perng CL, Tseng GY. A prospective randomized comparative trial showing that omeprazole prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. *Arch Intern Med* 1998;158:54-8.
31. Metz DC, Amer F, Hunt B, Vakily M, Kukulka MJ, Samra N. Lansoprazole regimens that sustain intra-gastric pH > 6.0: An evaluation of intermittent oral and continuous intravenous infusion dosages. *Aliment Pharmacol Ther* 2006;23:985-95.
32. Udd M, Töyry J, Miettinen P, Vanninen E, Mustonen H, Julkunen R. The effect of regular and high doses of omeprazole on the intra-gastric acidity in patients with bleeding peptic ulcer treated endoscopically: A clinical trial with continuous intra-gastric pH monitoring. *Eur J Gastroenterol Hepatol* 2005;17:1351-6.
33. Udd M, Miettinen P, Palmu A, Heikkinen M, Janatuinen E, Pasanen P, *et al.* Regular-dose versus high-dose omeprazole in peptic ulcer bleeding: A prospective randomized double-blind study. *Scand J Gastroenterol* 2001;36:1332-8.
34. Andriulli A, Annesse V, Caruso N, Pilotto A, Accadia L, Niro AG, *et al.* Proton-pump inhibitors and outcome of endoscopic hemostasis in bleeding peptic ulcers: A series of meta-analyses. *Am J Gastroenterol* 2005;100:207-19.