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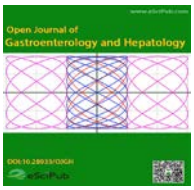

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Efficacy Of Potassium-Competitive Acid Blocker vs Proton Pump Inhibitor as First-Line and Second-Line Treatment for Helicobacter Pylori Eradication

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ABSTRACT

Introduction: Eradication of H. pylori reduced the risk of gastric cancer by 75%, thus, its therapy with high eradication rates is needed. Nowadays, the success rate of H.pylori eradication regimen (PPI-based) has dropped to less than 75% due to clarithromycin resistance and inadequate gastric acid suppression. Vonoprazan, a Potassium-competitive acid blocker (PCAB) was released for use in first-line and second-line treatment for H.pylori eradication. It shows better acid suppression effect in acid-related disease. **Aim:**The aim of this study was to compare the efficacy of PCAB and PPI as first-line and second-line treatment for H. pylori eradication. **Method:**We search the Medline, Google Scholar and Directory of Open Access Journals (DOAJ) databases in October 2019. The study selection process was plotted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. **Results:**In studies assessing first-line therapy, 776 patient were using PPI and 965 patient were using PCAB. In first-line therapy, PCAB has higher ITT and PP compared to PPI. According to Sue et al, in PPI group, more patient complain of diarrhea (49 vs 25; $p < 0.001$). In studies assessing second-line therapy, 1,069 patient were using PPI and 605 patient were using PCAB. Two studies showed no significant differences between PCAB and PPI in second-line therapy, but one study showed PCAB superiority (ITT PPI vs PCAB 85% vs 90% p=0.045; PP PPI vs PCAB 91% vs 96% p=0.008). There is no difference in adverse event between PCAB and PPI. **Conclusion:** In conclusion, PCAB has higher eradication rate (ITT and PP) compared to PPI as first-line therapy for H.pylori eradication. Further study is still needed in comparing efficacy of PCAB and PPI as second-line therapy. Both therapies were safe and well tolerated.

Keywords: potassium-competitive acid blocker, proton pump inhibitor, helicobacter pylori, acid

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Introduction:

Helicobacter pylori infection is associated with gastric cancer and peptic ulcer.(1) Eradication of *H.pylori* decreases the incidence of gastric cancer and gastroduodenal ulcers and has become a standard treatment to improve long-term outcomes in patient with *H. pylori* infection. Eradication of *H. pylori* reduced the risk of gastric cancer by 75%, thus, its therapy with high eradication rates is needed.(2) Eradication consists of first-line and second-line therapy (if first-line therapy failed to eradicate). First-line therapy consists of clarithromycin, amoxicillin and proton-pump inhibitor (PPI) twice daily for seven days. Second-line therapy consist of metronidazole, amoxicillin and PPI twice daily for seven days.(3)

Nowadays, the success rate of this regimen has dropped to less than 75% due to clarithromycin resistance(1) and inadequate gastric acid suppression.(3). From 2015, vonoprazan, a Potassium-competitive acid blocker (PCAB) was released for use in first-line and second-line treatment for *H.pylori* eradication. Vonoprazan directly inhibits H^+-K^+ exchange in a reversible manner resulting in effective, rapid, and long-lasting acid suppression superior to PPI.(1)

Until present, limited systematic review is available comparing PCAB and PPI as first-line and second-line therapy in eradicating *H.pylori* infection. This possibly due to PCAB is available in limited countries. Therefore, we performed this review to summarize and update the evidence. The aim of this study was to compare the efficacy of PCAB and PPI as first-line and second-line treatment for *H. pylori* eradication.

Materials and Methods

Study sample, design and setting

Patients with *H. pylori* infection and aged > 18 years old were included in this systematic review. *Helicobacter pylori* positivity was confirmed from the results of the ^{13}C-urea breath test, stool antigen test, or the presence of *H.pylori*-specific Immunoglobulin G antibodies in the serum. Only trials that compares the efficacy of PCAB and PPI for *H. pylori* eradication within 10 years were considered.

Treatment outcomes

A comparison of the primary outcome (Intention to Treat (ITT and Per Protocol (PP)) was made for patients with *H.pylori* infection. Serious adverse events and non-serious adverse events were secondary outcomes. An adverse event was considered be serious if it led to death, was life-threatening, or caused persistent disability.

Search strategy and literature review

Two independent reviewers search the Medline, Google Scholar and Directory of Open Access Journals (DOAJ) databases in October 2019. Relevant studies, screened based on the title and abstract were selected after conducting electronic search. Studies on animals and review articles were excluded. The study selection process was plotted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Results

Seven references were identified in the Medline, Google Scholar, and DOAJ databases, respectively. Two studies were duplicates and were removed. One study was not in English and were excluded. The abstracts were also filtered, leading to the removal of one study that met the exclusion criteria (not comparing with PPI). Three full-text studies were assessed for eligibility (Figure 1). Three studies were included in this systematic review (Table 1). Two studies study the efficacy of PCAB vs PPI as first-line therapy and second-line therapy and one study only in second-line therapy.

In using PPI, Sue et al. use more varieties of PPI such as lansoprazole, rabeprazole, esomeprazole, omeprazole and use two dosage of clarithromycin (200 mg or 400 mg). Nishizawa et al. further assess the effect of age

to eradication therefore they divide participant into two groups (≤ 50 years old and > 50 years old). Nabeta et al. only analyze the efficacy of PCAB and PPI in second-line therapy.

In studies assessing first-line therapy, 776 patient were using PPI and 965 patient were using PCAB (Table 2). In first-line therapy, PCAB has higher ITT and PP compared to PPI. According to Sue et al, in PPI group, more patient complain of diarrhea (49 vs 25; $p < 0.001$).

In studies assessing second-line therapy, 1,069 patient were using PPI and 605 patient were using PCAB. Two studies showed no significant differences between PCAB and PPI in second-line therapy, but one study showed PCAB superiority (ITT PPI vs PCAB 85% vs 90% p=0.045; PP PPI vs PCAB 91% vs 96% p=0.008). There is no difference in adverse event between PCAB and PPI.

Table 1. Charateristic of Included Study

Author	Year	Therapy	Treatment Groups	Age	N	Method
Nishizawa et l(1)	2016	First-line therapy	PCAB (vonoprazan)	50.4 ± 13.3	353	First-line therapy: 200 mg clarithromycin, 750 mg amoxicillin, and 20 mg vonoprazan vs 30 mg lansoprazole/10 mg rabeprazole) twice daily for 1 week.
			PPI (lansoprazole/ rabeprazole)	52.7 ± 13.8	2,173	
		Second-line therapy	PCAB (vonoprazan)	53.5 ± 13.3	85	Second-line therapy: 250 mg metronidazole,750 mg amoxicillin, and 20 mg vonoprazan vs 30 mg lansoprazole/10 mg rabeprazole) twice daily for 1 week
			PPI (lansoprazole/ rabeprazole)	51.7 ± 13	650	
Sue et al(2)	2016	First-line therapy	PCAB (vonoprazan)	64.3 ± 12.3	612	First-line therapy: clarithromycin 200/400 mg, amoxicillin 750 mg, and vonoprazan 20 mg vs lansoprazole 30 mg/rabeprazole 10 mg/esomeprazole 20 mg/omeprazole 20 mg) twice daily for 1 week
			PPI (lansoprazole/ rabeprazole/ esomeprazole/ omeprazole)	64.5 ± 12.7	603	
		Second-line therapy	PCAB (vonoprazan)	67.5 ± 11.3	211	Second-line therapy: metronidazole 250 mg, amoxicillin 750 mg, and vonoprazan 20 mg vs lansoprazole 30 mg /rabeprazole 10 mg/esomeprazole 20 mg/omeprazole 20 mg) twice daily for 1 week
			PPI (lansoprazole/ rabeprazole/ esomeprazole/ omeprazole)	63.9 ± 11.7	145	
Nabeta et al(3)	2019	Second-line therapy	PCAB (vonoprazan)	55.9 ± 12.5	274	Second-line therapy: 250 mg metronidazole,750 mg amoxicillin, and 20 mg vonoprazan vs 30 mg lansoprazole/10 mg rabeprazole) twice daily for 1 week
			PPI (lansoprazole/ rabeprazole)	55.6 ± 12.3	309	
PCAB: Potasium-competitive Acid Blocker; PPI: Proton Pump Inhibitor						

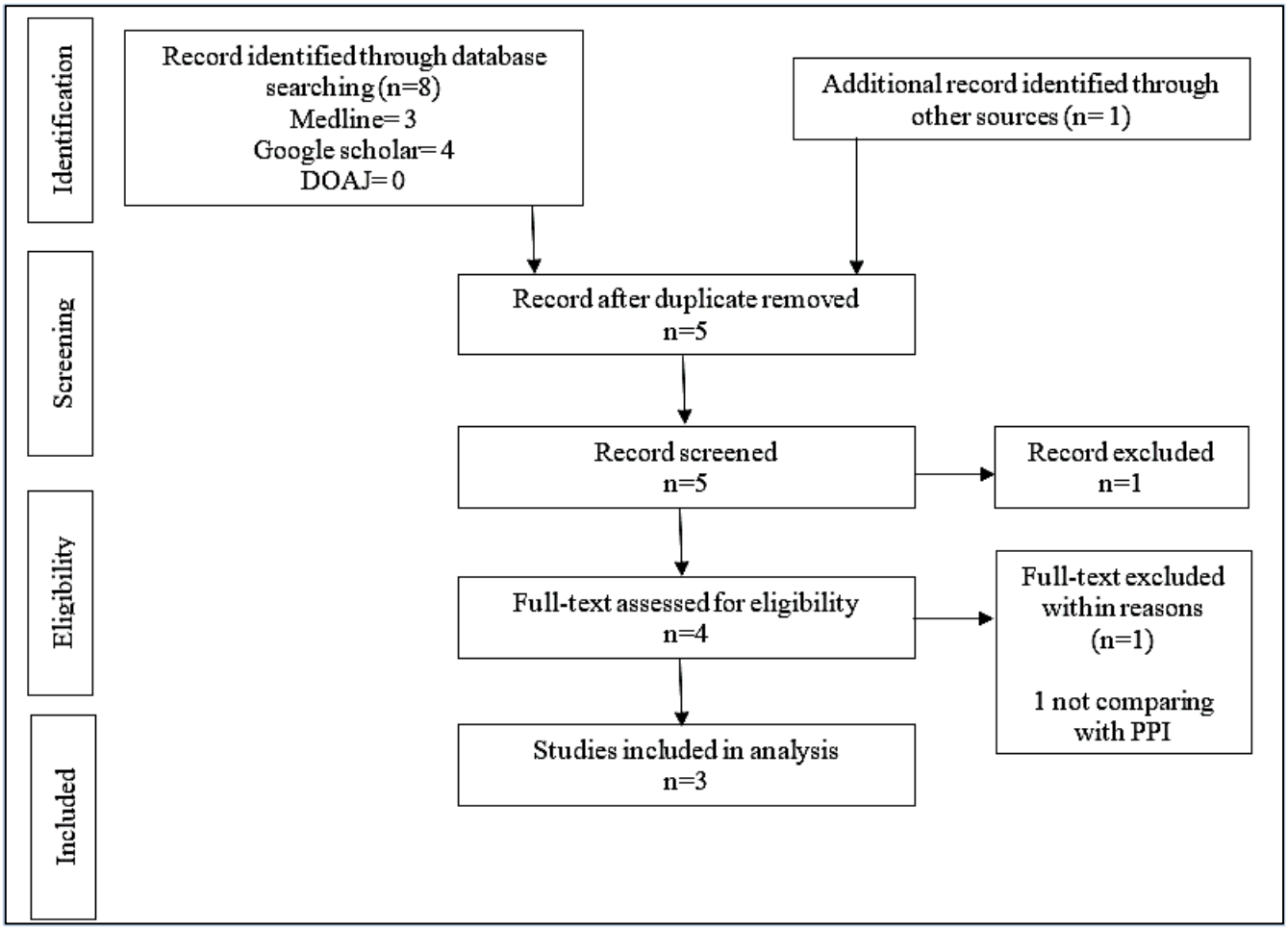

Figure 1. The Results of The Literature Search Process

Table 2. Outcomes of Studies

Author	Year	Therapy	Treatment Groups	ITT	PP	
Nishizawa et al	2016	First-line therapy	PCAB (vonoprazan)	62.30%	89.40%	ITT and PP is higher in PCAB (ITT p<0.001 and PP p<0.001)
			PPI (lansoprazole/ rabeprazole)	47.10%	66.80%	
		Second-line therapy	PCAB (vonoprazan)	71.80%	96.80%	No significant difference
			PPI (lansoprazole/ rabeprazole)	73.70%	90.50%	
Sue et al	2016	First-line therapy	PCAB (vonoprazan)	84.9% (95% CI: 81.9-87.6%)	86.4% (83.5089.1%)	ITT and PP is higher in PCAB (ITT p=0.0061) and PP p=0.0013)
			PPI (lansoprazole/ rabeprazole/ esomeprazole/ omeprazole)	78.8% (73.5-82.0%)	79.4 (76.0-82.6%)	
		Second-line therapy	PCAB (vonoprazan)	80.5% (74.5-85.6%)	82.4% (76.6-87.3%)	No significant difference
			PPI (lansoprazole/ rabeprazole/ esomeprazole/ omeprazole)	81.5% (74.2-87.4%)	82.1% (74.8-87.9%)	
Nabeta et al	2019	Second-line therapy	PCAB (vonoprazan)	90%	96%	ITT and PP is higher in PCAB (ITT p=0.045 and PP p=0.008)
			PPI (lansoprazole/ rabeprazole)	85%	91%	

PCAB: Potasium-competitive Acid Blocker; PPI: Proton Pump Inhibitor; ITT: Intention to Treat; PP: Per Protocol

Discussion

In this study, we found that PCAB-based therapy has higher eradication rate (ITT and PP) than PPI-based therapy in first-line therapy. In second-line therapy, there are two different results. The latest study stated that PCAB-based therapy has higher eradication rate (ITT and PP) than PPI-based therapy in second-line therapy. There are two possible explanations why past studies did not show statistically significant differences. First, smaller number of patient did not have enough power to detect a statistical significance. Second, variability in first-line therapy between two groups. It is assumed that *H.pylori* that survived PCAB-based first line therapy is more resistant than PPI-based, therefore did not show statistically significance result on second-line therapy. Nabeta et al. excluded patient that failed to eradicate *H.pylori* with PCAB-based first-line therapy, therefore resulting in precise comparison second-line therapy.(3)

Proton pump inhibitor has been used as the first-line drugs treatment in acid related disease, but it has several disadvantages, including being affected by genetic polymorphisms of CYP2C19, and being inactivated easily under acidic conditions. Multiple studies shows that PCAB is superior than PPI in acid-related disease.(4) They superior to PPI due to multiple reasons. First, PCAB provide better acid suppression effect. In comparison with PPIs, PCABs bind to the proton pump continuously in gastric parietal cells to reduce gastric acid secretion without requiring activation or being deactivated by the gastric acid.(4) Second, it is long-lasting due to slow dissociation.(5) Vonoprazan provided excellent pH > 4.0 more than 90% of the day and not influenced by the ambient pH in the stomach. Third, a less acidic environment due to PCAB will increases bacterial growth that increases susceptibility to acid-sensitive antibiotic such as clarithromycin and amoxicillin. Fourth, unlike PPI, PCAB is meal-independent. It will results in a similar serum concentration regardless of when it is taken relative to meals.(3) Compared to other PCAB, vonoprazan does not have hepatic toxicity.(5)

Potassium-competitive acid blockers provide additional benefit especially in clarithromycin-resistant patient. A PCAB-based therapy is more effective than PPI in eradicating *H.pylori*.(3) This could be due to synergistic actions between PCAB and antibiotic used.(1) Clarithromycin will increased the concentration of PCAB because it inhibits CYP3A4 that metabolizes PCAB.(3)

Nishizawa et al. further assess the effect of age to eradication therefore they divide participant into two groups ($\leq$ 50 years old and > 50 years old). They stated that PPI-based therapy demonstrated significantly lower eradication rate in young to middle-aged group ($p< 0.001$). This is probably due to higher rate of clarithromycin resistance in young to middle-aged group. However, age had no impact on eradication rate for PCAB and second-line therapy (metronidazole-based).(1)

In terms of adverse effect, according to Sue et al, in PPI group, more patient complain of diarrhea (49 vs 25; $p < 0.001$). Therefore PCAB-based therapy is safe and well tolerated.

Conclusion:

In conclusion, PCAB has higher eradication rate (ITT and PP) compared to PPI as first-line therapy for *H.pylori* eradication. Further study is still needed in comparing efficacy of PCAB and PPI as second-line therapy. Both therapies were safe and well tolerated.

Conflicts of interest:

Authors declare no conflicts of interest.

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