Does stopping the proton pump help with the gushing variceal pipes?

By Elaine Lo

Background

Is there a role for PPI in patients with bleeding esophageal varices?

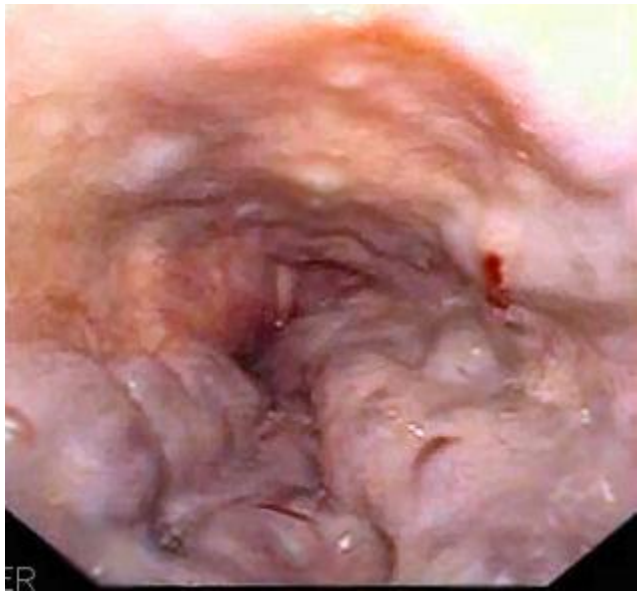
Good question.
I am not aware that there is any evidence for that.
It would make a great seminar topic.

Scenario

- 48 y.o. male with history of alcohol-related liver cirrhosis admitted through E.R. with upper GI bleed (UGIB)
- Vomited/vomiting fresh blood; hemodynamically unstable
- Packed cells transfused; pantoprazole infusion 8mg/h started
- Endoscopy confirmed: hemorrhage from esophageal varices
- Endoscopic variceal ligation (EVL) was done

- What do we do with the PPI now?

Varices



http://en.wikipedia.org/wiki/File:Esophageal_varices_-_wale.jpg
http://herutblog.wordpress.com/2011/09/

Variceal Hemorrhage

- Varices present in ~50% of cirrhotics at time of diagnosis
- 1-year rate of first variceal hemorrhage ~15%; mortality rate: 7-15%
- Median re-bleeding rate of 60%; mortality rate: up to 30%

World journal of gastroenterology: WJG, *18*(11), 1166
Current opinion in gastroenterology, *29*(3), 257-263[5]

Treatment

- Goals during active bleeding episode:
  - 1. Hemodynamic resuscitation
  - 2. Prevention & treatment of complications
  - 3. Treatment of bleeding

Treatment

- Supportive Care
- Antibiotics

- Upper endoscopy
- EVL or sclerotherapy
- Add: terlipressin/ somatostatin or octreotide

- Salvage treatment: transjugular intrahepatic portosystemic shunt (TIPS) or surgery

Rationale of PPI

- 1. PPI is effective for GI bleed
  - Stimulates platelet aggregation & formation of fibrin clots

- 2. Complications associated with endoscopic treatment, e.g. esophageal ulceration, motility dysfunction
  - Delayed healing in presence of acid

Guidelines

- **Canadian** – NONE!
- AASLD
  - No specific recommendation
  - Quoted study by Shaheen
    - "results favor use of PPI post EVL"
- Asia Pacific Association for the Study of the Liver
  - No specific recommendation
  - PPI as a measure to increase safety/ efficacy of EVL
- Chinese Society of Digestive Endoscopy
  - Suggests benefits based on theoretical benefits
- Pakistan
  - Needs further study

Hepatology, *46*(3), 922-938
NICE clinical guideline: Acute upper gastrointestinal bleeding: management June 2012
Hepatology international, *2*(4), 429-439
Chinese medical journal, *122*(7), 766
Management of variceal bleeding: PSG guidelines 2006. *Management*
Hepatology, *41*(3), 588-594

Inappropriate prescribing?

- Unnecessary prescription of PPI increases economic costs in daily clinical practice
- Only 12.3% of cirrhotic patients appropriate indication
- 63% of antacid therapy prescribed for inadequate indication in cirrhotics: 34% previous variceal bleed

Clinical Medicine, *3*(4), 387-388
Am J Manag Care, *11*(1), 29-36
Medical science monitor: international medical journal of experimental and clinical research, *14*(9), CR468-72
European journal of gastroenterology & hepatology, *20*(6), 512-518

Inappropriate prescribing?

REVIEW

Proton pump inhibitors in cirrhosis: Tradition or evidence based practice?

Francesca Lodato, Francesco Azzaroli, Maria Di Girolamo, Valentina Feletti, Paolo Cecinato, Andrea Lisotti, Davide Festi, Enrico Roda, Giuseppe Mazzella

- Main reason for PPI in cirrhotics might be prevention and treatment of esophageal complications after banding/ sclerotherapy.
- But evidence for protective role of PPI is scarce.

World journal of gastroenterology: WJG, *14*(19), 2980.

- So what is this scarce evidence?
- Is there new evidence?

Clinical Question

P	Patients with variceal hemorrhage	
I	Proton pump inhibitor	
C	Placebo/ standard of treatment	
O	Efficacy: - Ulcer size/ no. - Rebleeding - Hospitalization - Length of stay	Safety: - ADR - Withdrawal due to ADR

Search Strategy

Databases	Medline, Embase, Central, Google Scholar, IPA
Search Strategy	(Esophageal varices OR gastric varices OR variceal hemorrhage OR variceal bleeding) AND (Proton pump inhibitor OR PPI OR esomperazole OR omeprazole OR pantoprazole OR rabeprazole OR lansoprazole)
Limits	English, Humans
Results	4 RCT 3 Single-arm trials 2 Retrospective cohort

Evidence

- Sclerotherapy
- Ligation (+1 new trial)
- Long-term protective effect
- Acute phase management

Sclerotherapy

	Gimson et al 1990	Johlin et al 1992	Jaspersen et al 1995	Garg et al 1995
Design	Single arm trial			DB RCT
P	Patients with post-sclerotherapy ulcer, nonhealing despite prolonged treatment with H2RA/ sucralfate			Patients with history of variceal hemorrhage undergoing sclerotherapy
I	Omeprazole PO			Omeprazole 20mg daily PO until varices obliteration (n=23)
	40mg daily x 8 wk (n=10)	20mg BID (n=9)	40mg BID (n=14)	
C	-			Placebo (n=24)
O	Complete healing in all 10 cases, with 2 recurrences	Complete healing in 7 cases w/in 8 weeks	Complete healing in all 14 cases w/in 2 weeks	Slightly better with omeprazole but NSS for rebleeding, symptoms, esophageal ulcers and ulcer healing

Gastroenterology, *99*(6), 1829-1831.
Digestive diseases and sciences, *37*(9), 1373-1376
Journal of gastroenterology, *30*(1), 128-130
Gastrointestinal endoscopy, *55*(7), 784-793

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Sclerotherapy

	Gimson et al 1990	Johlin et al 1992	Jaspersen et al 1995	Garg et al 1995
Com-ments	Uncontrolled Non-healing ulcer Healing of ulcer not the most objective endpoint			DB RCT Prophylaxis No power calculation Ulcer in 70-80%; Healing >90% w/in 2 weeks → Need for routine prophylaxis?

Ligation (EVL)

	Shaheen et al 2005	Hidaka et al 2011
Design	DB RCT	SB RCT

Hepatology, *41*(3), 588-594
Journal of gastroenterology, *47*(2), 118-126

Ligation (EVL)

	Shaheen et al 2005
Design	DB RCT
P	Patients with history of variceal hemorrhage undergoing elective EVL
I	Pantoprazole 40mg IV post banding then 40mg PO daily x 9 days (n=22)
C	Placebo (n=22)
O	Smaller ulcers in treatment group ($37mm^2$ vs. $82mm^2$, $p<0.01$) NSS for ulcer number, symptom score

Ligation (EVL)

	Shaheen et al 2005
Comments	Rigorous methodology Significance of ulcer size? Benefit for hard outcomes not demonstrated Follow up endoscopy time not reported for each group (10-14 days) More healing with time? 4 weeks later?

Ligation (EVL)

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Hepatology, *41*(3), 588–594
Journal of gastroenterology, *47*(2), 118–126

Ligation (EVL)

	Hidaka et al 2011
Design	SB RCT
P	Patients with esophageal varices successfully obliterated by elective EVL
I	Rabeprazole10mg PO daily x 2 yrs (n=21)
C	No treatment (n=22)
O	Early termination Risk of bleeding and failure of treatment lower than no treatment group (HR 0.098, p=0.029)

Ligation (EVL)

	Hidaka et al 2011
Comments	Low dose PPI used due to PK changes in cirrhotics Excluded patients with: • postbanding ulceration despite PPI • ongoing pharmacological treatment →Child Pugh classification: A 77% (continued)

Ligation (EVL)

	Hidaka et al 2011 (continued)
Comments	Did not exclude those with a history of peptic ulcer (12%) Did not report PPI use prior to eradication Did not report GERD incidence/ motility of each group Results seem to support long-term PPI use but recommendation based on 5 extra bleeds and 2 extra severe complications in a selected group

Long-Term Protective Effect

	Garcia-Saenz-de-Sicilia et al 2010
Design	Retrospective cohort (12/1/2004-12/1/2006)
P	Patients with cirrhosis and endoscopic evidence of portal hypertension
I	PPI x $\geq$8 weeks (n=48)
C	No PPI (n=57)
O	NSS for bleeding related to portal hypertension (9 [PPI] vs. 8 [no PPI], p=0.51)

World journal of gastroenterology: WJG, *16*(46), 5869

Long-Term Protective Effect

	Garcia-Saenz-de-Sicilia et al 2010
Comments	No information about: 1) previous endoscopic procedure 2) previous bleed 3) portal pressure Significant baseline difference: PPI group: 1) more gastric/ esophageal varices (92% vs 70%, p=0.006) 2) trend of larger varices and more red signs Confounding by indication? (continued)

Long-Term Protective Effect

	Garcia-Saenz-de-Sicilia et al 2010 (continued)
Comments	PPI exposure definition: 8 weeks before 1st episode of bleed/ initial evaluation Hypothesis generating at best

Acute Phase Management

	Alaniz et al 2009	Lo et al 2013
Design	Retrospective cohort	DB NI RCT

Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, *29*(3), 248-254
Journal of gastroenterology and hepatology, *28*(4), 684-689.

Acute Phase Management

	Alaniz et al 2009
Design	Retrospective cohort
P	Patients receiving octreotide for variceal hemorrhage
I	Continuous pantoprazole infusion for >24h (n=53)
C	No pantoprazole or continuous pantoprazole infusion for <24h or intermittent use (n=77)
O	NSS for amount of packed RBC transfused NSS for subgroup analyses of infusion >72h and gastric varices

Acute Phase Management

	Alaniz et al 2009
Comments	Allowed for empiric use of PPI according to consensus guideline and clinical practice Baseline differences? No reporting for variceal size, red sign, portal pressure PPI infusion >24h: 1) Longer infusion of octreotide (70.9h vs. 48.4h, p=0.0001) 2) Trend of ↑blood product transfusion and rebleeding No power calculation May be sicker patient or treated more aggressively by physicians (continued)

Acute Phase Management

	Alaniz et al 2009 (continued)
Comments	No adjustment for physician – different standard in transfusion threshold/ goal Does not rule out advantage of PPI in acute setting, but questions excessive use of high-dose PPI

Acute Phase Management

	Alaniz et al 2009	Lo et al 2013
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Acute Phase Management

	Lo et al 2013
Design	Partially B NI RCT
P	Cirrhotic patients with acute esophageal variceal bleeding achieving hemostasis with EVL
I	Omeprazole 40mg IV daily x 5 days/ pantoprazole 40mg IV daily x 5 days + pantoprazole 40mg PO daily x 14 days (n=58)
C	Terlipressin 1mg IV q6h x5 days/ somatostatin 250mcg/h IV x 5 days (n=60)
O	NSS for initial hemostasis (<2d), very early rebleeding (2-5d) and treatment failure (<5d) Less ADR in PPI group (6% vs. 55%, p<0.001)

Main outcomes

	Vasoconstrictor group (n=60)	PPI group (n=58)	P
Treatment failure	2	1	NS
Failure to control acute bleed (<2days)	1 (*E varices)	0	NS
Very early rebleeding (2–5days)	1 (*E ulcer)	1 (*E ulcer)	NS
Rebleeding between 6–42days	5 *E ulcerx1, *E varicesx3, gastric varices x1	5 *E varices x4, gastric varices x1	NS
*E ulcers at 2wk	18/21 (86%)	14/22 (64%)	NS
*E ulcer >1.5cm	6/21 (29%)	1/22 (5%)	<0.04
Rubber band	3.5+0.5	3.2+0.6	NS
Hospital stay, mortality, transfusion need			NS

* E = esophageal

Acute Phase Management

	Lo et al 2013
Comments	Once hemostasis achieved by EVL, vasoconstrictor not as important as 1/3 bleeding due to EVL ulcer Excluded: 1) those on beta-blocker 2) gastric varices 3) seriously ill (11 fail to arrest bleeding, 12 Child-Pugh >13) Use of PPI prior to EVL not reported Benefits of terlipressin diluted by somatostatin (continued)

Acute Phase Management

	Lo et al 2013 (continued)
Comments	Only 1/3 patients receive follow-up endoscopy More esophageal ulcer but not more rebleeding in vasoconstrictor group Very encouraging, but would like to see more trials with more patients before replacing therapy with mortality benefit with PPI, especially in severely ill patients

Evidence

- Sclerotherapy
  - No role for routine prophylaxis
- Ligation (+1 new trial)
  - May ↓esophageal ulcer size and bleeding; optimal dose/ duration?
- Long-term protective effect
  - Role uncertain
- Acute phase management
  - Uncertain role for high dose
  - Potential role in ↓ulcer post EVL

Safety of PPI

- Short term – excellent

- Consequences of long term acid suppression?
  - SBP (meta-analysis OR 2.77)
  - C diff
  - Pneumonia
  - Fracture risk? Magnesium, B12 deficiency?

Annals of Pharmacotherapy, *46*(10), 1413-1418

Conclusion

- Over prescribing of PPI
- More evidence showing benefit and lack of benefit
  - Retrospective studies/ small trials with flaws in designs
  - Compared different endpoints
- Potential role in ↓esophageal ulcer from EVL
  - Evidence showing these ulcers to be self-limiting
  - Translate into less bleeding?
- Who would continue the high-dose PPI?
- Who would step the patient down to PO PPI?
  - For how long? What dose?

Thank You
Q & A