ROLE OF REBAMIPIDE IN POSTBANDING ULCERS VARICEAL AFTER BAND LIGATION: A RANDOMIZED PILOT TRIAL

Thesis

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Abstract

In the post banding first week the mean number of ulcers was 2.15 in the rebamipide group compared to 3.3 and 3.6 in the sucralfait and pantoprazole groups respectively. After two weeks of banding the rebamipide group has a mean of 1.25 ulcer while the mean was 2.2 ulcer in the sucralfait group compared to a mean of 2.35 ulcer in the pantprazole group and this differences were statistically significant.

Key word:

MAP , APC, REBAMIPIDE, ULCERS,

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Last but not least, I would like to show all my thanks to my patients hoping this can help to alleviate their pains.

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- **ABG:** Arterial blood gas
- **ADH:** antidiuretic hormone.
- **APC:** argon plasma coagulation.
- **AST:** aspartate aminotransferase.
- **CBC:** Complete blood count.
- **Cm:** Centimeter.
- **EGD:** Esophagogastroduodenoscopy.
- **EGF:** Epidermal growth factor.
- **eNOS:** endothelial nitric oxide synthase.
- **ERK:** Extracellular signal-regulated kinases.
- **ES:** Endoscopic sclerotherapy.
- **ET:** endothelin.
- **EVL:** Endoscopic variceal ligation.
- **GE:** gastroesophageal.
- **GI:** Gastrointestinal.
- **GTP:** Guanosine triphosphate.
- **H. pylori:** Helicobacter pylori.
- **HGF:** Hepatocyte growth factor.

- **HVPG:** hepatic venous pressure gradient.
- **MAP:** mitogen activated protein.
- **mL:** milliliter.
- **NASH:** non alcoholic steatohepatitis.
- **NO:** Nitric oxide.
- **NSAIDs:** Nonsteroidal anti-inflammatory drugs.
- **PHG:** portal hypertensive gastropathy.
- **PT:** Prothrombin time.
- **PTE:** Percutaneous transhepatic embolization.
- **TIPS:** Transjugular intrahepatic portosystemic shunt .
- **VEGF:** Vascular endothelial growth factor.
- **WHVP:** wedged hepatic venous pressure
- **ALT:** Alanine Aminotransferase
- **BMI :** body mass index
- **DM:** diabetes Mellitus.
- **GOT:** glutamic oxaloacetic transaminase.
- **GPT:** Glutamyl pyruvic transaminase.
- **HBsAg:** Hepatitis B surface antigen.
- **HCV AB:** Hepatitis C virus antibody.
- **kg/m²:** Kilogram per square meter.

- **NHTMRI:** National Hepatology and Tropical Medicine Research Institute .
- **PPI:** proton pump inhibitors.
- **RBS :** random blood sugar.
- **TB:** Tuberculosis.

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Introduction

Portal hypertension is the haemodynamic abnormality associated with the most severe complications of cirrhosis, including ascites, hepatic encephalopathy and bleeding from gastroesophageal varices. Variceal bleeding is a medical emergency associated with a mortality that, in spite of recent progress, is still in the order of 20% at 6 weeks ***(De Franchis, 2005)***. The management of the patient with cirrhosis and portal hypertensive gastrointestinal bleeding depends on the phase of portal hypertension at which the patient is situated, from the patient with cirrhosis and portal hypertension who has not yet developed varices to the patient with acute variceal hemorrhage for whom the objective is to control the active episode and prevent rebleeding (***Garcia-Tsao et al., 2007***).

Endoscopic variceal ligation (EVL) was originally developed for the treatment of hemorrhoids . It involves the placement of elastic O-ring ligatures over esophageal varices, causing strangulation of the vessels.Proposed for the treatment of esophageal varices as a method for obtaining hemostasis in acute bleeding ***(Laine et al., 1993)***. EVL has also been used electively for the prophylaxis of recurrent variceal bleeding. It has been proposed as a standard of care to electively perform serial sessions of EVL to obliterate varices in patients with a history of hemorrhage from esophageal varices. The use of EVL has been favored over endoscopic sclerotherapy because it has a similar efficacy in achieving hemostasis but with fewer complications ***(Stiegmann et al., 1992).*** Approximately 3 to 7 days after banding, the strangulated varix sloughs off, leaving a shallow ulcer that typically heals in 14 days ***(Young et al., 1993).***

Variceal banding ligation is associated with side effects of its own which can be classified as those resulting from elastic band ligation itself and its tissue effects. Minor complications such as transient dysphagia and chest discomfort, pain from ulceration and dysphagia **(*Toyoda and Fukuda, 2001*)**. Shallow ulcers at the site of each ligation are the rule and rarely bleed **(Stiegmann et al., 1992).**

Few data exist regarding adjuvant therapy for EVL. The few groups who have attempted to determine if adjuvant therapy reduces complications have reported mixed results ***(Nicholas et al., 2005). Nijhawan and Rai (1994)*** randomized 30 subjects undergoing elective EVL to treatment with either sucralfate or placebo. No difference in healing was found between the two groups. Conversely , treatment of sclerotherapy ulcers with sucralfate was shown to speed healing in a randomized controlled trial of 45 patients **(Yang et al.,1998)** . However **Lo et al. 2001** found that the combination of ligation nadolol and sucralfait (triple therapy) proved more effective than band ligation alone in term of prevention of variceal recurrence and upper gastrointestinal re-bleeding as well as variceal re-bleeding. ***Nicholas et al., 2005*** found that, pantoprazole reduces the size of post-banding ulcers after variceal band-ligation in a randomized controlled trial.

Some gastric mucosal protective agents have anti-inflammatory and anti-oxidant effects Rebamipide is an anti-ulcer drug, and has unique properties such as anti-inflammatory action ***(Bamba et al. 2003).*** Rebamipide's mechanisms of actions are different from anti-secretory drugs; it accelerates and improves the quality of ulcer healing and reduces ulcer recurrence rate. Numerous studies have been conducted to explain the

mechanisms responsible for these actions. Major properties of rebamipide include: stimulation of prostaglandin and mucus glycoprotein synthesis, inhibition of reactive oxygen species, inflammatory cytokines and chemokines, and inhibition of neutrophils activation ***(Arakawa et al. 2005).*** Rebamipide can protect against the occurrence of esophagitis and has highly promising potential as a new therapeutic agent for reflux esophagitis. It significantly reduced both macroscopic and microscopic injuries and increases in inflammatory mediators as reported in a rat model of mixed reflux esophagitis ***(Katada et al. 2005)***.

Rebamipide activates in gastric epithelial cells a genetic program that promotes angiogenesis and signals cell growth and tissue regeneration. In addition, rebamipide treatment directly stimulates angiogenesis in gastric microvascular endothelial cells. Thus rebamipide has two separate and distinct mechanisms of proangiogenic action: one through activation in gastric epithelial cells of proangiogenic growth factor genes and the second a direct angiogenic action on microvascular endothelial ***(Tarnawski 2004).***

Aim of the work

The aim of this study is to assess the use of mucosal protective agents with (rebamipide) in the setting of elective variceal band ligation to reduce the incidence and enhance healing of oesophageal post banding ulceration.

Chapter (1)

Esophageal Varices