

# Endoscopic Variceal Ligation and $\beta$ -Blocker Combination Versus Ligation Monotherapy as Variceal Esophagus Bleeding Secondary Prevention

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## ABSTRACT

**Background:** Variceal esophagus' risk of re-bleeding in the first year is 60-70%. Mortality rate of acute bleeding is 20-35%. Latest guidelines of esophageal rupture suggest endoscopic ligation and Non-selective  $\beta$ -Blocker combination for re-bleeding prevention. However, monotherapy still can be chosen, depends on the clinical judgement and patient preference. The previous meta-analysis still gave inconclusive results on therapy combination effectivity. Moreover, there is no side effect discussion between both treatment choices. Hence, this evidence-based case report analyses the effectivity of combination treatment for esophageal bleeding secondary prevention.

**Method:** Literature searching in Scopus, ProQuest, PubMed, ScienceDirect, and EBSCOhost used keywords and their synonyms. Three articles selected included two meta-analyses and one RCT. Critical appraisal on validity, importance, and applicability based on Oxford Center of EBM 2011 was conducted.

**Results:** Two meta-analysis prove treatment combination is significantly effective decreasing variceal re-bleeding. Ravipati et al. results in RR 0.601 (95% CI: 0.44 - 0.82). However, Kumar et al. shows non-significant result. On the other hand, three articles show that therapy combination failed to significantly lower the mortality rates RR 0,786 (95% CI: 0,45 - 1,39). This is due to the limitation of treatment combination to prevent cirrhotic progression and other complications. Moreover, this also is due to contraindications and non-suitability of the patients toward non-selective  $\beta$ -Blocker in 30-40% cases.

**Conclusion:** Endoscopic ligation and non-selective  $\beta$ -Blocker combination is recommended for variceal esophagus bleeding secondary prevention, but other treatments are needed to lower the mortality rate1.

**Keywords:** endoscopic variceal ligation, non-selective  $\beta$ -blocker, variceal Esophagus Bleeding

## ABSTRAK

**Latar belakang:** Risiko terjadinya perdarahan varises ulang dapat terjadi dalam 1 tahun pertama sebanyak 60-70% kasus, sedangkan mortalitas akibat perdarahan akut mencapai 20-35% kasus. Algoritma penanganan perdarahan variseal mulai merekomendasikan terapi kombinasi ligasi endoskopik dengan terapi Beta blocker nonselektif, namun monoterapi dapat diberikan sesuai penilaian klinis dan preferensi pasien. Beberapa meta-analisis sebelumnya masih menunjukkan hasil yang inkonklusif. Selain itu, belum terbahas mengenai efek samping antara monoterapi dengan terapi kombinasi. Maka dari itu, dilakukan laporan kasus berbasis bukti yang menelaah efektivitas penggunaan kombinasi terapi untuk pencegahan sekunder perdarahan variseal akut.

**Metode:** Pencarian literatur dilakukan dari Scopus, ProQuest, PubMed, ScienceDirect, dan EBSCOhost dengan menggunakan kata kunci beserta istilah lainn yang terkait. Seleksi menghasilkan 2 artikel meta-analisis dan 1 artikel Randomized Controlled Trial. Literatur terpilih ditelaah kritis berdasarkan Oxford CEEBM Critical Appraisal Tools, meninjau aspek validity, importance, dan applicability.

**Hasil:** Dua meta-analisis membuktikan terapi kombinasi signifikan efektif dalam pencegahan perdarahan variseal berulang. Pada Ravipati et al RR = 0,601 (95% CI: 0,44-0,82). Namun Kumar et al. memberikan hasil yang tidak signifikan. Dibuktikan pada ketiga artikel bahwa terapi kombinasi tidak menurunkan mortalitas secara signifikan. RR = 0,786 (95% CI: 0,45-1,39) Hal ini karena ketidakmampuan terapi kombinasi mencegah progresi sirosis dan komplikasinya walaupun mencegah perdarahan variseal sirotik berulang. Selain itu juga berkaitan dengan kecocokan dan kontraindikasi pasien, yakni sebanyak 30-40%.

**Simpulan:** Kombinasi ligasi variseal endoskopik dengan  $\beta$ -Blocker non selektif direkomendasikan untuk pencegahan sekunder perdarahan varises esofagus sirotik.

**Kata kunci:** ligasi variseal endoskopik,  $\beta$ -blocker non selektif, perdarahan varises esofaus, pencegahan sekunder perdarahan variseal.

## INTRODUCTION

Variceal esophagus bleeding is one of severe complications of portal hypertension Initial treatment of acute bleeding control is followed by the high risk of future rebleeding.<sup>1,2</sup> Without any further adequate management, 60-70% variceal re-bleeding cases will occur in the first year and 30-40% in the first six months.<sup>2</sup> Mortality of variceal esophagus bleeding reaches approximately 20-35%.<sup>2</sup> Hence, Secondary prevention procedures for survived patient from acute variceal bleeding are proposed.

In many years,  $\beta$ -Blocker pharmacotherapy and endoscopic sclerotherapy was the first line of treatment and prevention of variceal rebleeding.<sup>3</sup> Then, endoscopic variceal ligation was proven to be chosen treatment as it increased the safety and efficacy on variceal esophagus treatment.<sup>3</sup> Besides, pharmacology treatment is also developing nowadays. Both endoscopic ligation and pharmacological treatments work in different mechanism, where they could decrease portal tension and eradicate local varices.<sup>3</sup> Thus, both treatments have potential to be additively combined. This principal has been researched through clinical trials. Moreover,  $\beta$ -Blocker therapy could add protection effect on recurrent bleeding before the next obliteration step of variceal ligation.<sup>1,3</sup>

The latest algorithm in variceal esophagus bleeding management guidelines starts to recommend the combination of both treatments.<sup>4</sup> However, monotherapy (endoscopic ligation or pharmacotherapy alone) still can be chosen for the patient based on clinical judgement and patient preference.<sup>4</sup> Some previous meta-analysis gave inconclusive results

to decide which treatment alternative is the best. Moreover, different side effects of both choices have not been discussed and compared in the previous researches.<sup>1,2</sup>

Hence, this evidence-based case report is made from the latest articles to study the efficacy of combination therapy compared to endoscopic ligation monotherapy as secondary prevention of acute variceal esophagus bleeding.

## CLINICAL QUESTION

A 49 years old male patient came to Cipto Mangunkusumo Hospital with hematemesis 2 hours prior to admission. Hematemesis was in the form of fresh blood without any food, 250 cc volume, and happened without any specific trigger. His first hematemesis was 2 months prior to admission, with approximately 600 cc fresh blood. Then, patient was in pale appearance and lethargy. He was stabilized in Tangerang General Hospital Emergency Unit, then deny any further treatment. Six months prior to admission, patient realized icteric appearance on both eyes and skin, with intermittent fever. Sometimes, he realized melena in his defecations. He denies any pale feces and dark brown urine.

From physical examination, there was tachycardia, icteric sclera, gynecomastia, schuffner 3 splenomegaly, increased bowel sound (14 times per minute), and palmar erythema.

Laboratory examination showed prothrombin time (PT)/activated partial thromboplastin time (APTT) increments, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) increments, non-reactive HBsAg and non-reactive AntiHCV.

Esophagogastroduodenoscopy showed grade 3 varices esophagus, gastropathy, and erosive gastritis. Ultrasonography (USG) showed splenomegaly without any thrombus. Then, Fibroscan resulted on F2-F3 hepatitis non B non C.

Patient was diagnosed with grade 3 esophagus varices, non B non C hepatic cirrhosis (Child Pugh A) and erosive gastritis. Abdominal angiography computed tomography (CT) scan was planned for this patient. Pharmacological therapy given to the patient included intravenous fluid drops (IVFD) asering 500 mL/24 hours, somatostatin bolus 100 mcg, vitamin K 3x10 mg, tranexamic acid 3x1000 mg, cefotaxime 3x1g, and lansoprazole 1x30 mg, sucralfate 3x15 mL. Non-pharmacological therapy on this patient was 1700 kcal/day diet. Esophagogastroduodenoscopy (EGD) with endoscopic variceal ligation was then planned for this patient.

In patient with variceal esophagus bleeding, how is non-selective  $\beta$ -Blocker and endoscopic variceal ligation combination therapy compared to endoscopic ligation monotherapy for secondary prevention on recurrent esophagus bleeding?

**METHOD**

Literature searching was conducted on 7-14 October 2018 in PubMed, Science Direct, EBSCOhost, Scopus, and ProQuest database. Keywords used included “Esophageal varices bleeding”, “Variceal band ligation”, and “Beta blocker” and any other words related or synonyms, then they were combined in a Boolean (Table 2). First attempt on literature searching had no specific limit.

Through literature searching using the keywords mentioned above, 1813 articles were obtained. Articles

Database	Keywords	First attempt	Selection I	Final results
PubMed	(esophageal varices bleeding OR esophagus variceal rupture) AND (variceal band ligation OR endoscopic ligation) AND (beta blocker OR propranolol OR nadolol OR carvedilol)	525	13	1
Science Direct		300	8	1
EBSCOhost		181	10	1
Scopus		166	6	0
ProQuest		641	22	0

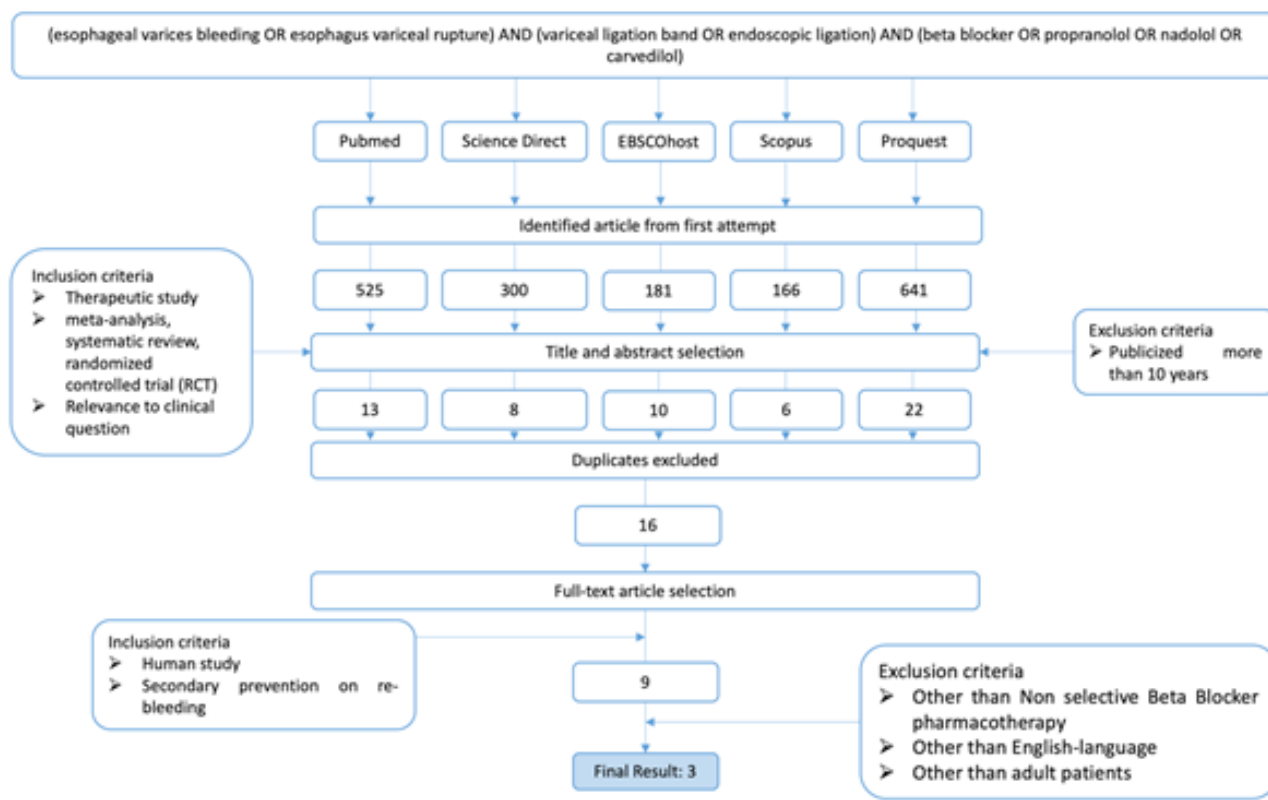


Figure 1. Flowchart of literature searching strategy

**Table 1. Critical appraisal of meta-analysis**

Meta-Analysis	Validity			Importance					Applicability			
	Clinical Question	Searching strategy	Appropriate Inclusion	Validity	Consistency	RR	RRR	p	Patient similarity	Feasibility in my setting	Benefits outweigh harms	
Ravipati et al, 2009		+	+	+	+	+	0.601 (95 CI: 0.440 - 0.820)	0.399	0.001	+	+	+
Shi et al, 2017		+	+	+	+	+	OR = 0.37 (95%CI: 0.16-0.86)				+	+

RR: relative risk; RRR: relative risk reduction

**Table 2. Critical appraisal of randomized controlled trial**

RCT	Validity					Importance				Applicability			
	Randomized	Similarity at start	Treated equally	All patients	Double blinded	RR	ARR	RRR	NNT	p	Patient similarity	Feasibility in my setting	Benefits outweigh harms
Kumar et al, 2009	+	+	+	+	+	0.89	0.02	11%	50	0.842	+	+	+

RRR: relative risk reduction; RRR: relative risk reduction; ARR: absolute risk reduction; NNT: number needed to treat

selection was conducted on some steps, including title and abstract selection, same articles selection, and full article selection. Title and abstract selection was based on inclusion criteria: therapeutic studies (meta-analysis, systematic review, and randomized controlled trial) and relevance to clinical question. Exclusion criteria included more than ten years' publication prior to this case report. From this selection stage, 59 articles were obtained. After same article reduction, the full-text article selection was conducted. In this stage, these inclusion criteria were used: human study and secondary prevention on re-bleeding objective study. Exclusion criteria used were pharmacological therapy other than non-selective Beta Blocker, other than English-language articles, and studies on patients other than adults. In the end, the whole selection process resulted in three articles, including two meta-analysis and a randomized controlled trial. Literature searching and selection was summarized in Figure 1.

Four articles obtained was critically appraised based on Oxford Center for Evidence Based Medicine year 2011 for therapeutic study and systematic review. Critical appraisal examined on three aspects: validity, importance, and applicability of each article.

**RESULTS**

Critical appraisal on validity aspect shows that all articles are proven to be valid and continued to the importance aspect of critical appraisal. (Summarized in Table 5, 6, 7, and 8). Appraisal is conducted depended on the outcome of each study which discuss the efficacy of combination therapy as variceal bleeding secondary prevention. The primary outcomes include all causes mortality, mortality due to re-bleeding, all causes re-bleeding, and variceal esophagus re-bleeding.

Secondary outcomes include varices eradication and varices recurrence. Outcome is measured as relative risk (RR), absolute risk reduction (ARR), relative risk reduction (RRR), number needed to treat (NNT), p value, odds ratio (OR), and P-score.

Meta analysis by Ravipati et al shows that combination therapy is significantly able to decrease all causes and variceal esophagus re-bleeding. However, combination therapy is not significant in decreasing all cause and re-bleeding caused mortality of the patients. Only risk ratio and risk ratio reduction can be calculated from this article. Hence, the critical appraisal on importance aspect of this meta-analysis is lack of data. In all aspects, relative risk of combination therapy usage are superior than ligation monotherapy. Especially in preventing varices re-bleeding, combination therapy reaches RR = 0.601 (95% CI: 0.440-0.820) with  $p < 0.001$ .

Outcome of the combination of endoscopic ligation with nadolol therapy in Shi et al. uses odd ratio value. This is due to lack of patients' data in each research of the meta-analysis. In this meta-analysis, combination therapy significantly lowers the acute re-bleeding

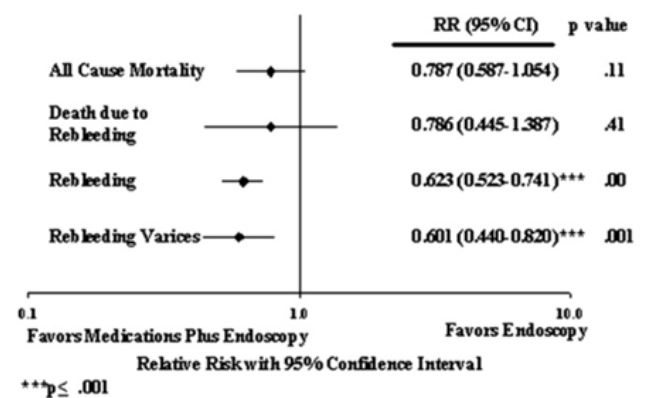


Figure 1. Forrest plot of Ravipati et al<sup>5</sup>

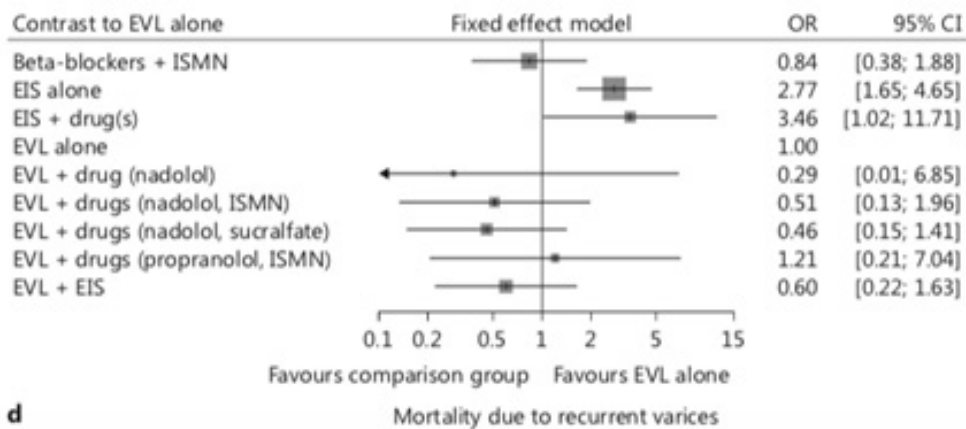
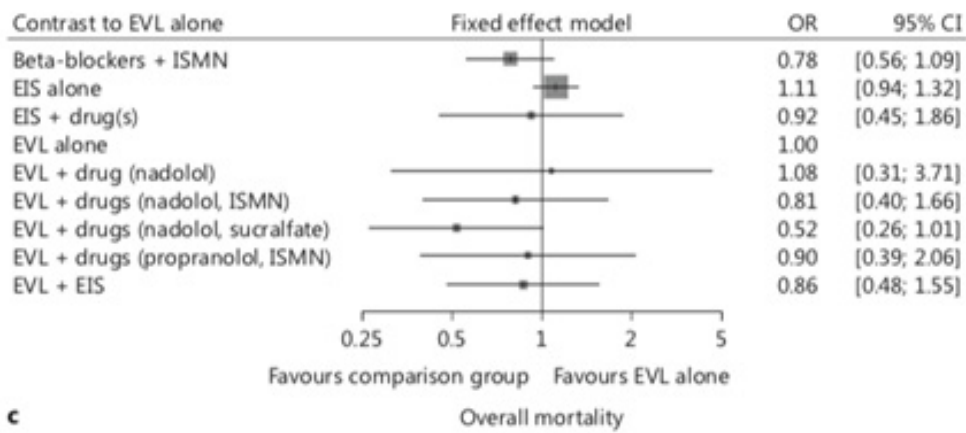
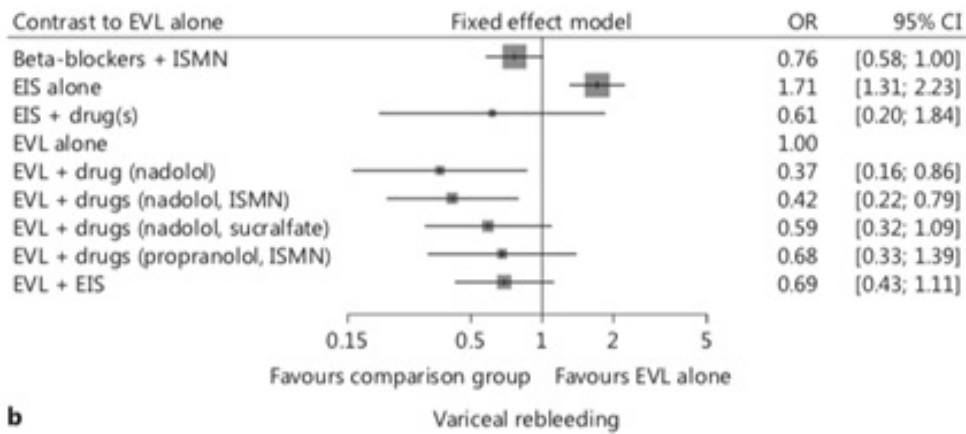
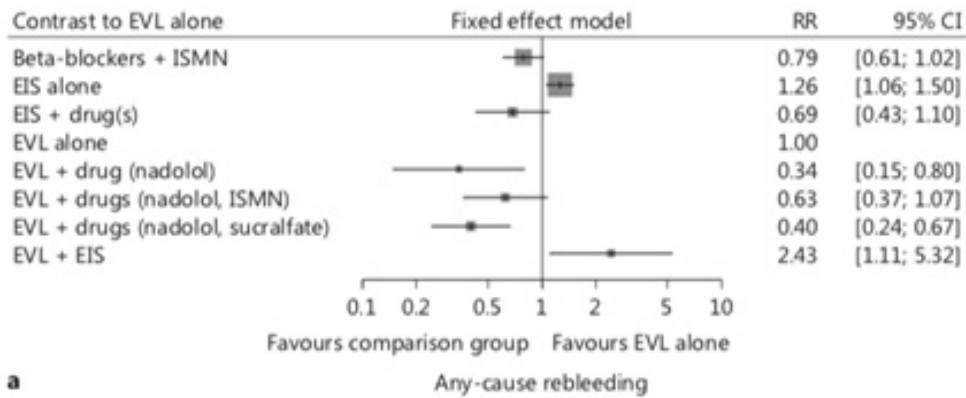


Figure 2. Forrest plot of Shi et al<sup>6</sup>



incidence. Nonetheless, combination therapy also fails to significantly lower the mortality rate, even it increases the all-causes mortality of varices esophagus patient. Based on P-Score performance on variceal re-bleeding prevention, combination therapy is also superior (P-Score = 0.8526), compared to ligation monotherapy with 0.1919 P-Score. Superiority of P-Score are also in all other aspects of outcome. Critical appraisal on importance aspect in meta-analysis by Shi et al. results in not sufficient of components, because there are not any control event rate (CER), experimental event rate (EER), RR, ARR, RRR, and NNT to calculate.

Randomized Controlled Trial by Kumar et al gives sufficient importance aspect of critical appraisal. However, all of the results are not significant, based on the p value results. The primary outcomes, including re-bleeding rate and mortality rate, are decreased by combination therapy. Besides, combination therapy insignificantly increases variceal eradication and lowers varices recurrence, superior than ligation monotherapy, as secondary outcomes of this randomized controlled trial (RCT).

Three articles are appraised on their applicability toward the patient in this case report. Applicability aspect is compared between patients in the literature and patient's characteristic of this case. Moreover, we appraised the benefits of combination therapy compared to potential side effects.

## DISCUSSION

Both meta-analysis by Ravipati et al (2009) and Shi et al (2017) proves that combination therapy is able to significantly decrease the rate of all cause re-bleeding and variceal re-bleeding. This is also supported by superior P-score of combination therapy, compared to endoscopic ligation monotherapy.<sup>5,6</sup> Mortality decrement also proven in combination therapy usage with superior P-Score than monotherapy, but with insignificant result. This superiority of combination therapy is supported by previous meta-analysis by de la Pena et al (2005) which proved the significant re-bleeding and mortality rate decrements.<sup>8,9</sup> This result also corresponds to American Association for the Study of Liver Disease 2016 guidelines and recommendations where combination therapy is the first line management.<sup>10</sup>

Rationally,  $\beta$ -Blocker has capability to add protection effect towards variceal re-bleeding before the next variceal obliteration by endoscopic ligation and prevent

variceal recurrences. It blocks  $\beta$ 1 receptor to lower cardiac output, then decreases portal tension.<sup>9,11-13</sup> Moreover,  $\beta$ 2 receptor blockage causes  $\alpha$ -adrenergic activation to stimulate splanchnic vasoconstriction and portal tension decrement.<sup>11-13</sup> Propranolol is the most frequent to use as non-selective  $\beta$ -Blocker pharmacotherapy to be combined with endoscopic ligation.<sup>5-7</sup> Besides, nadolol and carvedilol become alternatives. Propranolol is given 2 x 10-20 mg per day, then titrated up to 40 mg if heart rate reaches 55 bpm.<sup>5,6</sup> Full dosages usually reached in 2-3 weeks before the second Endoscopic ligation session. Therapy is evaluated every day in the first three months, then evaluated in the next 3 months.<sup>5-7</sup> It is concluded that even combination therapy is the best alternative, more suitable trials are needed before the recommendation is set.<sup>5,6</sup>

Different result was stated in RCT by Kumar et al which proves insignificant combination therapy usage's benefit on all aspects. Seventy-five percent of patients had no respond from  $\beta$ -Blocker treatment.<sup>7</sup> Contraindications and severe complications happened in 30-40% of patients, where they gave no appropriate hemodynamic response to lower portal tension and prevent re-bleeding.<sup>11,12</sup>

Endoscopists conduct endoscopic ligation on gastroesophageal junction upward in 5-8 cm length and helical way.<sup>5,7</sup> Ligation procedure use 5-8 elastic O-rings bands on varix in every session. Total ligation session is around 3-4 times until varices is completely obliterated.<sup>5,7</sup> Moreover, there is no guidelines to oblige specific endoscopic ligations time interval, but usually is done in 1-2 weeks interval. However, new researches suggest 3-4 weeks interval for better result.<sup>7</sup> The longer the ligation interval, the lower re-bleeding risk the patient has. This is caused by the longer period of time for partial varices recurrence to be more effectively located and ligated in the next session. Moreover, this decreases the bleeding caused by local ulcer in ligation site.<sup>5,7</sup> Optimum endoscopic ligation result gives no necessity of pharmacological combination, where it will not give any more significant benefits. This hypothesis is strongly supported in RCT by Kumar et al.

Insignificant mortality rate decrement result may be explained in RCT of Kumar et al which shows no significant decrement in other severe complications, such as: ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, and other hospitalization needs of the patients.<sup>7,11,12</sup> It is stated that  $\beta$ -Blocker has potential on increasing morbidity caused by its side effect, including headache, bradycardia, hypotension, and dyspnea. The unsuitability of patients

who get  $\beta$ -Blocker pharmacotherapy reaches up to 30-40%.<sup>7</sup>

## CONCLUSION

Based on critical appraisal on two meta-analysis and one randomized controlled trial, correlation between combination therapy and secondary prevention of variceal esophagus bleeding is still inconsistent. However, we still recommend this combination therapy based on two highest evidence level of literatures, which states significant results on variceal re-bleeding decrement. Moreover, further examination is needed in 12-24 hours before initiating therapy to check any contraindications and patient's suitability to non-selective  $\beta$ -Blocker therapy. We also conclude that combination therapy will not decrease mortality rate of the patient with post cirrhotic acute variceal esophagus bleeding. Hence, other treatments are needed to alter the cirrhotic progression and its other complications to lower the mortality rate.

We suggest other further research to study the justification between combination therapy's complications and its cost-effectiveness aspect for variceal esophagus bleeding secondary prevention. Thus, we can evaluate comprehensively to be basic principal for physician's clinical judgement and patient's preference in deciding which modality to prevent variceal esophagus re-bleeding.

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