

Secondary Prevention of Esophageal Variceal Bleeding Using Transjugular Intrahepatic Portosystemic Shunt Compared to Endoscopic Band Ligation plus Beta-Blocker

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ABSTRACT

Aim: This study aims to compare the effectiveness of transjugular intrahepatic portosystemic shunt (TIPS) against combination therapy in the secondary prevention of esophageal variceal bleeding.

Method: Literature search was conducted using 4 databases (PubMed, Cochrane, Ovid MEDLINE, and Ovid Embase) and individual hand searching. The selected studies were then critically appraised for their validity, importance, and applicability.

Results: A total of 136 results were retrieved, and 2 systematic reviews and meta-analysis of randomized controlled trials (RCTs) were selected. Both studies showed that TIPS significantly decreased incidence of esophageal variceal rebleeding but had no significant effect on reducing overall mortality when compared to combination therapy. Study by Lin et al found that TIPS was significantly better than combination therapy for reducing mortality from variceal rebleeding, but study by Jing et al found no significant difference.

Conclusion: TIPS is superior to combination therapy in reducing the incidence of esophageal variceal rebleeding. Nevertheless, its effectiveness in reducing mortality needs further investigation. Future research should look into its complications and cost-effectiveness in developing countries like Indonesia.

Keywords: beta-blocker, endoscopic band ligation, esophageal variceal bleeding, transjugular intrahepatic portosystemic shunt, secondary prevention

ABSTRAK

Tujuan: Studi ini bertujuan membandingkan efektivitas transjugular intrahepatic portosystemic shunt (TIPS) terhadap terapi kombinasi dalam pencegahan sekunder perdarahan varises esofagus.

Metode: Pencarian literatur dilakukan menggunakan 4 database jurnal (PubMed, Cochrane, Ovid MEDLINE, dan Ovid Embase) serta pencarian secara manual. Studi yang terpilih kemudian ditelaah dari segi validitas, kepentingan, dan aplikabilitasnya.

Hasil: Sebanyak 136 studi didapatkan dari pencarian literatur, lalu 2 tinjauan pustaka sistematis dan meta-analisis dari uji acak terkendali dipilih untuk telaah kritis. Kedua studi menemukan bahwa TIPS menurunkan insidens perdarahan varises esofagus secara signifikan tetapi tidak mempunyai efek signifikan dalam menurunkan mortalitas secara umum dibandingkan terapi kombinasi. Studi oleh Lin dkk. menunjukkan bahwa TIPS jauh

lebih baik dibandingkan terapi kombinasi dalam menurunkan mortalitas akibat perdarahan varises, namun studi oleh Jing dkk. tidak menemukan perbedaan yang signifikan.

Kesimpulan: TIPS ditemukan lebih baik dibandingkan terapi kombinasi dalam menurunkan insidens perdarahan varises esofagus ulangan. Namun, efektivitas TIPS dalam menurunkan angka kematian memerlukan studi lanjutan. Diperlukan penelitian lebih lanjut terkait komplikasi dan efektivitas biaya dari TIPS di negara berkembang seperti Indonesia.

Kata kunci: beta-blocker, ligase varises, pencegahan sekunder, perdarahan varises esofagus, transjugular intrahepatic portosystemic shunt

INTRODUCTION

Esophageal varices are classic complication of cirrhosis that arise due to portal hypertension. The term refers to dilated esophageal veins which connect the portal and systemic circulations, and they require prompt surveillance as esophageal varices may rupture anytime.¹ Esophageal varices have been reported in around 50% of patients with cirrhosis, and variceal bleeding or hemorrhage might occur in 25% of these patients within 2 years.²⁻⁴ Bleeding stemming from esophageal varices is said to be the third leading cause of upper gastrointestinal tract bleeding.¹ Even if patients survive variceal bleeding the first time, the majority can develop rebleeding that may result in death.^{1,2}

Prevention of variceal bleeding is key to reducing mortality associated with esophageal varices. Primary prophylaxis involves administering nonselective beta-blockers (NSBBs) such as propranolol. An alternative option to NSBBs is endoscopic band ligation (EBL), which is performed via endoscopy to ligate the varices with rubber rings.^{4,5} Despite primary prophylaxis efforts, esophageal varices can still rupture in some patients and increase their risk of mortality. This rationale justifies the role of secondary prophylaxis, which can be defined as prevention of rebleeding in patients who have experienced prior episode(s) of esophageal variceal bleeding. Current recommendations call for combination therapy using NSBBs and EBL to be the gold standard choice for secondary prophylaxis.^{4,5} Nevertheless, in spite of the current guideline, the risks of rebleeding and mortality remain high. In addition, NSBBs and EBL each pose their own risks that may be unfavorable in some patients.^{3,6} Therefore, an alternative option with better safety profile and efficacy for secondary prevention of esophageal variceal bleeding is needed.

Transjugular intrahepatic portosystemic shunt (TIPS) is a minimally invasive procedure in which a stent is inserted to connect portal veins to adjacent blood vessels with lower blood pressure. Currently,

it is mainly indicated for secondary prophylaxis of esophageal variceal bleeding when combination therapy with NSBBs and EBL fails.^{1,4} Assessing the aforementioned limitations of NSBBs and EBL, however, early use of TIPS for secondary prevention should be considered. A randomized clinical trial by Garcia-Pagan et al found significantly higher survival rate in patients receiving TIPS than in those receiving NSBBs and EBL.⁷ Another trial by Shi et al found that TIPS was superior to combination therapy in terms of reducing mortality rate due to rebleeding.⁸ In Indonesia, the use of TIPS is still rare and therefore relatively understudied. Thus, in this evidence-based case report, we seek to summarize evidence from recent studies which compared the use of TIPS versus combination therapy using NSBBs and EBL for the secondary prevention of esophageal variceal bleeding.

CASE ILLUSTRATION

A 39-year-old Indonesian male patient was brought to the ER with a chief complaint of vomiting blood (hematemesis) starting from 1 day before admission. The blood was said to be bright red in color with jelly-like consistency, around 100 cc in volume, and preceded by nausea. Fever, dyspnea, heartburn, diarrhea, constipation, abdominal pain associated with eating, long-term consumption of non-steroidal anti-inflammatory drugs (NSAIDs), or other symptoms were not reported. 2 years prior, the patient had experienced hematemesis with similar features to this current episode. The hematemesis was followed by black, tarry stool consistent with characteristics of melena. Since then, the patient had only received symptomatic drugs. No history of endoscopic band ligation was reported. The patient had a history of alcohol consumption every 3 months in his youth. He also smoked half-pack of cigarettes a day for 24 years.

The attending physician is aware that combination therapy using beta-blockers and endoscopic band ligation is the current gold standard for preventing

future episodes of esophageal variceal bleeding. She wonders whether transjugular intrahepatic portosystemic shunt (TIPS) could offer better secondary prevention outcomes for the patient.

CLINICAL QUESTION

In patients with prior episode of esophageal variceal bleeding, does transjugular intrahepatic portosystemic shunt (TIPS) offer better outcomes compared to combination therapy using endoscopic band ligation (EBL) and beta-blocker?

Table 1. PICO framework

PICO framework	
Patient/problem (P)	Patients with prior episode of esophageal variceal bleeding
Intervention (I)	Transjugular intrahepatic portosystemic shunt (TIPS)
Comparison (C)	Endoscopic band ligation + beta-blocker (combination therapy)
Outcome (O)	Incidence of rebleeding, rebleeding-related mortality, overall mortality
Type of clinical question	Intervention
Study design	Randomized controlled trial (RCT), systematic reviews, and meta-analysis of RCTs

METHOD

Searching Strategy

Literature search was conducted between 15-17th of June 2022 on several databases: PubMed, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials, Ovid MEDLINE, and Ovid Embase. Manual searching from systematic reviews was also implemented to identify additional resources. The key terms used in the search included “esophageal variceal bleeding”, “transjugular intrahepatic portosystemic shunt”, “beta-blocker”, “endoscopic band ligation”, “secondary prevention”, and their synonyms as depicted in Table 2. A total of 136 results were obtained, and 59 duplicates were found and removed. The remaining records then underwent title, abstract, and full text screening following certain inclusion and exclusion criteria.

Table 2. Literature search strategy

Database	Search strategy	Results
PubMed		29
Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials	((("esophageal variceal bleed**" OR "esophageal varices" OR "oesophageal variceal bleed**" OR "oesophageal varices" OR "bleeding esophageal varices" OR "bleeding oesophageal varices" OR "esophageal variceal hemorrhage") AND ("transjugular intrahepatic portosystemic shunt" OR (TIPS))) AND ((beta-blocker* OR beta blocker* OR pharmacotherap* OR β -blocker*) AND ("endoscopic variceal ligation" OR EVL OR "endoscopic band ligation" OR EBL))) AND (secondary prevent* OR secondary prophylaxis OR rebleeding OR bleeding OR efficacy OR effectiveness)	16
Ovid MEDLINE		30
Ovid Embase		60
Hand-searching from systematic review		1

Eligibility Criteria

The eligibility criteria for this case report were made according to the PICO formulated above. The inclusion criteria were: 1) adult patients with previous episode of esophageal variceal bleeding and no ongoing episode of active bleeding; 2) TIPS as intervention of interest; 3) combination therapy using only beta-blocker and EBL as reference; 4) outcomes of interest focused on secondary prevention only; 5) study designs of either RCT or systematic reviews and meta-analysis only; 6) human studies.

Meanwhile, the exclusion criteria were: 1) pediatric patients; 2) patients with no history of esophageal variceal bleeding or patients with history of only gastric variceal bleeding; 3) patients who had received liver transplant or failed previous treatment (refractory bleeding); 4) non-English studies; 5) non-human studies; 6) inaccessible studies; 7) study designs of case reports, commentaries, guidelines, protocols, conference abstracts, cohort studies, and case controls studies.

Article Selection and Critical Appraisal

A total of 136 results were initially obtained from literature search through the 4 databases and hand-searching. Following removal of duplicate records, 77 studies were gathered and screened through their titles and abstracts. Of those, 71 studies did not meet the aforementioned eligibility criteria. Subsequently, the remaining 6 records were then further assessed for eligibility through their full texts. From the 6 full texts, 2 were excluded due to having wrong comparison (TIPS was not compared to beta-blocker + EBL only) while another 2 were excluded because they were already included in the systematic reviews and meta-analysis. Hence, the remaining 2 studies were included in this case report. The study design for both studies is systematic review and meta-analysis of RCTs. The tool used to appraise the validity, importance, and applicability of the studies was the Oxford critical appraisal worksheet for systematic review by Oxford Center for Evidence-Based Medicine (CEBM).⁹

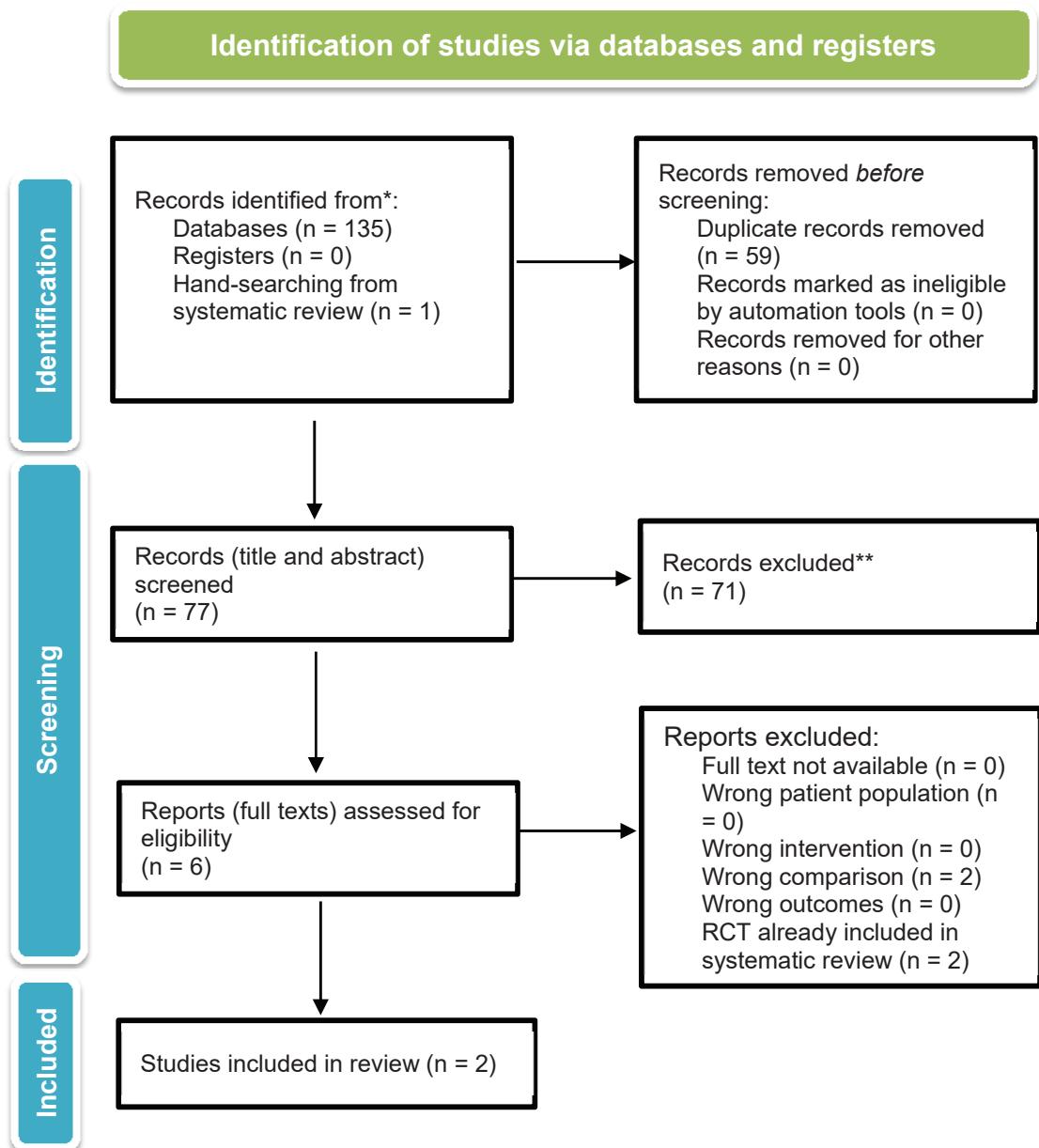


Figure 1. Flowchart illustrating search strategy and article selection

Table 3. Study characteristics

Author	Population	Intervention*	Comparison	Outcome	Conclusion	Level of evidence ^{1,2}
Lin et al (2017) ¹⁰	Adult patients older than 16 years of age with at least one previous episode of esophageal variceal bleeding	TIPS EBL only NSBBs only	Combination therapy using NSBBs and EBL	TIPS had no significant effect on overall mortality (RR = 1.39, 95% CI: 0.92-2.09, $I^2 = 53.7\%$, $p = 0.115$) when compared to combination therapy	TIPS was superior to combination therapy in decreasing rebleeding, rebleeding-related mortality, but not overall mortality. We recommend TIPS for the secondary prevention of esophageal variceal bleeding.	1 (Systematic review of randomized trials)
Jing et al (2021) ¹¹	Adult patients with liver cirrhosis with only one previous episode of esophageal variceal bleeding	Interventional therapy: TIPS Endoscopy: EBL, EIS, EBL + EIS Drugs: beta-blockers, beta-blockers + isosorbide-5-mononitrate	Interventional therapy: TIPS Endoscopy: EBL, EIS, EBL + EIS Drugs: beta-blockers, beta-blockers + isosorbide-5-mononitrate	TIPS had no significant effect on reducing overall mortality when compared to combination therapy (OR = 0.73, 95% CI: 0.34-1.55) but significantly reduced esophageal variceal rebleeding (OR = 0.28, 95% CI: 0.13-0.58)	TIPS was more effective than combination therapy in reducing the incidence of rebleeding, rebleeding-related mortality, and overall mortality. We recommend TIPS for the secondary prevention of esophageal variceal bleeding.	1 (Systematic review of randomized trials)

TIPS: transjugular intrahepatic portosystemic shunt, NSBBs: nonselective beta-blockers, EBL: endoscopic band ligation, EIS: endoscopic injection sclerotherapy

*Both meta-analyses compared multiple interventions with one another, but this case report only focused on the comparison between TIPS and combination therapy using NSBBs and EBL. Any other combination was ignored and not included in this report.
**Jing et al compared multiple interventions to one another, hence there were multiple comparators instead of one. This case report only focused on the comparison between TIPS and combination therapy using NSBBs and EBL.

RESULTS

Study Characteristics

The two selected studies by Lin et al and Jing et al respectively are both systematic reviews of meta-analysis of RCTs.^{10,11} The characteristics of each study are displayed in Table 3.

Critical Appraisal

Critical appraisal of the included studies was done using the Oxford critical appraisal worksheet for systematic review by Oxford Center for Evidence-Based Medicine (CEBM).⁹ Validity, importance, and applicability of each study was carefully examined.

Validity

Table 4. Validity appraisal of studies by Lin et al and Jing et al^{10,11}

Parameter	Lin et al	Jing et al
Does the systematic review address a focused question (PICO)?	Yes	Yes
Did they define clear eligibility criteria to direct the search and select articles for inclusion?	Yes	Yes
Did the search find all the relevant evidence?	Yes	Yes
Have the studies been critically appraised?	Yes	Yes
Did they only include high quality studies?	Yes	Yes
Have the results been totaled up with appropriate summary tables and plots?	Yes	Yes
Did they assess and explain any heterogeneity between studies?	Yes	Yes

A summary of the validity of the two included studies can be found in the Table 4. Both studies fulfilled all the validity criteria, thus suggesting high accuracy and reliability of the results presented. This indicated that the studies by Lin et al and Jing et al respectively followed a scientifically sound approach when analyzing the evidence from their included trials. Both studies addressed a focused clinical question by evaluating the effectiveness of multiple secondary prophylaxis interventions in the prevention of rebleeding and mortality from esophageal variceal bleeding. For these studies to be included in our report, their analysis had to include a comparison between TIPS and combination therapy using NSBBs and EBL only as this is the case report's point of interest. Regarding eligibility criteria, both systematic reviews had clearly outlined the inclusion and exclusion criteria including the type of study design (RCTs only) in their Methods section. Both Lin et al and Jing et al utilized

3 databases (PubMed, EMBASE, Cochrane Central databases) for their search and performed manual search on the reference lists of retrieved trials. In the Methods section, both studies explained that they used the RCT Cochrane risk of bias tool to appraise the quality of eligible trials. The risk of bias criteria included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome evaluation, incomplete outcome data, selective reporting, and other biases. Both reviews also included only RCTs, which are highly appropriate study designs to answer clinical question about intervention. The majority of the trials showed low risk of bias on quality assessment, but most of them were marked "unclear" regarding blinding of participants and personnel as well as blinding of outcome assessment. Nevertheless, it is important to note that the use of blinding method for these trials may not be entirely feasible. For example, since the two interventions being compared (TIPS vs NSBBs + EBL) were completely different in nature, the participants or personnel were likely to notice the difference. Finally, both studies included appropriate summary tables and plots as well as assess the heterogeneity between studies using chi-square tests.

Importance

The outcomes of interest in this report include overall mortality, rebleeding from esophageal varices, and rebleeding-related mortality following the two interventions being compared. Lin et al expressed these outcomes as relative risk (RR) with 95% confidence interval (CI), whereas Jing et al expressed these outcomes as odds ratio (OR) with 95% confidence interval (CI). Meta-analysis by Lin et al found that TIPS had no significant effect on overall mortality (RR = 1.39, 95% CI: 0.92-2.09, $I^2 = 53.7\%$, $p = 0.115$) when compared to combination therapy using NSBBs and EBL. However, TIPS was shown to be superior to combination therapy for decreasing esophageal variceal rebleeding (RR = 2.20, 95% CI: 1.22-3.99, $I^2 = 75.1\%$, $p = 0.045$) as well as mortality associated with variceal rebleeding (RR = 5.66, 95% CI: 1.02-31.40, $I^2 = 0.0\%$, $p = 0.490$). Combination therapy was around 2 times as likely to result in rebleeding and around 5 times as likely to result in rebleeding-related mortality when compared to TIPS. Meanwhile, evidence from Jing et al supported the findings that TIPS did not have a significant effect on reducing overall mortality when compared to combination therapy (OR = 0.73, 95% CI: 0.34-1.55) but significantly reduced esophageal

variceal rebleeding (OR = 0.28, 95% CI: 0.13-0.58). In contrast to Lin et al, Jing et al demonstrated that TIPS did not have a significant effect on rebleeding-related mortality when compared to combination therapy (OR = 0.36, 95% CI: 0.09-1.43).

Applicability

Table 5. Applicability appraisal of studies by Lin et al and Jing et al^{10,11}

Parameter	Lin et al	Jing et al
Is your patient so different from those in the study that the results cannot help you?	No	No
Is the treatment feasible in your setting?	Unclear	Unclear
Will the potential benefits outweigh the potential harms of the treatment for your patient?	Yes	Yes

The participants included in study by Lin et al were adult patients older than 16 years of age with at least one prior episode of esophageal variceal bleeding, whereas the participants in study by Jing et al were cirrhotic patients with only one previous episode of variceal bleeding. The associated chief complaints were similar among all patients, which were vomiting of blood and presence of black stool referred to as hematemesis and melena respectively. There may be slight variations among those patients compared to the patient illustrated in this case report, but these differences are not significant enough to rule out the applicability of the gathered evidence. Regarding feasibility of TIPS in our setting, it is unclear as it depends on multiple factors: expertise of the clinician, cost compared to combination therapy, availability of resource, and the patient's personal values. Prior reports had argued that TIPS might increase the risk of hepatic encephalopathy, but these were debunked by other reports and so the evidence is still unclear. The aforementioned benefits of TIPS in the secondary prevention of esophageal variceal bleeding could therefore be said to overcome its potential harms. Moreover, coupled with recent technological advancements and its minimally invasive nature, TIPS has increasingly become safer and more tolerable.

DISCUSSION

Collective evidence from the meta-analysis by Lin et al and Jing et al suggested that TIPS significantly lowered incidence of esophageal variceal rebleeding but did not have any significant effect on overall mortality when compared to combination therapy using NSBBs and EBL. However, the two studies

showed conflicting reports regarding whether TIPS was significantly better than combination therapy for lowering mortality from variceal rebleeding. These findings may be explained by referring to the mechanism by which TIPS addresses esophageal varices. TIPS involves passing a catheter down the jugular vein to form a shunt between the hepatic vein and portal vein to decompress portal venous hypertension. Hence, its mechanism directly addresses the pathophysiology behind esophageal varices which is portal hypertension. Portal hypertension can give rise to esophageal varices because the blood cannot flow freely through the liver due to damage and fibrosis. In order to bypass the liver, the circulation will be redirected through portosystemic anastomoses, one of which may occur at the esophagus causing formation of esophageal varices.¹² According to Loffroy et al, TIPS has been proven to be more than 90% effective in managing bleeding from gastroesophageal varices.¹³ Future research is needed to further comprehend the usefulness of TIPS for reducing risk of mortality.

On the other hand, the rationale behind combination therapy using NSBBs and EBL is based on their individual mechanisms of action that are thought to complement each other. Similar to TIPS, NSBBs help control esophageal varices by directly reducing the portal pressure. They act on $\beta 1$ receptors to decrease cardiac output as well as on $\beta 2$ receptors to cause splanchnic vasoconstriction and reduced portal blood flow.^{11,14} However, a significant proportion of patients have contraindications or adverse drug reactions towards this group of drugs.¹¹ The contraindications include conditions like insulin-dependent diabetes, asthma, and peripheral vascular disease. The adverse effects include feelings of lightheadedness and fatigue.⁴ Meanwhile, EBL works by inducing occlusion of the varices through thrombosis. The procedure involves capturing the varices within a small rubber band placed at the end of the endoscope.¹⁵ Unlike TIPS and NSBBs, it does not directly address the portal hypertension. Although it is generally effective for medium to large varices, EBL typically necessitates repeated sessions to completely eradicate varices and can be associated with post-ligation bleeding, ulcers, and esophageal perforation.^{4,16} While TIPS is usually reserved for those who do not respond well to combination therapy, the above findings combined with the limitations of combination therapy could justify a gradual shift to TIPS as the preferred method for secondary prevention.

Despite the apparent benefits of TIPS, it is important to note that this procedure may carry certain

risks particularly hepatic encephalopathy and stent dysfunction.^{1,17,18} As blood from portal circulation is completely diverted away from the liver to the systemic circulation, ammonia produced in the intestines will bypass the liver and may cause encephalopathy in the brain.¹⁸ Hepatic encephalopathy may range from mild cognitive deficit to serious comatose state.¹⁹ This, however, could potentially be prevented by administration of lactulose and rifaximin prior to TIPS procedure.²⁰ Moreover, since these complications were more likely due to the use of uncovered stents in the past, polytetrafluoroethylene (PTFE)-covered stents have now been increasingly used to reduce the incidence of adverse effects.^{18,21} Future research should focus on finding more effective strategies to reduce the incidence of TIPS-associated complications. In terms of cost, TIPS was reported to cost significantly more than combination therapy using NSBBs and EBL. However, the difference in cost was offset by the greater positive effect of TIPS on quality-adjusted life-years (QALYs), thereby implying that TIPS is cost-effective.²² Study by Kwan et al found similar findings, adding that TIPS may be considered cost-effective in countries where quality of health is prioritized but less so in countries where healthcare resources are limited.²³ In Indonesia, the use of TIPS is reserved only for a very small pool of patients due to its limited availability and expensive cost. Covered stents are currently not covered by the national healthcare scheme. Hence, future research should look into cost-effectiveness of TIPS in Indonesia in order to determine this study's findings' applicability.

This case report has an advantage in which the two included studies are systematic reviews and meta-analysis of RCTs, which are the most appropriate study design to address therapeutic clinical questions. Both studies fulfilled all validity criteria and almost all applicability criteria according to the critical appraisal tool used. Despite its strengths, this case report is not without limitations. First, it was unclear whether blinding of participants and personnel as well as outcome assessment were properly performed in the RCTs included in the systematic reviews. These may potentially influence the overall quality of the evidence. Second, the degree of esophageal varices severity may vary between patient populations from different RCTs, therefore impacting comparability between studies. Future investigations should be aimed at exploring the complications associated with TIPS and how they might influence its efficacy and safety profile.

In relation with the patient illustrated in this case report, the attending physician may consider the use of TIPS instead of combination therapy for secondary prevention of future esophageal variceal bleeding if the patient's values are more aligned with the objective improvement of health rather than with cost of the therapy. However, if there are financial burdens, scarce medical resources, or limited clinical expertise, the combination of NSBBs and EBL may still be sufficient to a certain extent.

CONCLUSION

Conclusion

In conclusion, the two studies by Lin et al and Jing et al agree that TIPS is significantly better than combination therapy using NSBBs and EBL for lowering the incidence of esophageal variceal rebleeding. However, its benefits on overall mortality and mortality from rebleeding remain unclear. Considering the benefits of TIPS as well as the limitations of combination therapy, it is reasonable to gradually shift to TIPS as the first-line method for secondary prevention of esophageal variceal bleeding. Future research should look into the cost-effectiveness and availability of TIPS in Indonesia.

Recommendation

More high-quality studies, particularly RCTs and systematic reviews, are needed to provide more concrete evidence regarding the efficacy of TIPS for secondary prevention of esophageal variceal bleeding compared to that of combination therapy. Future trials should include large sample sizes and patients with varying degree of esophageal varices in order to avoid selection bias or other bias. Moreover, blinding of participants and personnel and outcome evaluation must also be properly conducted whenever possible. Regarding recommendations for the patient in this case report, it is imperative that the physician first explore the patient's needs and values. As outlined above, the decision on whether TIPS or combination therapy is preferred as secondary prevention modality is affected by not only medical expertise and resources availability but also the patient's values. Future research should also aim at managing the possible complications arising from TIPS.

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