Aim: to investigate the side effects and survival of endoscopic variceal ligation by using Indonesian Endoscopic Ligator versus Endoscopic Variceal Sclerotherapy

Methods: we studied the medical records and endoscopy reports of patients who underwent endoscopic variceal ligation (EVL) or endoscopic sclerotherapy (EST) from January 2003 until December 2006. EST was done using ethoxysclerol injection; and ligation was done using a home-made Indonesian endoscopic ligating device. Patient characteristics, side effects of EVL and EST, as well as survival and length of stay were collected. Data of side effects was analyzed by chi-square test.

Results: there were no statistically significant differences of patients characteristics among both groups. The side effects in EVL group (29.2%) were less frequent than the EST group (60.9%) (p = 0.009). The death side effect in the EVL group (1.0%) was less frequent than in the EST group (21.7%) (p<0.001). The four-year survival in patients who had EVL and EST were 91.7% and 16.7%, respectively (p<0.001).

Conclusion: EVL had fewer side effects than EST in the treatment of esophageal varices bleeding. Death in the EVL group was lower than in the EST group.

Key words: side effects, EVL, EST, esophageal varices, endoscopic ligator.

INTRODUCTION

Ruptured esophageal varices is the most frequent cause of upper gastrointestinal bleeding, particularly in developing countries.1,5 It is found approximately in 30% of patients with major upper gastrointestinal hemorrhage and the mortality rates range about 15% to 40%.2

Portal hypertension, a main characteristic of liver cirrhosis, is the most common cause of esophageal varices.6-11 Toubia et al demonstrated that varices develop in 5% to 15% of patients who have cirrhosis annually and increase by 4% to 10% annually. Most patients who have cirrhosis develop varices, but only one third of them experiences variceal bleeding.1 The risk of variceal bleeding within 2 years is approximately 20-35% following the esophageal varices, and the risk of dying due to the initial variceal bleedings increases up to 50%.12-14

Treatment of variceal bleeding has been one of the most controversial subjects in medicine including sclerotherapy, oblitative angiotherapy, operation and ligation.15,16 Nowadays, there are a lot of methods to stop variceal bleeding. However, high mortality rate persists around 30% to 50%.17,19 The best current treatment for rupture of esophageal varices is endoscopic esophageal varices ligation (EVL) and endoscopic sclerotherapy (EST).2,5 In spite of their advantage, both treatments may cause adverse side effects including chest pain, ulceration, hemorrhage, esophageal strictures, bacteremia, bacterial peritonitis, pulmonary infections, etc. Endoscopic ligation treatment showed to be at least as effective as sclerotherapy but it has fewer side effects.2,5,20,22 In Indonesia, sclerotherapy is usually done by using the
ethoxysclerol and sclerotherapy needle; while ligation is usually performed using a home-made endoscopic ligating device, known as the FMUI endoscopic ligator which has been developed at the Faculty of Medicine, University of Indonesia. The home-made ligator is much cheaper than other ligators used worldwide and it is quite effective. We review our experience and focus on the side effects and patients’ survival of both treatment modalities in patients with liver cirrhosis.

METHODS

Our retrospective study included all patients who underwent EVL or EST and developed side effects from January 2003 until December 2006. We evaluated the medical records and endoscopy reports, which included age, sex and ethnicity. Patients with liver cirrhosis were categorized into EVL group and EST group. Data of patients were considered eligible, if the patients had 1) patients with liver cirrhosis aged 14-85 years; 2) patients with indication for ligation and sclerotherapy. Incomplete data and hepatoma (hepatocellular carcinoma or HCC) case were excluded.

No oral drugs were given to all patients prior to EVL and EST procedures. Both EVL and EST were performed with local anesthesia (xylocaine) and for some patients who were anxious we gave premedication by intravenous sedation (midazolam) and local xylocaine spray. The procedures were performed by experienced gastroenterologists in Cipto Mangunkusumo Hospital.

EVL was performed using a home-made endoscopic ligating device, the FMUI endoscopic ligator. It was begun in the region of gastroesophageal junction with subsequent ligations performed more proximally at 3, 6, 9, 12 o’clock position. One or more ligations were applied on each esophageal varices based on the size of varix. Our endoscopic ligator was a multiband ligator which consisted of 5 ligator bands placed on the tip of gastroscope. Two operators were needed to perform the ligation, i.e. a doctor and a nurse. The doctor held the gastroscope, directing the tip of scope and performing suction of esophageal varices. The nurse pulled the cord on the tip of channel biopsy gastroscope for unwinding the bands and subsequently performed ligation on esophageal varices. Such technique was performed repeatedly until all varices had been ligated. EVL was done every 10-14 days until the targeted variceal obliteration was achieved up to grade 0 or grade I.

EST was done using sclerosant of 1% ethoxysclerol. Intravariceal or perivariceal injections of 10 – 15 mL were given in the proximal 1-2 cm of the gastroesophageal junction, i.e. at 3, 6, 9, 12 o’ clock position. An endoscopic esophageal sclerotherapy needle (Wilson Cook Products) sized 23G was used for all EST session. The treatment was repeated weekly until the varices had become obliterated achieving grade 0 or grade I.

We reviewed the side effects and patients’ survival in both groups. The side effects were classified as unexpected and expected side effects. Esophageal ulcer was considered as the expected side effect; while unexpected side effects included acute fever, sore throat, chest pain, 24-hour-upper gastrointestinal rebleeding, dysphagia, chronic rebleeding, dyspepsia, and death. We also reviewed the patients’ survival, which included total hospitalization days and total life-survival days following the procedures.

Rebleeding was defined as upper gastrointestinal hemorrhage that occurred after endoscopic procedure was performed. Chronic rebleeding was defined as prolonged hemorrhage after 5-7 days of hospitalization. Esophageal ulcer was diagnosed if there was mucosal break of any size or at any location in the esophagus following the EVL or EST.

Statistical Analysis

We used Statistical Package for Social Sciences (SPSS v. 11.0.0) for Windows for statistical analysis. Chi-square test was performed to analyze the side effects. Mann-Whitney test and Kaplan-Meier estimation was done to calculate the patients’ survival and length of stay in the hospital. Findings were expressed as percentage; p value less than 0.05 was considered as statistically significant.

RESULTS

One hundred and nineteen (88 males, 31 females) medical records were examined. Subjects were categorized into EVL group and EST group. EVL were performed in 96 (80.7%) patients; while EST were performed in 23 (19.3%) patients. The characteristics of patients in both groups did not differ in terms of clinical features. (Table 1) The varices eradication rates were 69.79% in EVL group and 60.9% in EST group, and the difference was not statistically significant (p>0.05).

Summary of side effects in EVL versus EST group is shown in Table 2. The patients who got unexpected side effects in the EVL group (29.2%) were less frequent than the EST group (60.9%) and it was
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Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Endoscopic Variceal Ligation (EVL) n (%)</th>
<th>Endoscopic Sclerotherapy (EST) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: Male/Female</td>
<td>72/24 (75/25)</td>
<td>167/69 (69/30.4)</td>
</tr>
<tr>
<td>Mean of age</td>
<td>48.03 ± 13.23</td>
<td>46.91 ± 11.30</td>
</tr>
<tr>
<td>Ethnic:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Java</td>
<td>59 (61.46)</td>
<td>12 (52.2)</td>
</tr>
<tr>
<td>- Sumatra</td>
<td>19 (19.79)</td>
<td>3 (12.9)</td>
</tr>
<tr>
<td>- Others</td>
<td>18 (18.75)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>Child-Pugh Status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- A</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>- B</td>
<td>35 (36.46)</td>
<td>9 (39.13)</td>
</tr>
<tr>
<td>- C</td>
<td>61 (63.54)</td>
<td>14 (60.87)</td>
</tr>
<tr>
<td>Varices eradication rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(grade 0-1 achieved):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- yes</td>
<td>67 (69.79)</td>
<td>14 (60.9)</td>
</tr>
<tr>
<td>- no</td>
<td>29 (30.21)</td>
<td>9 (39.1)</td>
</tr>
</tbody>
</table>

The mortality was 1% in the EVL group and 21.7% in the EST group. (Table 2) Most deaths were due to rebleeding. The other mortality in EST group was due to septicemia or septic shock. The difference in mortality rate between the two groups were statistically significant (p<0.001).

The mean length of stay in the EVL group was shorter than in the EST group (11.83 vs 13.86) but the difference was not statistically significant (p>0.05).

Table 2. Side effects of EVL and EST

<table>
<thead>
<tr>
<th>Endoscopic procedure</th>
<th>EVL (n=96)</th>
<th>EST (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients with unexpected side-effects (%)</td>
<td>28 (29.2)</td>
<td>14 (60.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Unexpected side-effects:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Acute Fever</td>
<td>2 (2.1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>- Sore throat</td>
<td>3 (3.1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>- Chest pain</td>
<td>1 (1.0)</td>
<td>1 (4.3)</td>
<td>0.351</td>
</tr>
<tr>
<td>- 24 hrs Upper GI bleeding</td>
<td>8 (8.3)</td>
<td>4 (17.4)</td>
<td>0.397</td>
</tr>
<tr>
<td>- Dysphagia</td>
<td>2 (2.1)</td>
<td>1 (4.3)</td>
<td>0.478</td>
</tr>
<tr>
<td>- Chronic Rebleeding</td>
<td>3 (0.05)</td>
<td>3 (13.0)</td>
<td>0.699</td>
</tr>
<tr>
<td>- Dyspepsia</td>
<td>1 (1.0)</td>
<td>5 (21.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Death</td>
<td>96 (100)</td>
<td>23 (100)</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: 1 patient may have more than 1 side-effect; Statistic analysis with chi square test.

The mean life-survival following the procedure in the EVL group was higher than in the EST group (463.05 vs 200.25) and the difference was statistically significant (p=0.028). (Table 3)

Kaplan-Meier estimation of survival curves demonstrated 4-year-survival of 91.7% in EVL group and 16.7% in EST group. It showed significant difference between both groups, i.e. the survival in EVL group was higher than EST group. (Figure 1)

Table 3. Survival and Hospitalization days of Patients with EVL and EST

<table>
<thead>
<tr>
<th>Endoscopic Procedure</th>
<th>EVL (n=96)</th>
<th>EST (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean length of stay in the hospital (days) (range)</td>
<td>11.83 (1-80)</td>
<td>13.86 (3-37)</td>
<td>0.083</td>
</tr>
<tr>
<td>Mean life-survival days following the procedures (range)</td>
<td>463.05 (30-1460)</td>
<td>200.25 (0-850)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Note: statistic analysis with t test

DISCUSSION

This 4-year retrospective study found that EVL procedure was performed more frequently than EST procedure in patients with liver cirrhosis and portal hypertension who had esophageal varices bleeding (96 vs 23 procedures). Such data are consistent with the higher number EVL utilization as previously reported in randomized trial.23-26 EVL has been recently preferred by physicians all over the world for controlling and eradicating esophageal variceal bleeding. Patients in EVL and EST groups had similar characteristics and did not show statistically significant differences.

The advantage of endoscopic sclerotherapy (EST) for variceal bleeding has been proven in controlling and eradication the bleeding of esophageal varices.2,4 However, EST has some drawbacks and it is usually associated with various side effects, including rebleeding, infection, sepsis, ulceration, etc.1,4 that may limit its effectiveness. Therefore, endoscopic ligation (EVL) has emerged to provide better treatment compared to EST.
Our study demonstrates that the proportion of patients who had chronic rebleeding side effect was 9.4% in EVL group and 13% in EST group as shown in Table 2. The data demonstrate that rebleeding rates were generally lower with EVL than with EST, being similar to previous studies.2,9,19 Laine L, et al demonstrated that rebleeding tended to be less frequent with ligation than with sclerotherapy; 10 of 38 (26%) compared with 17 of 39 (44%) (OR 0.52; CI 0.37 to 0.74).28 Other studies also found that rebleeding rates in EVL group are also less frequent than in EST group.4,19,29 Bleeding can occur from esophageal ulcers, which required hospitalization and transfusion. One study reported bleeding complication caused by esophageal ulcer post-EVL occurred in 9.33% of total patients.17 A meta-analysis of 13 studies of EVL versus EST demonstrated that EVL reduced the relative risk of rebleeding by 37%.26 Toubia et al. indicated that 70% of patients experience recurrent variceal hemorrhage within 1 year,1 and these patients have a 70% 1-year mortality. The risk of rebleeding is greatest within the first 6 weeks, with more than 50% of rebleeding occurring within 3 to 4 days.1 Villanueva et al indicated that EVL may eradicate esophageal varices faster than EST.6 Kuran et al, demonstrated that the number of sessions required to achieve varices eradication was found significantly less in EVL group compared to EST group (2.5±1.6 vs 6.6±4.0).9 Approximately, 3 to 4 EVL treatment sessions are required to achieve eradication. EVL obviously has demonstrated fewer side effects; therefore, it is prefered in the management of esophageal variceal bleeding.

Other study revealed the occurrence of esophageal ulcers 100%, both in Post EVL and Post EST procedures.2,4,6,9,17,18 In this study, the ulcers which occurred in the ligation (EVL) and EST group was also the same 100%, and this complication was already expected as one of the complications due to mucosal necrosis. Mostly, the ulcer size was between 3 to 7 mm in circumference, and extended from esophagogastric junction to 8 cm above. The ulcer was identified 10-14 days after the initial procedure. From our previous study ulcers occurred in 100% after EVL. The mean diameter of esophageal ulcer after EVL procedure on day 10th was 5.42 ± 2.22 mm and on day 14th was 2.99 ± 2.04 mm.23 We have no data on the diameter of esophageal ulcer after EST procedure.

Overall, our study demonstrates greater number of side effects in the EST group (60.9%) compared to the EVL group (29.2%), which is statistically significant (p<0.01). Such findings are similar to previous studies that demonstrate fewer side effects of ligation compared to sclerotherapy.1,4 It is interesting that our study indicates slightly less side effects in the EVL procedure compared to other study (29.2% vs 31%).17 It is probably correlated to
the home-made ligation devices applied in this study or other factors. However, further study shall be conducted to provide significant data on such correlation.

Our study indicates significantly less number of death due to rebleeding in EVL group compared to EST group (1% vs 17.4%; p<0.01), which is similar to other studies. The mortality rate in EST group of our study was also similar to the mortality rate in the literatures, i.e. 21% vs. 35%-70%. However, existing literature shows that despite various treatments, the mortality rate of variceal bleeding remains high, ranging from 30 to 50%. Such high mortality rate in patients with liver cirrhosis is not affected only by the ligation or sclerotherapy techniques but it also depends on the existing complications, side effects, underlying disease and severe comorbidity in those patients. It is expected that by modulating and treating such factors, in addition to good ligation or sclerotherapy technique, the high mortality rate can be minimized.

Length of hospital stay tended to be shorter with ligation compared with sclerotherapy. Data from various studies worldwide have demonstrated that the length of hospital stay in patients with EVL is obviously less than patients with EST, which is similar to our study. However, our study did not show significant results (p>0.05).

Significant improvement of survival after variceal bleeding in EVL group was found compared to EST group. Kaplan-Meier log-rank estimation of survival curves also showed that the 4-year survival rate in EVL group was significantly higher than the EST group (p<0.01). Some literatures show similar result indicating that the survival is lower in EVL group than EST group, but other studies shows that there is no significant difference regarding the survival between both group.

There are some limitations in our study. We did not explore the cause of cirrhosis although the Child-Pugh status between the EVL and EST group were similar. Laine et al. has confirmed that there were no significant differences between both treatments in terms of rebleeding or death based on severity of liver disease or size of varices. Another limitation is that we did not assess the risks of rebleeding in our study. Some specific factors have been associated with failure to control bleeding and rebleeding, including spurring varices, gastric variceal bleeding, active bleeding at endoscopy, severe initial bleeding, HPVG greater than 20 mmHg, infection and portal vein thrombosis. Some other factors also increase the risk of rebleeding, i.e. age greater than 60 years, large esophageal varices, severe liver disease, continued alcoholism, renal failure and the presence of a hepatoma. Furthermore, no pharmacological treatment either nitrates or non-selective beta-blockers has been conducted in both groups since it is unusual to administer such treatment in our center.

CONCLUSION

Endoscopic Variceal Ligation (EVL) had fewer side effects than Endoscopic Sclerotherapy (EST) in the treatment of esophageal varices bleeding. Death in the Endoscopic Variceal Ligation (EVL) group was lower than in the Endoscopic Sclerotherapy (EST) group and the 4-year survival of Endoscopic Variceal Ligation (EVL) group was higher than the Endoscopic Sclerotherapy (EST) group.

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