Comparison of Histoacryl® plus Lipiodol® versus Histoacryl® plus vitamin D3 in the management of isolated fundal varices: A retrospective comparative study

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Abstract

Introduction: According to recent guidelines Histoacryl® (N-butyl-2 -Cyanoacrylate) injection is the first line of therapy for the endoscopic obliteration of gastric varices. Lipiodol is commonly used to facilitate the injection of Histoacryl® but it is expensive. In this study, we compare Lipiodol with Vitamin D3 injection as priming agents for Histoacryl injection in terms of efficacy and safety in the management of isolated fundal varices.

Materials and Methods: This is a retrospective comparative study conducted at Gastroenterology Unit, Lady Reading Hospital Peshawar. Patients’ information was collected from March 2012 to January 2020 from medical records. One hundred and seventy-one (171) patients, who had presented with upper gastrointestinal bleeding and had isolated fundal varices (IGV-1 according to Sarin Classification) on endoscopy, were included in the study. Patients were divided into two groups based on endoscopic treatment using Histoacryl plus Lipiodol or Histoacryl plus Vitamin D3. Data was statistically analyzed in terms of successful hemostasis, re-bleeding, variceal obliteration, mortality, and adverse events related to treatment, using SPSS version 25.

Results: From March 2012 to January 2020, 171 patients met the criteria. 7 cases lost follow-up, and all the cases in both groups were treated successfully. There were no adverse events related to the procedure in either group. Twenty-six patients developed upper GI re-bleeding, which did not differ significantly between the two groups. There was also no difference between the groups in terms of treatment failure, complications, varices obliteration, and mortality.

Conclusion: Vitamin D3 is as safe and effective as Lipoidol when used as a priming agent for Histoacryl injection for the obliteration of isolated fundal varices and can be used as a cheaper alternative to Lipiodol.

Keywords: Fundal varices, Histoacryl (N-butyl-2 -Cyanoacrylate), Vitamin D3, Lipiodol.
Bleeding from varices is responsible for up to 10% of upper gastrointestinal bleedings.1 In cirrhotic patients, mortality due to variceal hemorrhage reaches 10-30%.2,3 Re-bleeding may occur in the absence of therapeutic intervention and the rate of re-bleeding is highest during the first 6 weeks, which requires a reliable secondary prophylactic treatment.4 Although less common than esophageal varices gastric varices may be present in up to 20% of patients having portal hypertension and there is a 4-65% chance of gastric varices to bleed within 2 years after the diagnosis.5,6 Gastric Varices have a poorer prognosis, as they result in a much heavier blood loss and a higher bleeding and thus higher mortality rate.4,7 In a large study which included 568 patients, initial endoscopy showed gastric varices in 20% of patients and 9% of patients developed gastric varices over a mean follow up of 24.6 ± 5.3 months, however, this was after eradication of esophageal varices and a mortality of 45% was reported.5 Contrary to this a recent study reported the 6 weeks mortality of GV bleeding to be only 16.7%.2 Another study which included 117 patients with non-bleeding fundal varices showed that the cumulative risk for gastric variceal hemorrhage at 1, 3, and 5 years was 16%, 36%, and 44%, respectively with a total of 34/117 patients bleeding6; which was higher than another study of 604 patients which showed a cumulative incidence of gastric variceal hemorrhage at 4.8%, 19.9%, and 23.2% at 1, 3, and 5 years respectively.9 Risk factors of gastric variceal hemorrhage include site inside the fundus, CTP class, red spot, and variceal size.10 Endoscopic variceal band ligation (EVBL) is the current treatment of choice in bleeding esophageal varices but is not as successful in bleeding gastric varices. Various treatments for bleeding gastric varices are; endoscopic injection of tissue adhesives, Trans-jugular Intrahepatic Portosystemic Shunt (TIPS), and Balloon-occluded Retrograde Trans-venous Obliteration (BRTO).11 Since 1984, Histoacryl injection has been reported to be an effective treatment for gastric variceal hemorrhage with primary hemostasis in 70–95% of cases with acute gastric variceal hemorrhage and re-bleeding rate of 0–28% in the first 48 hours.12-14 N-Butyl-2-Cyanoacrylate polymerizes into a plastic cast from liquid glue when comes into contact with blood in varix and achieves control of acute bleeding. A recent meta-analysis on complications (end-organ infarction, systemic embolization, bacteremia, and visceral fistula) of patients treated with N-Butyl-2-Cyanoacrylate reported it to be comparatively safe and effective.15-16 Use of N-Butyl-2-Cyanoacrylate with an oil-based carrier like Lipiodol is recommended as a first-line treatment for gastric varices.14-16 However, Lipiodol is an expensive product and increases the cost of treatment. Recently a study has been done on olive oil as a cheaper alternative to Lipiodol with promising results.18 However, sterilizing olive oil is a cumbersome job therefore we have used injectable Vitamin D3 as an oil-based carrier in place of Lipiodol in our unit. In this study, we have attempted to compare the efficacy and safety of Lipiodol and injectable vitamin D3 as oil-based carriers for Histoacryl to obliterate fundal varices endoscopically.

Materials and Methods

This retrospective comparative study was conducted at Gastroenterology Unit, Lady Reading Hospital, Peshawar. Patients’ data were collected retrospectively from medical records from March 2012 to January 2020. One hundred and seventy-one (171) patients, who had presented with upper gastrointestinal bleeding and had isolated fundal varices (IGV-1 according to Sarin Classification) on endoscopy, were included in the study. Patients who had sclerotherapy previously and other comorbidities like diabetes mellitus, CKD, COPD, and malignancy were excluded from the study. Patients were divided into two groups based on endoscopic treatment using Histoacryl plus Lipiodol or Histoacryl plus Vitamin D3. All procedures were carried out by experienced endoscopists. Successful hemostasis was defined as hemodynamic stability, no rebleeding episode, or drop in hemoglobin within 24 hours of endoscopic treatment. Re-bleeding was defined as evidence of hematemesis and/or melena, hemodynamic instability (a drop of >20m mmHg in systolic pressure from baseline, drop in hemoglobin of 2 mg, or a transfusion requirement of ≥ 2 units of packed cells after 24 hours). Patients underwent follow-up endoscopy at two and four weeks intervals to look for the obliteration of varices. Quantitative variables like age were expressed as mean ± SD. Frequencies and percentages were calculated for qualitative variables like gender, etiology, Child Class, Primary hemostasis, Re-bleeding, Number of sessions, and eradication of varices. Data were analyzed using SPSS version 25.
Results

A total of 171 patients were selected from medical records that presented with upper GI bleeding and had isolated fundal varices on upper GI endoscopy. Out of these 90 patients received Histoacryl plus Lipiodol and 81 patients received Histoacryl plus Vitamin D3 as an endoscopic treatment for fundal varices. Both groups were comparable in terms of age, gender, etiology, and Child class as shown in the table given below. In the Lipiodol group, 56 (62.2%) were male and 34 (37.7%) were female. The etiology of cirrhosis and portal hypertension in this group was HCV, HBV, and other causes in 67 (74.4), 7 (7.7%), and 16 (17.7%) patients respectively. In the Lipiodol group, 10 (11%) patients had Child class A, 38 (42.2%) had Child class B and 42 (46.6%) had Child Class C. In the Vitamin D3 group, 47 (58%) were male and 34 (42%) were female. The etiology of cirrhosis and portal hypertension in this group was HCV, HBV, and other causes in 61 (75.3%), 9 (11%), and 11(13.5%) patients respectively. In the Vitamin D3 group 7 (8.6%) patients had Child class A, 30 (37%) had Child class B and 44 (54.3%) had Child Class C.

Table 1:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lipiodol Group</th>
<th>Vitamin D3 Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male/ Female)</td>
<td>56 (62.2%)/</td>
<td>47 (58%)/</td>
</tr>
<tr>
<td>Age (Mean ± Standard Deviation)</td>
<td>51.53 ± 11.85</td>
<td>10.260</td>
</tr>
<tr>
<td>Etiology (HCV/ HBV/ Others)</td>
<td>67/ 07/ 16</td>
<td>61/ 09/ 11</td>
</tr>
<tr>
<td>Child Class (A/ B/ C)</td>
<td>10/ 38/ 42</td>
<td>07/ 30/ 44</td>
</tr>
</tbody>
</table>

Primary hemostasis was achieved in all patients in both groups. 4 patients in the Lipiodol group and 3 patients in the Vitamin D3 group had lost follow-up. Rebleeding was seen in 14 (15.5%) patients in the Lipiodol group and 12 (14.8%) patients in the Vitamin D3 group. In the Lipiodol group, 76 (84.4%) patients had a single session and 14 (15.5%) patients had two sessions to eradicate the varices while in the Vitamin D3 group 70 (86.4%) patients had a single session and 11 (13.5%) patients had two sessions to eradicate the varices. No procedure-related complications were seen in either group. Good ablation of varices was seen in all (100%) patients in both groups who had to follow up. No early or late adverse events were seen in either group.

Table 2:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lipiodol Group</th>
<th>Vitamin D3 Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Hemostasis</td>
<td>90 (100%)</td>
<td>81 (100%)</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>14 (15.5%)</td>
<td>12 (14.8%)</td>
</tr>
<tr>
<td>No. of Sessions (1/2)</td>
<td>76 (84.4%)/ 70 (86.4%)</td>
<td>14 (15.5%)/ 11 (13.5%)</td>
</tr>
<tr>
<td>Eradication</td>
<td>90 (100%)</td>
<td>81 (100%)</td>
</tr>
</tbody>
</table>

Discussion

Gastric variceal hemorrhage is a life-threatening condition in portal hypertensive patients. Emergency treatment of gastric variceal bleeding includes correction of intravascular volume and vasoactive drugs (octreotide or terlipressin). Although rare but serious adverse events of glue injection have been reported in previous studies. Treatment of gastric variceal bleeding includes endoscopic (sclerosing agents) or non-endoscopic (radiological or surgical). Histoacryl with Lipiodol injection has demonstrated initial hemostasis rates ranging from 88-100%. With Histoacryl and vitamin D3 based injection, endoscopic hemostasis was achieved in 100% of cases in this study. The rate of fundal variceal re-bleeding in our study was 14.8%. This re-bleeding rate is slightly lower than the previously reported 17-59% in the literature. Unlike esophageal varices, endoscopic management of gastric varices bleeding is not well established. Non-endoscopic methods, such as TIPPS and surgical portosystemic shunt creation, although well established and effective, are technically difficult, more invasive, and have higher rates of complications. In this study the efficacy of Histoacryl regarding primary hemostasis is 100% which has been reported in previous studies. Reported re-bleeding ranged from 22-59% with Histoacryl injection for the management of acute gastric variceal bleeding. In our study re-bleeding rate was 15.5% and 14.8% in the Lipiodol group and vitamin D3 group respectively which is lower than reported in the literature. The reason might be that we included isolated fundal varices in our study which have lower re-bleeding rate. No significant complications of Histoacryl were observed in this study. Although rare but serious adverse events of glue injection have been
reported including cases of fatal pulmonary embolism.\textsuperscript{29} Hwang and colleagues described the complications of glue injection in 5.2% of patients; including 3.1% early re-bleeding and 0.3% embolic complications like stroke, DVT, coronary embolism, splenic infarction, and non-fatal pulmonary embolism.\textsuperscript{30} Kang et al reported infective complications in 34% and abdominal pain in 17% in their study of 127 patients.\textsuperscript{24} No significant complication or adverse event was observed in this study in either group of patients.

## Conclusion

The present study shows that Vitamin D3 is as safe and effective as Lipiodol when used as a priming agent for Histoacryl injection for the obliteration of isolated fundal varices and can be used as a cheaper alternative to Lipiodol.

## References