Morphological Changes in Esophagus Following Endoscopic Sclerotherapy with 3% Aqueous Phenol

S K Mathur, J M Vora, A N Supe, S T Plumber, S R Naik

Departments of Surgery (Division of Surgical Gastroenterology), Pathology and Gastroenterology, Seth G S Medical College and K E M Hospital, Parel, Bombay 400 012

Abstract

Autopsy studies have shown that a majority of sclerosants presently used for endoscopic variceal sclerotherapy achieve their end result by a process of necrotizing inflammation of the esophageal wall followed by fibrosis and thrombosis, rather than bland thrombosis of varices. We have been using 3% phenol in water for variceal sclerotherapy and found it to be an effective sclerosant. To study the effect of this sclerosant on varices and the esophageal wall, autopsies were performed in 15 patients who died following sclerotherapy. Histopathological examination of sections from the esophagus showed (a) fresh thrombus in the varices immediately following injection, (b) intimal damage with medial sclerosis and superficial mucosal ulceration after one week, (c) organization and recanalization with marked medial sclerosis at 3-4 weeks, and (d) complete obliteration of varices after 6-12 weeks. None of the patients was found to have esophageal necrosis, perforation or mediastinitis. Thus, 3% aqueous phenol appears to be an effective and safe sclerosant for variceal sclerotherapy.

Key words: Variceal sclerotherapy, sclerosants

Introduction

The mechanism of action of sclerosing agents currently used for endoscopic esophageal variceal sclerotherapy (EST) is not fully understood. Intravascular injection of a sclerosant presumably produces thrombosis secondary to intimal damage, followed by intravascular fibrous organisation and obliteration of the veins. However, autopsy studies of the esophagus in patients dying after intravariceal sclerotherapy revealed necrotizing inflammation of the esophageal wall, followed by fibrosis and thrombosis. These changes resemble those following paravariceal injection of some agents.

We have previously shown that endoscopic intravariceal sclerotherapy with 3% aqueous solution of phenol achieves effective obliteration of esophageal varices. We report the histopathological changes in the esophagus in patients dying at varying time intervals following EST with aqueous phenol.

Material and Methods

Of 339 patients with portal hypertension who underwent EST, 77 patients died at various time intervals following the procedure. Necropsy was performed in 15 of these 77 patients. All these patients had at least one documented bleed from varices before EST was done.

Sclerotherapy was performed through a forward viewing flexible fiber-endoscope, using a sterile 23 gauge needle. Initially 3 to 5 ml (later 2 to 3 ml) of 3% aqueous phenol was injected inside each varix at the gastroesophageal junction and higher up at a distance of 7-7 cm above the upper limit of the varical column; between 27 ml and 40 ml of sclerosant was injected at each sitting. No accessories were used during or after the procedure. Patients received repeated injections at intervals of 3 to 7 days for the first 5 sessions and later at monthly intervals until complete obliteration of varices. At follow up endoscopy, observations were recorded regarding the patency of varices, ulceration, necrosis and other changes in the esophageal mucosa.

At autopsy, observations were made regarding evidence of retrograde thrombosis in the portal and left gastric veins and the presence of esophageal perforation and periesophageal adhesions. The stomach and esophagus were removed as one specimen and opened longitudinally. Macroscopic findings about patent, thrombosed and obliterated varices, as well as about muscular ulcerations and necrosis were noted. Sections for histological examination were taken from the esophagus and stomach at a distance of 1, 10 and 15 cm above and 1 cm below the gastroesophageal junction. After paraffin processing, sections were stained with hematoxylin and eosin, Masson's trichrome and elastic van Gieson stain (EVG) for elastic and connective tissue. Sections were examined for the presence of fresh or organized thrombus, and evidence of intimal damage, sclerosis of the media, obliteration of the varical lumen, mucosal ulceration and esophageal wall necrosis or inflammation.

Results

The etiology of portal hypertension was liver cirrhosis in a majority of patients (13 of 15), and all except one belonged to Child's class C. Non cirrhotic portal fibrosis and portal vein thrombosis were causes of portal hypertension in the other two patients. The number of EST sessions these patients received before death ranged from one to six (mean 1.9 ± 1.38). The time interval between first injection and death
ranged from 1 to 107 days (mean 20 ± 36.12), whereas the interval between the last injection and death varied from 1 to 89 days (mean 11.86 ± 22.59; Tables 1 and 2). The cause of death was persistent variceal hemorrhage in 5 patients, liver cellular failure in three patients, bleeding gastric erosions in two patients and myocardial infarction in one patient. Four patients died of post operative complications following elective shunt surgery. In none of the patients was death related to sclerotherapy or the sclerosant.

Table 1: Distribution of patients according to interval between first EST session and death and number of EST sessions

<table>
<thead>
<tr>
<th>Interval between first EST and death (in days)</th>
<th>No of EST sessions</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1—2</td>
<td>1 2 3</td>
<td>2</td>
</tr>
<tr>
<td>3—7</td>
<td>1 1 1</td>
<td>3</td>
</tr>
<tr>
<td>15—30</td>
<td>1 1 1</td>
<td>3</td>
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<tr>
<td>&gt;30</td>
<td>1 1 1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>5</td>
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</table>

Table 2: Distribution of patients according to interval between last EST session and death and number of EST sessions

<table>
<thead>
<tr>
<th>Interval between last EST and death (in days)</th>
<th>No of EST sessions</th>
<th>Total</th>
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<tbody>
<tr>
<td>1—2</td>
<td>1 2 3</td>
<td>2</td>
</tr>
<tr>
<td>3—7</td>
<td>1 1 1</td>
<td>3</td>
</tr>
<tr>
<td>8—15</td>
<td>1 2 1</td>
<td>3</td>
</tr>
<tr>
<td>16—30</td>
<td>1 1 1</td>
<td>3</td>
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<td>&gt;30</td>
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<tr>
<td>Total</td>
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Endoscopic findings
Immediately following sclerotherapy, varices appeared pale and collapsed as compared to un.injected varices. Accidental paravascular injection led to formation of white blebs. Superficial ulcers covered with white slough were seen in 15% of the patients at 3 to 7 days interval. After 3 to 4 weeks, thrombosed varices had a beaded appearance without any tortuosity. After successful obliteration of all varices, the esophageal mucosa was seen to be smooth except for a few mucosal tags. Complications such as deep esophageal wall necrosis, precipitate bleeding from varices, mediastinitis and perforation were not seen in any patient.

Autopsy findings
No patient was found to have retrograde thrombosis of the portal or left gastric vein or perforation of the esophagus.

Histological changes
Following single sclerotherapy session: In the initial phase up to 1 to 3 days after sclerotherapy, injected varices were found to have fresh antemortem thrombus. There was marked submucosal edema with acute inflammatory response, but no mucosal ulceration (Fig 1a). At 1 week interval, there was evidence of intimal damage and mild medial sclerosis (Fig 1b); the submucosa and muscle layer showed mild to moderate mixed cellular infiltration. The presence of intravariceal organised and partially recanalised thrombus, with marked medial sclerosis and narrowing of the main varices, were findings at the 17th and 89th days (Fig 1c). Thrombosis was also seen in small venules. There was evidence of submucous fibrosis also.

Following multiple sclerotherapy sessions: In patients who had received two or more sclerotherapy sessions before and died within one week of the last injection, some varices contained fresh and others showed organised thrombus. All varices were obliterated in patients who had received more than 3 sclerosing sessions and died after 6-12 weeks interval (Fig 1d). In one case, the main variceal column was replaced by multiple small channels in the submucosa (Fig 2), indicating organisation and recanalisation. Muscle necrosis was seen in only one case who had received six injections over a short period to control recurrent varical bleeding. Superficial mucosal ulcerations were seen in five patients who died within 15 days of sclerotherapy. There was no difference in qualitative histological findings in patients receiving two or more sessions.

![Histological picture](image)

(a) Histological picture 48 h after injection showing fresh thrombus in the injected variceal lumina (EVG × 63).
(b) Intimal damage, mild medial sclerosis of varice and mixed cellular infiltration in submucosa of esophagus one week after injection (EVG × 160).
(c) Organisation and recanalisation of thrombus with narrowing of varices (arrow) 3-4 weeks after injection (EVG × 160).
(d) Histological picture 12 weeks after injection session. No patent varices (EVG × 160).
Discussion

Our necropsy studies show that following intravariceal injection of aqueous phenol, initial thrombosis of varices occurs within a week, followed by organization and recanalization at 3-4 weeks and fibrosis with obliteration by 6-12 weeks. These findings are similar to sequential changes reported by us in dog veins after intravenous injection of phenol. These results also confirm the autopsy findings reported by others following intravariceal injection of sodium tetradecyl sulphate, sodium morrhuate and ethanolamine olate, and nitro and paravariceal injection of ethoxysclerol.1,2,6,7

Although the final effect of the different agents appears to be similar, there are differences in the mechanism of action. Occlusion of varices with phenol appears to be due to variceal intimal damage with resultant organizing thrombosis and medial sclerosis. We reported similar findings in dog limb veins following intravenous injection of phenol.8 In contrast, other agents were shown to produce necrotising destruction of varices with esophageal wall fibrosis rather than mere organised thrombotic occlusion of varices.1,3,8 Evans et al6 noted thrombosis of submucosal varices and superficial and deep tissue necrosis within hours of EST, ulceration after 7 days, and fibrosis one month after injecting 5% sodium morrhuate. Five percent sodium morrhuate, ethanolamine olate and sodium tetradecyl sulphate were shown to produce large zones of tissue necrosis due to seepage of sclerosant into the interstitial tissue.1,8 Although we did not observe deep ulcerations or necrosis with 3% aqueous phenol, submucosal fibrosis was present, suggesting some leakage of sclerosant. Submucosal fibrosis without mucosal ulceration was also shown following paravasal injection of 3% phenol in arachis oil.9

In one case we observed replacement of the main varices by multiple submucosal small vascular channels. Such mucosal channels probably result from fibrosis in the submucosal mucosa and thrombosis of the main varices. These channels, being located in deeper tissues, are unlikely to bleed.

Serious complications have been reported with 5% sodium morrhuate, ethoxysclerol, 3% sodium tetradecyl sulphate and ethanolamine olate; these include hemorrhage from deep ulcers eroding the variceal wall, bacterial phlebitis, supplicative perihepatitis, mediastinitis, perforation of the esophagus and empyema.1,3,6,9 In the present autopsy study we did not come across any of these reported complications. Similarly, none of the surviving patients showed evidence of the above complications. The use of 3% aqueous phenol as a sclerosant is, therefore, safe.

Evans et al6 opined that "an agent which would induce thrombosis and fibrosis without ulceration and necrosis could clearly be an advance on the present sclerosing agents such as ethanolamine olate and STD." From our findings we believe that 3% aqueous phenol is close to this ideal in terms of efficacy and safety.

References