Original Article

N-butyl-2-cyanoacrylate, iso-amyl-2-cyanoacrylate and hypertonc glucose with 72% chromated glycerin in gastric varices

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Abstract

AIM: To compare n-butyl-2-cyanoacrylate, iso-amyl-2-cyanoacrylate and a mixture of 72% chromated glycerin with hypertonc glucose solution in management of gastric varices.

METHODS: Ninety patients with gastric varices presented to Endoscopy Unit of Ain Shams University Hospital were included. They were randomly allocated into three groups; each group included 30 patients treated with intravariceal sclerosant injections in biweekly sessions till complete obturation of gastric varices; Group I (n-butyl-2-cyanoacrylate; Histoacryl®), Group II (iso-amyl-2-cyanoacrylate; Amcrylate®) and Group III (mixture of 72% chromated glycerin; Scleremo® with glucose solution 25%). All the procedures were performed electively without active bleeding. Recruited patients were followed up for 3 mo.

RESULTS: 26% of Scleremo group had bleeding during puncture vs 3.3% in each of the other two groups with significant difference, (P < 0.05). None of Scleremo group had needle obstruction vs 13.3% in each of the other two groups with no significant difference, (P > 0.05). Rebleeding occurred in 13.3% of Histoacryl and Amcrylate groups vs 0% in Scleremo group with no significant difference. The in hospital mortality was 6.6% in both Histoacryl and Amcrylate groups, while it was 0% in Scleremo group with no significant difference. In the first and second sessions, the amount of Scleremo needed for obturation was significantly high, while the
amount of Histoacryl was significantly low. Scleremo was the less costly of the two treatments.

CONCLUSION: All used sclerosant substances showed efficacy and success in management of gastric varices with no significant differences except in total amount, cost and bleeding during puncture.

Key words: Gastric varices; N-butyl-2-cyanoacrylate; Iso-amyl-2-cyanoacrylate; Hypertonic glucose solution; 72% chromated glycerin

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Core tip: We compared n-butyl-2-cyanoacrylate (Histoacryl®), iso-amyl-2-cyanoacrylate (Amcrylate®) and a mixture of 72% chromated glycerin (Scleremo®) with hypertonic glucose solution (25%) in management of gastric varices. The study included 90 patients who were randomly allocated into three groups, and each group included 30 patients treated with sclerosant injections in biweekly sessions till complete obturation: Group I (Histoacryl®), Group II (Amcrylate®) and Group III (Scleremo® with Glucose 25%). Patients were followed up for 3 mo. We concluded that all used sclerosants showed efficacy and success in management of gastric varices, without significant differences, except in total amount, cost and bleeding during puncture.

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INTRODUCTION

Varices occur in approximately 50% of cirrhotic patients[1,2]. Gastric varices (GV) are less common than esophageal varices (EV), with a prevalence of approximately 20% in patients with portal hypertension[3], and about 15%-25% of GV bleed during the patient’s lifetime[4,5].

The management of GV has not been well studied as that of EV. Both the evaluation and treatment of GV are still controversial[6,7].

Cyanoacrylates are synthetic glues that rapidly polymerize on contact with water or blood[8]. Injection therapy with cyanoacrylates is now considered to be the first-line endoscopic intervention for bleeding GV and for the secondary prevention of gastric variceal bleeding[9].

N-butyl-2-cyanoacrylate (Histoacryl®, Germany) has been used extensively in endoscopic therapy for the last 10 years. Another N-butyl-2-cyanoacrylate (Glubran®, Italy) was recently approved for endoscopic use in Europe[10].

Scleremo, a compound of 72% chromated glycerin, is a polyalcohol that is often considered to be a sclerosant chemical irritant, as it causes cell surface protein denaturation leading to thrombo-fibrosis[11]. The compound is commonly used in Europe, but it has not been approved by the FDA for use in the United States[12].

This work aimed at comparing n-butyl-2-cyanoacrylate (Histoacryl®), iso-amyl-2-cyanoacrylate (Amcrylate®) and a mixture of 72% chromated glycerin (Scleremo®) with a hypertonic glucose solution (25%) in the management of GV in Egyptian patients.

MATERIALS AND METHODS

Patients and methods

This prospective randomized study was conducted on ninety patients who presented with GV at the Endoscopy Unit of Ain Shams University Hospital. Patients with non-variceal causes of upper gastrointestinal bleeding and those with severe co-morbidities were excluded.

The patients were randomly allocated into three groups. Each group included 30 patients who were treated with sclerosant injections in biweekly sessions until the complete obturation of the GV was achieved, with follow-up of 3 mo: (1) Group I (Histoacryl® Group); (2) Group II (Amcrylate® Group); and (3) Group III (Scleremo® with Glucose 25% Group).

The three groups were matched for age, gender, cause of liver cirrhosis (viral hepatitis B or C), Child score and endoscopic findings (including the number, grade of the EV and the size of GV).

All of the included patients underwent: (1) a complete clinical evaluation; (2) laboratory investigations: CBC, liver profile, viral markers (HBs Ag, HB core Ab, HCV Ab) using the ELISA technique; (3) child classification according to the modified Child Pugh’s criteria[13]; (4) abdominal ultrasonography for liver and spleen size, portal vein diameter and ascites; (5) upper gastrointestinal endoscopy using the Pentax video endoscope EG 3440. The EV were classified according to their size at the gastrosophageal junction into 4 grades according to Westaby et al[14]; The GV were classified into either gastro-EV or isolated GV according to Sarin et al[15]; and (6) therapeutic interventions: The intravariceal injection technique was performed according to Soehendra et al[16].

The Histoacryl® was diluted as 0.5 mL histoacryl: 0.8 mL lipidol as a contrast agent to dilute the adhesive material to fill the entire varix and to prevent rapid hardening and the obstruction of the needle. The mixture was injected slowly to minimize the risk of embolization and was followed by the injection of 2 mL of distilled water. The first mL of water was injected to force the material into the varix, and the second mL was injected during the withdrawal of the needle to prevent its obstruction[8].
The Amcrylate® was injected slowly followed by injection of 2 mL distilled water without mixing with any other substances[17].

The Scleremo® was mixed with glucose 25% in a ratio of 1:1. The mixture was injected very slowly and with the waiting for moments inside the variceal lumen after injection to give enough time for the sclerosing material to be in contact with the vessel wall. There was no need for an injection of distilled water[11].

Informed consent was obtained from all of the included patients, and the study protocol was approved by the ethical guidelines committee.

All of the procedures were performed electively, without active bleeding. The patients who had bleeding that occurred immediately or after the procedure were treated with additional injections.

The primary end point of this study was the obturation of the GV. The secondary endpoint was the occurrence of bleeding, whether from the puncture site during or immediately after the injection or delayed bleeding (in-hospital or after discharge) and mortality.

**Statistical analysis**

The statistical review of the study was performed by a biomedical statistician.

The quantitative variables are presented as the mean and the SD. An unpaired (t) test was used for the comparisons.

The qualitative variables are presented as numbers and percentages. The $\chi^2$ test was used for the comparisons.

A value of $P < 0.05$ was considered to be statistically significant (S), $P < 0.01$ was considered to be highly significant (HS), and $P > 0.05$ was considered to be non-significant (NS).

**RESULTS**

This study included 90 Egyptian patients with chronic liver disease. There were 58 males (64.4%, mean age: 50.88 ± 9.08 years) and 32 females (35.6%, mean age: 49.28 ± 8.11 years). A total of 74 patients (82.2%) had hepatitis C virus (HCV), 12 patients (13.3%) had hepatitis B virus (HBV), and 4 patients (4.4%) had both HCV and HBV. According to the Child-Pugh classification, 18 patients (20%) were class A, 36 patients (40%) were class B, and 36 patients (40%) were class C.

The recruited patients were randomly allocated into three groups that were matched for age, gender, cause of chronic liver disease, Child score and endoscopic findings. Each group included 30 patients who were treated with sclerosant injections in biweekly sessions until the complete obturation of GV was achieved. The groups consisted of Group I (the Histoacryl® Group), Group II (the Amcrylate® Group) and Group III (the Scleremo® with glucose 25% Group).

There were non-significant ($P > 0.05$) differences among the 3 groups regarding previous bleeding or previous sclerotherapy for EVs (93.3%, 66.6% and 93.3%, for Groups I, II, and III, respectively) as shown in Table 1.

| Table 1  | Previous bleeding and previous sclerotherapy for esophageal varices in the 3 groups n (%) |
|---------|---------------------------------|
|          | Histoacryl | Amcrylate | Scleremo with glucose | $\chi^2$ | P value |
| Previous bleeding | None | 2 (6.6) | 10 (33.3) | 2 (6.6) | 11.6 | > 0.05 |
| Once | 20 (66.6) | 8 (26.6) | 20 (66.6) | NS |
| Twice | 2 (6.6) | 8 (26.6) | 4 (13.3) | |
| 3 times | 2 (6.6) | 0 (0) | 0 (0) | |
| 4 times | 4 (13.3) | 4 (13.3) | 4 (13.3) | |
| Previous sclerotherapy | None | 2 (6.6) | 10 (33.3) | 2 (6.6) | 16.5 | > 0.05 |
| Once | 6 (20) | 6 (20) | 0 (0) | NS |
| Twice | 6 (20) | 0 (0) | 4 (13.3) | |
| 3 times | 2 (6.6) | 6 (20) | 8 (26.6) | |
| 4 times | 14 (46.6) | 6 (20) | 16 (53.3) | |

EV: Esophageal varices; NS: Non-significant.

The endoscopic findings for the 3 studied groups are shown in Table 2. There were non-significant differences among the 3 groups for the location, the size of the GV and associated EV ($P > 0.05$).

Table 3 shows the non-significant differences among the 3 groups regarding the rate of the obturation of the GV ($P > 0.05$). In the first month, the rate of the obturation was 66.6%, 53.3% and 46.6%; in the second month, the rate of the obturation was 86.6%, 80% and 73.3% and in the third month, the rate of the obturation was 93.3%, 93.3% and 100% in the Histoacryl, Amcrylate and Scleremo groups, respectively.

Regarding the number of sessions needed for the obturation of the GV; in the Histoacryl group, 33.3% of the patients needed one session and 66.6% needed two sessions. In the Amcrylate group, 26.6% of the patients needed one session, 70% needed two sessions and 3.3% needed three sessions. In the Scleremo group, 20% of the patients needed one session, 66.6% needed two sessions and 13.3% needed three sessions.

The amount of the sclerosant used per session is shown in Table 4. In the first and second sessions, a significantly high amount of Scleremo was used compared with the Amcrylate and Histoacryl ($P < 0.05$). In the third session, there was insignificant differences among the amounts of the 3 sclerosant materials used ($P > 0.05$).

Regarding problems with the endoscopy, eight patients (26.6%) in the Scleremo group had bleeding of their GV during the puncture compared with one patient (3.3%) in each of the other two groups, with a significant difference ($P < 0.05$). None of the patients in the Scleremo group had needle obstructions during the injections compared with four patients (13.3%) in each of the other two groups, with non-significant differences ($P > 0.05$).
Bleeding in the Scleremo group during the puncture was controlled by injecting more of the sclerosing mixture and leaving the needle in the puncture site for few minutes to allow for the blood to clot and occlusion of the puncture to occur. In 2 of the cases in the Scleremo group (Child C) this maneuver failed to stop the bleeding, and an injection of Histoacryl was used to control the bleeding.

Rebleeding (within 5 d of the injection) occurred in 4 cases (13.3%) in both the Histoacryl and the Amcrylate groups, while no cases (0%) of rebleeding were recorded in the Scleremo group, with a non-significant difference (P > 0.05).

Two of the patients (6.6%) in each of the Histoacryl and Amcrylate groups died in the hospital 2 d after the injection (due to hepatic coma), while the mortality rate in the Scleremo group was 0%, with a non-significant difference (P > 0.05).

There were insignificant (P > 0.05) differences among the 3 groups in complications in the form of chest pain (6.6%, 6.6% and 13.3%) in the Histoacryl, Amcrylate and Scleremo groups, respectively, transient dysphagia (13.3%) in the Amcrylate group only, low grade fever in the Histoacryl group only (6.6%); and ulceration in both the Histoacryl and Amcrylate groups only (13.3% vs 6.6%).

Regarding the total cost of the sclerosant materials used in the current study, Scleremo was the least costly compared with the Histoacryl and Amcrylate, as shown in Table 5.

### DISCUSSION

In contrast to the treatment of EV, the endoscopic treatment of GV is still controversial[18]. Treatment options for GV that have been studied in prospective trials include injections of cyanoacrylate-based tissue adhesives, alcohol, sclerosants, and band ligation[3,4,19-21]. The results from this limited number of small studies had varying success rates and were uncontrolled, making it difficult to draw definitive conclusions about their efficacy or the superiority of one therapy over another[22].

The purpose of this prospective randomized study was to compare the efficacy of n-butyl-2-cyanoacrylate (Histoacryl)®, iso-amyl-2-cyanoacrylate (Amcrylate)® and a mixture of 72% chromated glycerin (Scleremo)® with a hypertonic glucose solution (25%) in the management of GV in Egyptian patients.

The present work shows the obturation of varices in all of the groups, with no significant differences (P > 0.05) after three months of follow-up. We observed that the obturation of the GV occurred sooner and with fewer sessions in both the Histoacryl and Amcrylate groups than in the Scleremo group. Similarly, it has been previously reported that glue injections had achieved variceal eradication in approximately 75% of patients (range: 50%-100%)[19].

In comparison with the other types of sclerosants that were used in previous studies, obliteration was achieved in only 32% of the sodium tetradecyl sulphate group and 81% of the hypertonic (50%) glucose water group (P < 0.05) in the study of Chang et al[7].

The Scleremo (72% chromated glycerin) was useful
primarily in the sclerosis of small vessels. Its principal advantage is that it rarely causes extravasation necrosis; its viscosity also allows maximum surface contact time and avoids the risk of an oily base causing the formation of an embolus. The main problems with Scleremo are that it is difficult to work with because it is extremely viscous, that it can be quite painful on injection, and that the chromate moiety is highly allergic.[22]

To our knowledge, there is no previous Egyptian study that addresses the efficacy of Scleremo in the management of GV. In the current study, Scleremo with glucose 25% was characterized as being more economical, with a clean and smooth endoscopic field of vision and fewer side effects. However, bleeding from the puncture site, specific dealing during the injection, its high amount and number of sessions required and a delay in the obturation of the varices were its disadvantages.

El-Wakil[11] investigated the efficacy of Scleremo in the management of bleeding EV and demonstrated that the rate of the eradication of EV in the Scleremo group was 75% in comparison with 60% in the Ethanolamine Oleate group.

In the present study, none of the patients in the Scleremo group had needle obstruction during the injection in comparison with four patients (13.3%) in each of the other two groups, with a non-significant difference (P > 0.05). Chang et al.[7] reported the frequent obstruction of the injection needle when using Histoacryl during the treatment of active gastric variceal bleeding, although it achieved a nearly 100% success rate for the initial hemostasis.

In the current study, rebleeding occurred in 4 cases (13.3%) in both the Histoacryl and Amcrylate groups, while no cases (0%) were recorded in the Scleremo group, with an insignificant difference. Previous studies of glue injections for GV have shown a rebleeding rate ranging from 23%-50%.[3,21]

In the current study, the mortality rate was (6.6%) in both the Histoacryl and the Amcrylate group compared with 0% in the Scleremo group, with a non-significant difference.

El-Wakil[11] reported that the mortality rate was 5% in the Ethanolamine Oleate group, while no fatalities were reported in the Scleremo group during the management of bleeding EV.

Kind et al.[23] treated 174 cirrhotic patients who had actively bleeding GV with cyanoacrylate and then by weekly sessions until their varices were eradicated. The hemostasis, early rebleeding and hospital mortality rates after the cyanoacrylate treatment were 97.1%, 15.5% and 19.5%, respectively. In approximately 75% of the patients, the GV were successfully obliterated.

In the present work, all of the groups reported some minor complications, with non-significant differences among them, in the form of chest pain (6.6%, 6.6% and 13.3%) for the Histoacryl, Amcrylate and Scleremo groups, respectively, transient dysphagia in the Amcrylate group only (13.3%), low grade fever in the Histoacryl group only (6.6%) and ulceration in both the Histoacryl and Amcrylate groups only (13.3% vs 6.6%).

It has been previously reported by Ljubicic et al.[24] that fever, retrosternal discomfort and dysphagia frequently occur with Histoacryl injections and usually resolve within 48 h.

In the study of El-Wakil[11], the Scleremo showed fewer complications than Ethanolamine Oleate in the form of chest pain (15% vs 40%), transient dysphagia (15% vs 40%) and low grade fever (5% vs 20%). A large post-sclerotherapy ulcer occurred in (10%) of patients in the Ethanolamine Oleate group, while no ulcers were reported in the Scleremo group.

All of the sclerosant substances that we used (Histoacryl, Amcrylate and Scleremo with glucose 25%) showed both efficacy and success in the management of GV, with no significant differences among them except in the total amount required, their cost and incidences of bleeding during the puncture; however, they did vary in their superiority in some aspects.

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COMMENTS
Background
The endoscopic treatment of gastric varices (GV) is still a matter of debate. Treatment options for GV that have been studied in prospective trials include the injection of cyanoacrylate-based tissue adhesives, alcohol and sclerosants. The results from this limited number of small studies had varying success rates and were uncontrolled, making it difficult to draw definitive conclusions about their efficacy or the superiority of one therapy over another.

Research frontiers
Cyanoacrylates are synthetic glues that rapidly polymerize on contact with water or blood. Scleremo, a compound of 72% chromated glycerin, is a polyalcohol that is considered to be a chemical irritant sclerosant that causes cell surface protein denaturation leading to thrombo-fibrosis. The authors compared n-buty1-2-cyanoacrylate (Histoacryl®), iso-amyl-2-cyanoacrylate (Amcrylate®) and a mixture of 72% chromated glycerin (Scleremo®) with hypertonic glucose solution (25%) in the management of GV. All of the sclerosants showed efficacy and success in the management of GV; they differ in the total amount required, cost and the occurrence of bleeding during the puncture.

Innovations and breakthroughs
This is the first Egyptian study that addresses the efficacy of Scleremo® in the management of GV; it is characterized as being economical and clean, with a smooth endoscopic field of vision and few side effects.

Applications
This study may represent a future strategy for the use of a mixture of 72% chromated glycerin (Scleremo®) with a hypertonic glucose solution (25%) in the management of GV.

Terminology
Variceal obliteration employs the injection of sclerosant substances leading to the plugging and thrombosis of the varices and an immediate cast of the vessel, followed by the consequent sloughing of the cast after 1-2 wk.

Peer-review
This is a well-researched and well-written article that will be of interest to the readers and will add to the literature on the management of this condition. The endoscopic treatment of GV is still a matter of debate, and controversy exists
on their evaluation and possible pharmacologic and endoscopic treatment. Additionally, Scleremo appears to be the least costly alternative.

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