



## Safe and successful endoscopic initial treatment and long-term eradication of gastric varices by endoscopic ultrasound-guided Histoacryl (N-butyl-2-cyanoacrylate) injection

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**Abstract:** **OBJECTIVE:** Optimal endoscopic treatment of gastric varices is still not standardized nowadays. Actively bleeding varices may prohibit a successful endoscopic injection therapy of Histoacryl® (N-butyl-2-cyanoacrylate). Since 2006, we have treated gastric varices by standardized endoscopic ultrasound (EUS) guided Histoacryl injection therapy without severe adverse events. **MATERIAL AND METHODS:** We present a large single-center cohort over 7 years with a standardized EUS-guided sclerotherapy of all patients with gastric varices. Application was controlled by fluoroscopy to immediately detect any glue embolization. Only perforating veins located within the gastric wall were treated. In the follow up, we repeated this treatment until varices were eradicated. **RESULTS:** Utmost patients (36 of 40) were treated during or within 24 h of active bleeding. About 32.5% of patients were treated while visible bleeding. Histoacryl injection was always technically successful and only two patients suffered a minor complication. Acute bleeding was stopped in all patients. About 15% (6 of 40) of patients needed an alternative rescue treatment in the longer course. Three patients got a transjugular portosystemic shunt and another three underwent an orthotopic liver transplantation. Mean long-term survival of 60 months was excellent. **CONCLUSION:** Active bleeding of gastric varices can be treated successfully without the necessity of gastric rinsing with EUS-guided injection of Histoacryl.

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# *Safe and successful endoscopic initial treatment and long term eradication of gastric varices by EUS-guided Histoacryl (N-butyl-2-cyanoacrylate) injection*

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## *Abstract*

*Objective:* Optimal endoscopic treatment of gastric varices is still not standardized nowadays. Actively bleeding varices may prohibit a successful endoscopic injection therapy of histoacryl (N-butyl-2-cyanoacrylate). Since 2006 we treat gastric varices standardized EUS-guided without severe adverse events.

*Material and methods:* we present a large single center cohort over 7 years with a standardized endoscopic ultrasound guided sclerotherapy of all patients with gastric varices. Application was controlled by fluoroscopy to immediately detect any glue embolization. Only perforating veins located within the gastric wall were treated. In the follow-up we repeated this treatment until varices were eradicated.

*Results:* Utmost patients (36 of 40) were treated during or within 24 hours of active bleeding. 32.5% of patients were treated while visible bleeding. Histoacryl injection was always technically successful and only 2 patients suffered a minor complication. Acute bleeding was stopped in all patients. 15% (6/40) of patients needed an alternative rescue treatment in the longer course. 3 patients got a transjugular portosystemic shunt and another 3 underwent an orthotopic liver transplantation. Mean long term survival of 60 months was excellent.

*Conclusions:* Active bleeding of gastric varices can be treated successfully without the necessity of gastric rinsing with EUS guided injection of histoacryl.

## *Keywords*

Bleeding - endoscopic ultrasonography- gastric varices- histoacryl- injection

## *Introduction*

Liver cirrhosis complicated by development of varices induces significant morbidity with increased mortality. Esophageal varices are nowadays preferentially treated by rubber band ligations, rescue maneuver may consist of polidocanol injection, stenting, balloon tamponade and the implantation of a transjugular portosystemic shunt [1]. Gastric varices occur less frequently in cirrhotics, but their presence is troublesome in many different meanings [2]. First of all, bleeding episodes are more severe and life-threatening. Secondly their anatomic

characteristics hinder a simple therapeutic approach. These gastric varices are ramified and the net-like configuration can spread all over the fundus. Culprit lesions with ongoing bleeding or fibrin clots as signs of a recent bleeding episode do have often more than one feeding portal hypertensive vessel. The rubber band principle is therefore not working, neither are simple local mechanical interventions like clips effective.

To date three different treatment options are available: endoscopic treatment, transjugular porto-systemic shunting (TIPSS) [3] and the most recent described balloon-occluded retrograde transvenous obliteration (BRTO) [4]; the latter two are confined to an interventional radiology service. From all endoscopic interventions only the injection of N-butyl-2-cyanoacrylate with or without coil application promises valuable success. However without active bleeding site, identification of gastric varices might be difficult. Because of the substantial amount of perigastric collaterals in these patients, it seems to be prudent to focus glue treatment on the perforating veins, which cannot be identified endoscopically according our own experience. These veins might be the culprit lesions to bleed, although no trial has ever proven this theory. Re-bleeding rates over 20% may be an indirect argument as well [5]. EUS can detect in over 80% these perforating veins [6]. The endoscopic appearance of suspected gastric varices may be misleading. The endoscopically visible extrinsic tube- or finger-like impression of the gastric wall is generated both by intramural and extramural varices. To treat these varices without EUS is in fact with high success feasible, but requires larger amounts of histoacryl (4ml mean), what may rise complication rate [7]. With this approach, all suspected varices had to be treated and success is proven by hard palpation with the needle sheet. Large folds in hypertensive gastropathy may cover or mimic gastric varices. MRI, CT-Scan or EUS is superior to simple endoscopic judgement of gastric varices [8]. Large extramural varices as diagnosed in portography mimic often endangered varices, although they are not at bleeding risk. Glue embolisations to the lung, kidneys and through an open foramen ovale into brain or spleen [9] are feared.

During active bleeding the amount of blood frequently makes endoscopic hemostasis very difficult. Rinsing of the blood filled stomach is time consuming and may result in inadequate hemostasis.

To overcome the above mentioned shortcomings of visual guided injection therapy, the use of endoscopic ultrasound (EUS) seemed to be the logical evolution. Only intramural varices at risk can be treated. During active bleeding, rinsing of the stomach is not necessary and the success is immediately observed and, if needed, additional injection and/or coil treatment can be done.

We report on our experience on EUS-guided histoacryl-therapy, because we feel it should be the standard approach instead of the simple endoscopic approach as reported by others [7].

### Methods

From 1999 until November 2013 all patients with bleeding gastric varices (image 1) at our tertiary referral centre (university hospital) were prospectively collected and retrospectively analysed. Esophageal varices were treated primarily with endoscopic rubber band ligation (EBL). For histoacryl treatment we focussed on isolated gastric varices at the fundus (IGV1), further distal gastric varices (IGV 2) in corpus or antrum were not considered to be ideal for the injection approach because due to the lack of evidence.

Gastro-esophageal varices (GOV) were treated by EBL. This approach was recently shown to be equivalent to histoacryl injections [10].

Either active bleeding was directly observed during endoscopy or they have had bleed within the last 24 hours. Four patients (10% in the EUS group) with large (>10mm) gastric varices without bleeding episodes were treated in the same way as well with intention of primary prophylaxis. This particular indication was done in highly selected individuals after interdisciplinary discussion including referral physician, hepatologist and the endoscopist.

Intention was to achieve hemostasis primarily by repeated injection therapy of N-butyl-2-cyanoacrylate, as rescue treatments figured linton-balloon-sondes and TIPSS implantation. No BRTO was performed. After successful treatment, eradication of the varices in the follow-up EUS-guided endoscopies was attempted, if patients survived the initial event.

Primary endpoint was immediate bleeding control, second endpoints were survival, need for different treatment options and complications.

In concomitant esophageal and gastric varices, the latter ones were primarily treated and in case of success, coexisting esophageal varices were approached by rubber band ligation in the same session.

All patients received sandostatin intravenously. After a bolus of 100µg, a continuous infusion with 50µg per hour was installed for 5 days. All patients got 2g ceftriaxon once a day for 5 days. Airway protection by tracheal intubation was applied based on an individual basis. Since 2006 all bleeding gastric varices were treated EUS-guided and use of fluoroscopy was forced even in the ICU.

After conventional gastroscopy, EUS with a linear probe (GF UE 160, 7.5 MHz, Olympus, Hamburg, Germany and Pentax EG 3870 UTK 3.8, Hamburg, Germany) was performed.

Only strictly intramural varices (image 2) below the esophagogastric junction were considered to be treated, if they showed a diameter of 3mm or more or if active bleeding was observed.

To get the best position for puncture a chronological order is followed: the most likely varix has to be located by endoscopy and EUS. Secondly the needle has to be introduced. Rotating and slightly bending the echo-endoscope, it has to be pulled, out until a stable position nearby the varix is achieved. To enable a proper puncture, the needle was inserted into the varix as perpendicular as possible with just a slight angulation of the echoscope tip and a little distance to the mucosa as possible (see scheme 1). N-butyl-2-cyanoacrylate (B. Braun, Melsungen, Germany) was mixed in a 1:1 fashion with lipiodol (Guerbet-US, Bloomington, USA) to get 1ml portions. A 22G EUS FNA-Needle (Cook Echotip, Winston-Salem, Ireland) was used to puncture the varix (image 3). After losing resistance of the needle having passed the gastric wall, the tip was placed in the middle of the varix and the stylet subsequently removed. A flush of aqua destillata under direct visualization by EUS had to prove the proper localization of the needle tip in the lumen of the varices. A strictly to the vessel confined swirl had to be proven. The histoacryl mixture was then injected followed by 1-3ml of Aqua destillata.

During this four-hand-procedure, one examiner focussed on the EUS, the other controlled the variceal plugging under fluoroscopy (image 4). Suspicion of shunting or embolization led to an immediate cessation of the injection. If in cases of emergency fluoroscopy was not available, EUS guided injection and control of success was possible.

In 2012 we added the new described [11] coil and histoacryl-injection to our endoscopic armamentarium. We choose this modality in very large varices to occlude the lumen more effectively and safely.

EUS-guided so called glue-therapy was repeated in 4-8 week intervals until eradication was proven by EUS (image 5). Follow-Up after eradication was done by gastroscopy and EUS every 6 month or on demand in case of bleeding.

## Results

From 1999 to 2013 a total of 103 histoacryl treatments, corresponding to 7.4 events per year were done at our institution. Beginning in 2006, all fundus varices were treated EUS-guided. A total of 40 patients equal to 5.7 per year were treated by the standardized EUS-guided approach since then. Demographic data are shown in table 1. Remarkable is the high portion of non-cirrhotic patients with portal hypertension due to portal vein thrombosis. In these 40 patients we performed a total of 57 EUS-guided histoacryl-injections, with an average of 1.4 (range 1-7) sessions per patient.

Majority of treatments (96%) were done under fluoroscopy. In the others, fluoroscopy was not performed due to logistic reasons like ICU- or emergency room- circumstances (fluoroscopy not available, not applicable due to room size or bed configuration). 1.9 portions (range 1-10) of the above mentioned histoacryl mixture were injected in average, no direct embolization was observed. Two complications occurred in our cohort. One patient suffered from a spontaneously stopped GI bleeding in the stomach 3 months after the treatment. An ulceration nearby the penetrating histoacryl was diagnosed, as described recently [12]. A second patient experienced a transient bacteraemia within 24 hours successfully treated with intravenous antibiotics. Duration of treatment was extended to 2 weeks in comparison to the regular duration of 5 day schedule in all patients. .

Bleeding was immediately stopped or controlled in 100% of patients treated by histoacryl therapy with concomitant sandostatin infusion. A rescue treatment for the long term management was needed in 6/40 (15%) patients, each 3 of them underwent a TIPSS-implantation or an orthotopic liver transplantation.

EUS guided injection was done in 13/40 (32.5%) patients during active bleeding. Most patients (23 pts. = 57.5%) underwent EUS and sequentially guided histoacryl-therapy after the index bleeding episode within 24 hours of hospitalization in term of secondary prophylaxis or planned semi-elective bleeding treatment. Only 10 % (4/40) of our collective underwent the procedure as primary prophylaxis.

Two patients with large gastric varices in the primary prophylaxis group underwent successful two respectively one combined coil (MR eye Cook, Bloomington, USA, 15mm/15cm 1x respectively 8mm/10cm 2x) and histoacryl sessions without complications.

Mean survival of all patients was 60 months (range 0.5 – 517), 6/40 (15%) patients didn't survive the follow up period and 1 patient was lost to follow up after 3 years and 2 months. Mean survival time of the 6 deceased patients was 21 months (range 0.5 – 44). Two of the non-survivors died due to progressive hepatocellular carcinoma, the other 4 in liver insufficiency.

Only 1 patient (2.5%) died closed to the histoacryl-treatment during hospitalisation: a 60 years old female patient with alcoholic cirrhosis developed a hepatorenale syndrom Typ I leading to death within 16 days.

The cohort of 35 patients without EUS guidance from 1999-2006 had totally 48 histoacryl treatments with a success rate of 94% (45/48) and 2 patients experienced glue embolies to the lung.

### Discussion

Standard treatment of gastric varices is still not defined. Modalities vary from pure endoscopic to interventional radiological methods as BTRO or TIPSS implantation. The endoscopic approach in addition promotes different techniques from histoacryl injection under direct visual control to combined EUS-guided application of histoacryl and coil. Which is best and practicable in daily routine remains to be answered.

Although not randomized nor compared with a control group, we could draw important conclusions from our retrospective analysis, because of the standardized treatment technique over 7 years for an exact defined patient collective.

We cannot provide a complete data set of all variceal bleedings at our institution for this time period, which is a shortcoming of this study. Strict inclusion of IGV1 varices at the fundus together with the known decline in upper GI bleedings [13] over the last decades may explain our low final number of gastric varices treated by EUS guided glue injections. Notably this number additionally decreased in comparison to the period 1999 – 2006.

Anyhow is our low incidence of 7.4 bleeding events per year similar to 7.7 events per year in a two centre retrospective collective in Germany and Egypt [7].

In our prospective cohort we could show an excellent success concerning hemostasis and a long-term survival in patients with bleeding gastric varices. To point out is our long follow up of 60 months mean in the survivor group. Also deceased patients showed a mean survival rate of 21 months. Injection of histoacryl intended for primary prophylaxis seems to be safe as well, although we only included 4 patients without foregoing bleeding. The in hospital mortality of 2.5% is lower than reported by others between 4% [14] and 9.3% [15]. Compared to the landmark study of 1996 [16] with achievement of immediate hemostasis in 89%, we had no early re-bleeding episodes as shown in the US pilot study in 2004 [17] and no severe adverse event as reported by the group of Sohendra (6). In patients treated without EUS-guidance before 2006 we could not achieve the above-mentioned hundred per cent hemostasis; 3 out of 48 bleeding events could not be stopped (94% success rate). 2 patients with glue treatment without EUS-guidance suffered from histoacryl embolies; once to the lung arteries and in the second one to the kidney veins. Both adverse events were without symptoms and diagnosed by CT scans. Both patients received a warfarin therapy and were long term survivors.

To identify varices within the esophageal wall seems logical, because only the strictly intramural veins bear a risk to bleed. EUS is a non-invasive diagnostic procedure with immediate impact on treatment decisions. Its use to detect collaterals in esophageal varices was prospectively randomized studied with a trend to lower bleeding recurrence rates in the EUS group [18]. In 2000, the use of EUS-guided histoacryl-treatment repeated bi-weekly to eradicate gastric varices was compared to on demand treatment [19]. Late re-bleeding rates were significantly lower and a trend to reduced mortality was suggested. Patient characteristics with mostly esophagogastric varices and a minority of isolated gastric varices is a limiting factor for the proper interpretation of these figures. A preliminary case study of 5 patients proved the concept [20], that the treatment of their intramural so called perforating varices is crucial to achieve long lasting hemostasis. Recently the same group published a multicentre study including 30 patients from 9 centers [21]. All procedures were EUS-guided, 11 patients were treated with coils and 19 patients with histoacryl only. Feasibility and efficacy was proven, but the adverse event rate of 40% was quite high. In our single center cohort only 1 patient of 40 (2.5 %) experienced an adverse event; suggested transient bacteremia was treated successfully with intravenous antibiotics. We did not routinely CT scans of the chest in our patients. Therefore we are not able to report on asymptomatic lung embolies, which seems to be a not uncommon event with 30% in the work of Romero-Castro [21].

Not having prospective randomized studies comparing conventional and EUS-guided histoacryl therapy, endorsement of EUS as standard is difficult. Considering our results and data from others, nevertheless remain concrete arguments for the EUS approach. EUS allows reliable application of glue into mucosal varices. Radiological coiling or histoacryl application is unable to prove that the vessel is in the mucosa and may not result in successful closure of the bleeding vessel. Deposition into tissue itself is less frequent than when injected endoscopically under visual control only, if a proper "swirl" sign with EUS is obtained. Perpendicular puncture with direct contact of the echoscope to the varix allows a proper insertion of the needle. Due to the sometimes high resistance of the gastric wall tissue, varices have to be penetrated and secondly the needle is drawn back in the centre of the intended vessel. During the complete treatment, the EUS examiner focusses on the needle tip in the varix itself, which allows an exact application of the glue. A four-hand doctor's procedure with the help of two assistant nurses is recommended. Using EUS, the endoscopist can directly proof the clotting effect in the particular varix and add sequentially histoacryl boluses, as long the veins have still blood flow, what stands for a higher bleeding recurrence [22]. In case of active, even massive bleeding EUS controlled histoacrylate injection is successfully possible without the time consuming gastric rinsing. In these cases, EUS guided

treatment can immediately be started after initial diagnostic endoscopy without further delay. In EUS-guided treatments up to 30% of patients suffer from histoacryl embolisms, although in most cases asymptomatic [21]. Histoacryl has always to be mixed with lipiodol to make it visible in imaging such as CT scans.

The additional use of coils in combination with histoacryl [11] seems promising, although we treated only two patients by 3 sessions in our series. With regard to the feared glue embolisation, this novel modification may even lower the embolization risk further especially in large diameter varices.

The EUS-guided approach produced no additional adverse events in comparison to the endoscopical injection therapy and its additional time expenditure seems negligible. No glue-associated damage of the endoscopes occurred.

Taken all the mentioned considerations together, we judge the EUS-guided approach as safe, effective and available in daily routine and emergency situations. The additional injection of coils is promising and needs further investigation.

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