Expert Report

HISTOACRYL®

for the treatment of
haemorrhage of oesophageal and gastric fundus varices

HISTOACRYL®

2. INTRODUCTION

Oesophageal and the rarer gastric fundus varices are caused by high portal vein pressure, usually as a consequence of cirrhosis of the liver; or, in rare cases in the absence of liver disease; as a result of the thrombosis of the splenic vein or portal vein. Their rupture leads to life-threatening haemorrhage. If there is no liver disease but a thrombosis of the portal vein or the splenic vein then there is an indication for the setting-up of a portosystemic shunt or for a splenectomy. Usually, however, the cause is cirrhosis of the liver with restriction of liver function. Circa 60% of patients with cirrhosis of the liver have oesophageal varices (Calès et al. 1988). Varix rupture occurs in about 30% - 40% of patients with cirrhosis of the liver and oesophageal varices, who have not yet suffered haemorrhage (Sauerbruch et al. 1991). After a haemorrhage of an oesophageal varix the risk of recurrence is as much as 70% (Calès et al. 1990).
Haemorrhage of oesophageal varices in cirrhosis of the liver still has a high mortality rate. Approximately half these patients die immediately as a result of the haemorrhage or as a result of the liver failure caused by the haemorrhage (Calès et al. 1988, Sauerbruch et al. 1991). About one third of patients with cirrhosis of the liver die as a consequence of a haemorrhage of varices (Calès et al. 1988). These data reveal the necessity for improving the treatment of acute haemorrhage and prophylaxis against a recurrence of haemorrhage.
Several new therapeutic procedures have been established in the last 25 years. In addition there has been a fundamental evaluation of the risks and success rates today for the haemostasis of acute varix haemorrhage.

Current treatment methods
Treatment of acute haemorrhage: The most widely spread method is endoscopic sclerosis of haemorrhaging oesophageal varices. In Germany sclerotherapy consists of an intra- or paravariceal injection of 1% polidocanol solution during the acute haemorrhage. It is possible to staunch acute oesophageal varix haemorrhage in more than 90% of cases in this manner. The local injection of polidocanol is repeated several times at 4 - 8 day intervals. The polidocanol injection consolidates the ruptured varix and the tissue toxicity of the substance causes a local thrombosis of the varix and an inflammation with fibrosis of the vascular wall (Soehendra et al. 1983). The tissue toxicity causes the following complications to occur (median complication rates from 12 studies) sclerosis ulcer (31%), haemorrhage (9%), stenosis of the oesophagus (8%), perforation of the oesophagus (2%), pleural effusion (6%), pneumonia (6%), fever (14%) and individual cases of pericarditis and portal vein thrombosis (Sauerbruch et al. 1991). Polidocanol, a local anaesthetic, rarely precipitates allergic reactions and bradycardic cardiac arrhythmias. The cumulative rate for all complications in endoscopic sclerosis lies between 20 and 40%, the procedure-dependent mortality is 2% (Sauerbruch et al. 1991). The causes of death were aspiration, haemorrhage or perforation of sclerosis ulcer and very rarely pericardial tamponade.
Alternative nonsurgical procedures are balloon tamponade, endoscopic ligature of the varix and transjugular, intrahepatic, portosystemic Stent shunt (TIPS). Balloon tamponade is similar (Söderlund et al. 1985) or less effective (Barsoum et al. 1982, Paquet et al. 1985) than sclerotherapy for the haemostasis of acute varix haemorrhage. After a single balloon tamponade there are more early recurrences of haemorrhage. Endoscopic ligature of the varix is more difficult to carry out if the haemorrhage is severe, since a ligature apparatus must be attached to the endoscope and this limits the field of vision and makes aspiration of the escaping blood more difficult. However, very experienced practitioners of this technique, such as the first investigator to describe it, can staunch an acute varix haemorrhage as frequently by endoscopic ligature as by sclerotherapy (Stiegmann et al. 1992).

Prophylaxis against recurrent haemorrhage: After treatment of an acute haemorrhage prophylaxis against further haemorrhage is generally carried out in Germany by endoscopic sclerosis with polidocanol. After the emergency treatment an average of 4 elective sclerotherapy sessions are required at intervals of 7 - 10 days until the varix has been eradicated (Sauerbruch et al. 1991). The complete eradication of the oesophageal varices can be achieved in ca. 70% of the cases. However, about one third of patients suffer a recurrence of haemorrhage before complete eradication of the varices (Sauerbruch et al. 1991). The danger of a recurrence of haemorrhage is greatest during the first week after the initial haemorrhage. The causes of these recurrent haemorrhages are either ulceration of the mucous membranes, which is a frequent sequel of sclerotherapy, or the not yet eliminated varices themselves. The tissue toxicity and the risk of early recurrence of haemorrhage are a severe disadvantage of the sclerosis technique. Alternative nonoperative methods for elective prophylaxis of recurrent haemorrhage are treatment with β-blockers, endoscopic varix ligation and TIPS.
During treatment with β-blockers recurrence of haemorrhage is just as frequent as during sclerotherapy (Pagliaro et al. 1992). Endoscopic varix ligature (EL) is superior to endoscopic sclerotherapy (ES) for recurrent

haemorrhage prophylaxis. In the most recent meta analysis (10 randomized controlled studies; EL 422 patients, ES 424 patients; mean duration of observation 9.5 months) endoscopic varix ligature was followed on average by significantly less cumulative complication rates (23% as compared to 41% for ES), recurrence of haemorrhage (27 % as compared to 46% for ES) and a higher rate of survival (74% compared with 64%) (Bernard B et al. 1995). TIPS is an effective but technically very complicated procedure for prophylaxis against recurrence of haemorrhage. The incidence of haemorrhage recurrence can be reduced to ca. 10%. However, it leads to chronic hepatic encephalopathy in 20-30% of patients with advanced cirrhosis of the liver (Child-Pugh stages B and C). Re-intervention is frequently necessary, since there are 10% - 20% thrombotic shunt blockages and 20% - 30% shunt stenoses within 2 years (Conn 1993). The mean survival time after TIPS is not longer than after endoscopic sclerotherapy or ligature. In contrast to endoscopic sclerotherapy conventional shunt or transection surgery does lead to less recurrent haemorrhage but there is more frequent hepatic encephalopathy, and no improvement in survival rate (Sauerbruch et al. 1991).

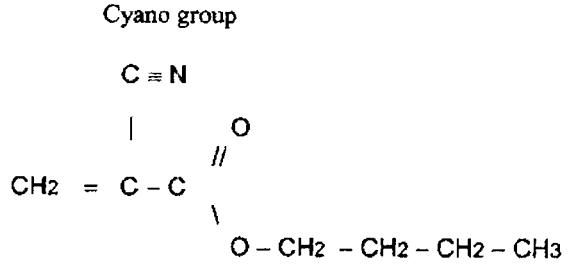
The utility of additional beta-blocker (propranolol) medication during sclerotherapy has not been proved (Jensen et al. 1989, O'Connor et al. 1989, Vinel et al. 1992, Westaby et al. 1989). In contrast acid inhibition appears to exert a favourable effect: It was possible to show that omeprazole reduced the haemorrhage risk for ulceration of the oesophagus resulting from sclerotherapy, but the number of patients involved was small.(Gimson et al. 1991).

3. CHARACTERIZATION OF THE MEDICAL PRODUCT

Histoacryl® is a cyanoacrylate-based tissue adhesive that polymerizes on the tissue to be glued after application, i.e. the liquid monomer reacts with the hydroxyl ions of the tissue fluids and is converted into a solid, wound-sealing substance.

GENERAL CHEMICAL DESCRIPTION

Histoacryl® is, like a whole series of technical adhesives, based on N-alkyl cyanoacrylates:
In this case it is n-butyl 2-cyanoacrylate:



Alkyl groups = n-butyl group

The alkyl group is responsible for the adhesive strength, the cyano group for the bonding to the body protein and the acylate group for the polymerization.

The rapidity of polymerization is a function of the length of the alkyl side chain. Alkyl cyanoacrylates with 4 carbon atoms can polymerize within seconds of tissue contact. In addition, the length of the alkyl side chain influences other physical-chemical properties e.g. the wettability and flexibility. Cyanoacylates with short alkyl chains, such as methyl cyanoacrylate, are very flexible, the butyl derivative, in contrast, less so.

All cyanoacrylates, independent of their side chains, produce heat on polymerization, the short-chain methyl cyanoacrylate produces most.

To summarize, it can be said of the chemistry that the length of the alkyl chain is of decisive importance for the polymerization, for the adhesive power and for the tissue reaction resulting from the heat produced.

COMPOSITION

1 ampoule Histoacryl® contains:		
Butyl 2-cyanoacrylate (Enbucrylat)	0.5 g	
Food dye E 141 Chlorophyll, oil-soluble	0.175 mg	AMFarbV
Hydroquinone (stabilizer)	0.25 mg	USP XXII
Sulphur dioxide (stabilizer)	0.025 mg	USP XXII
Phosphoric acid (stabilizer)	0.003 mg	DAB 10

SYNTHESIS
The monomeric adhesives are prepared from the polymers; the synthesis takes place by reaction of formaldehyde and alkyl cyanoacetates. The adhesive itself is produced by cracking at 175-240 °C followed by vacuum

distillation. The various cyanoacrylate monomers are totally miscible. This makes it possible, to a certain extent, to obtain desired effects by blending.

REMOVAL OF THE POLYMER

The polymerized adhesives can be removed from skin and instruments by acetone or dimethylformamide. For toxicological reasons only acetone should be used.

STORAGE AND KEEPING INSTRUCTIONS

Histoacryl® should be stored below +5 °C. The adhesive should only be removed from the tube immediately before use.

MECHANISM OF ACTION

Histoacryl® is suitable for the elimination of varices because it rapidly polymerizes on contact with anions, in particular the hydroxyl anions of the blood, in an exothermic reaction and thus sets (Pevsner et al. 1982). Intra-arterially injected n-butyl cyanoacrylate first produces an immediate vascular stenosis or thrombosis as a result of the plastic cylinder introduced intravascularly. Then, however, there is an inflammatory reaction with foreign body granuloma, lymphohistiocytic infiltration and some foci of vascular wall necrosis (Vinters et al. 1985). Finally there is a fibrosis in the region of the injection. The direct obliteration of the varices effected by the plastic cylinder and the fibrosis are thought to act synergetically and reduce the risk of the haemorrhage recurring in the cases of oesophageal varices. After injection into submucosal varices the cylinders of n-butyl cyanoacrylate are injected into the lumen from the oesophagus wall within 1-4 months (Ramond et al. 1989, Gotlib 1990, Soehendra et al. 1991).

4. TOXICOLOGY/FUNCTION TESTING

Toxicology

DESCRIPTION AND AIM OF THE TEST PROGRAM

The investigation described forms part of a toxicological test program for Histoacryl®. The haemolysis test on human erythrocytes, the systemic injection test, the implantation test, the intracutaneous test, the cytotoxicity test and the mutagenicity testing in the form of the Ames test and the mouse lymphoma test were carried out.

Haemolysis of human erythrocytes

DESCRIPTION AND AIM OF THE TEST
The aim of this test was to determine the haemolytic properties of Histoacryl®.

SUMMARY OF THE RESULTS
The eluate of the Histoacryl® test sample was tested in the haemolysis test. Histoacryl® did not cause any haemolysis of human erythrocytes in vitro. The test sample fulfilled the requirements of the test.

Intracutaneous test according to USP XXII

DESCRIPTION AND AIM OF THE TEST
The investigation was intended to test by intracutaneous injection of rabbits whether substances elutable from the test sample had locally irritating or toxic properties.

SUMMARY OF THE RESULTS
Histoacryl® was subjected to an intracutaneous test according to USP XXII and fulfilled the conditions of this test.

Systemic injection test according to USP XXII

DESCRIPTION AND AIM OF THE TEST
The investigation was intended to test whether a single intravenous administration of eluates from Histoacryl® to mice produced system-immanent toxic reactions.

SUMMARY OF THE RESULTS
Histoacryl® was subjected to a systemic injection test according to USP XXII and fulfilled the conditions of this test.

Implantation test according to USP XXII

DESCRIPTION AND AIM OF THE TEST
The investigation was intended to test the tissue toleration of Histoacryl® on intramuscular implantation into rabbits and macroscopic inspection (72 hours after implantation).

SUMMARY OF THE RESULTS
Histoacryl® was subjected to a test for toleration by tissue according to USP XXII and fulfilled the conditions of this test.

Cytotoxicological testing of eluates
in the microtitration test

DESCRIPTION AND AIM OF THE TEST
The investigation was intended to test whether eluates of Histoacryl® contained toxic impurities that have an influence on the growth and metabolism of cultivated 3T3 mouse fibroblasts in the microtitration test.

SUMMARY OF THE RESULTS
The test eluate produced over 24 hours at 37 °C did not cause any significant inhibition of the growth of cultivated cells and, hence, is not to be regarded as cytotoxic.

Mutagenicity test according to the Ames test

DESCRIPTION AND AIM OF THE TEST
The investigation was intended to test whether noncytotoxic, slightly cytotoxic and cytotoxic concentrations of Histoacryl® or eluates from polymerized Histoacryl® were mutagenic for Ta 1535, TA 1537, Ta 98 and TA 100 strains of Salmonella typhimurium.

SUMMARY OF THE RESULTS
In this investigation Histoacryl® was tested for mutagenicity in procaryontics (bacteria). Histoacryl® did not exhibit any mutagenic effects under the conditions of the test, while positive control substances induced mutagenicity.

Mutagenicity test using the mouse lymphoma test

DESCRIPTION AND AIM OF THE TEST
The investigation was intended to test whether noncytotoxic, slightly cytotoxic and cytotoxic concentrations of Histoacryl® or eluates from polymerized Histoacryl® were mutagenically positive in the "LK5178/Y TK+/– mammalian cell" test.

SUMMARY OF THE RESULTS
In this investigation Histoacryl® was tested for mutagenicity in eucaryontics. Histoacryl® did not exhibit any mutagenic effects under the conditions of the test, while positive control substances induced mutagenicity.

5. THERAPEUTIC APPLICATION IN HUMANS

Mode of application

The success of treatment in sclerotherapy lies in stilling the haemorrhage instantly and preventing recurrence of haemorrhage by eradicating the varices. The limiting factor is that for several weeks there is a high probability of the haemorrhage recurring before the complete thrombosis of the varices has occurred. The thought behind the application of cyanoacrylates is initially to provide for rapid eradication of the varices. (Binmoeller, Soehendra 1995).

Combined therapy: Most users of cyanoacrylates today prefer the intravariceal injection of n-butyl cyanoacrylate/lipiodol for large variceal channels combined with the sclerotherapy of smaller variceal channels by intra/paravariceal injection of 1% polidocanol.

Frequency of treatment/treatment interval: If immediate haemostasis is achieved, elective injections follow at intervals of 5 - 7 days until all varices have been obliterated. Already injected variceal channels should not be treated more frequently than every 5 - 7 days. The treatment should be continued until there is complete thrombosis or eradication of the varices.

Endoscopic obliteration of oesophageal and gastric fundus varices with Histoacryl®: Liquid Histoacryl® alone would immediately damage the endoscope by setting. Before the use of Histoacryl the biopsy channel of the endoscope should be rinsed with silicone oil. In addition, the Histoacryl® should be diluted with Lipiodol® to avoid setting. The X-ray contrast agent contained in the Lipiodol allows detection of the intravascularly injected Histoacryl on conventional X-rays.
Binmöller and Soehendra (1995) have reported the upper limits for Histoacryl injection into oesophageal or gastric fundus varices as 0.5 ml and 1.0 ml per session respectively. Intravariceal injections (oesophageal varices) are made of ca. 1.3 ml mixed Histoacryl® and Lipiodol® Ultra Fluid (Byk Gulden) in a ratio of 0.5 ml to 0.8 ml. A maximum of 4 injections can be made, i.e. not more than 4 x 1.3 ml per session or a maximum of 8 injections, i.e. 8 x 1.3 ml injections per week. In general 1 varix channel only receives one such injection at each therapeutic endoscopy. All grade 3 or 4 varices (i.e. varices with a diameter of at least 5 mm) can be obliterated in this manner in one or two endoscopic sessions within a week with Histoacryl (Gotlib). In order to document the absence of embolism it is recommended that a radiographic examination of the thorax be carried out within 24 hours of the injection of Histoacryl.

Combined therapy with 1% polidocanol: Small varices (grade I to II) are less suitable for the intravascular administration of Histoacryl. They are subjected to sclerotherapy with 1% polidocanol. The endoscopic sclerosis is carried out with Aethoxysklerol® (1% polidocanol) via an endoscopically inserted sclerosis needle by injecting up to 3 ml 1% polidocanol intravascularly and paravascularly per injection site. Account must be taken of the fact that large individual doses of 1% polidocanol of more than 3 ml per injection or larger total quantities (more than 25 ml per session) can rapidly lead to ulceration, often before the varix channels are completely thrombosed. The danger of haemorrhage is then increased. Bleeding varices at the edges of ulcers are suitable for obliteration by injection with Histoacryl/Lipiodol. Conversely, because of the rapid ulceration the combined injection of 1% polidocanol into varix channel which has already been injected with Histoacryl should be avoided. After the eradication of varices by Histoacryl/Lipiodol smaller recurring oesophageal varices at the cardia should be eradicated by polidocanol sclerosis in order to avoid the formation of further recurring varices resulting from polidocanol-induced fibrosis of the submucosa (Gotlib 1990, Soehendra et al. 1991).

Clinical experience until now

N-Butyl cyanoacrylate has been in use clinically for more than 15 years in interventional radiology for the intravascular embolization of arteries and treatment of arterial and arteriovenous malformation (Vinters et al. 1985). In addition, it has been in use for several years for the obliteration of oesophageal and fundus varices (Ramond et al. 1989, Feretis et al. 1990, Soehendra et al. 1991).

After failure of sclerotherapy with polidocanol, endoscopic varices obliteration with the plastic adhesive n-butyl cyanoacrylate has been used in the staunching of bleeding in cases of acute haemorrhage of oesophageal varices (Feretis et al. 1990, Soehendra et al. 1991).

In a retrospective, uncontrolled study of the use of n-butyl cyanoacrylate on 168 patients Soehendra et al. (1991) have reported a reduction of the rate of recurrence of haemorrhage by 60% (from 30% to 12%) compared to historic controls, treated by conventional sclerosis with 1% polidocanol. At the same time the hospital mortality rate fell from 32% to 12%. The rate of complications for obliteration was no higher than after sclerosis (polidocanol).

Good results have been obtained with n-butyl cyanoacrylate in the treatment of gastric varices both for the acute haemostasis and an elective eradication of varices (Ramond et al. 1989, Feretis et al. 1990).

Summary of therapeutic studies

Author	Treatment	Patients	Active bleeding		Haemostasis	Recurrent bleeding
		(n)	n	%	%	
Gotlib et al. 1984	Cyanoacrylate alone	96	21	22	95	36% (9 months)
Ramond et al. 1986	Cyanoacrylate alone	49	15	31	93	42% (1 year)
Feretis et al. 1990	Combined#	67	18	78	96	11.9%
Rauws et al. 1991	Combined#	39	27	69	100	41% (3 months)
Mostafa et al. 1993	Combined#	100	100	100	100	10%
Pretis et al. 1993	Combined#	29	18	62	100	6.1%
Dal Monte et al. 1994	Combined#	71	36	51	94	10.6%
Thakeb et al. 1995	Combined#	58	n.d.	n.d.	100	8.6%
Binmoeller, Soehendra 1995	Combined#	407	258	63	100	10.1%

combined: cyanoacrylate + polidocanol

6. ADVERSE EFFECTS OF THE MEDICAL PRODUCT

Local complications and side effects: When such quantities of Histoacryl® are introduced into the lumen of the vessel it cures immediately and causes both immediate stenosis and a thermal reaction with the desired sclerosis of the varix. After a few days the n-butyl cyanoacrylate casts lead to mucosal necrosis and, hence, are discharged into the lumen of the oesophagus or the stomach. Haemorrhages as a result of necrosis/ulceration and chronic scarred oesophageal stenoses were less frequent after the obliteration of varices by n-butyl cyanoacrylate polymer than after sclerosis with polidocanol, the previous standard therapy (Feretis et al. 1990, Soehendra et al. 1991). The use of Histoacryl® should primarily be restricted to large oesophageal varices. In the cases of small-diameter oesophageal varices care should be taken that administration is strictly intravascular since paravariceal injections can cause considerable tissue ulceration. Such small-diameter oesophageal varices are better treated by sclerosis with 1% polidocanol.

Specific risks: Over a period of 5 years Gotlib (1990) did not observe any deaths, where there could be a causal relationship with the method, in 317 patients, whose oesophageal varices had been treated with Bucrylat or Histoacryl. Complications,such as stenosis.(reversible by bougienage), bacteraemia and fever were only observed in individual cases. Similarly Binmöller and Soehendra (1995) did not observe serious complications in a group of 407 patients over a period of 9 years.
However, there have been reports of individual severe complications. Thus, Mostafa et al. (1993) reported a fatal pulmonary embolism, Thakeb et al. (1995) reported a case of lethal septic portal vein thrombosis after embolism of n-butyl cyanoacetate in the portal vain. Binmöller and Soehendra (1995) see the three- to four-fold overdose of Histoacryl (up to 10 ml Histoacryl/Lipiodol® per varix channel) as the probable cause of these complications.

There are reports in the literature that do not exclude a potential carcinogenicity of the cyanoacrylate monomer. Until now none of more 2000 patients, who have undergone treatment of varices with cyanoacrylates, have provided evidence of possible carcinogenicity (Samson, Marshall 1987). It is true that n-butyl cyanoacrylate is only slowly degraded by the body intravascularly or in the tissues; on the other hand, the Histoacryl cylinder is ejected into the oesophageal lumen so that long-term effects can virtually be excluded (Binmöller, Soehendra 1995).

Animal experiments with n-butyl cyanoacrylate have not revealed a greater incidence of malignomas (Vinters et al. 1985). Neither has a single case of the occurrence of malignoma been recorded after millions of applications to humans (outer skin and various other indications) over the last 25 years.

General risks: (skin/eyes): Improper, too thick application of the adhesive can lead to thermal damage to the tissue as a result of the polymerization process. Large areas of too compactly applied adhesive layers prevent connective-tissue healing of the wound and are absorbed with difficulty. Inadvertent over-application of adhesive can be removed in the first few seconds with a dry swab.

If there is undesired adhesion and deposition of the substance, particularly in the eye, when Histoacryl® is used, this resolves itself within a few days.

No other reports of adverse medical product effects are known to have been reported for Histoacryl®.

7. SUMMARY AND CONSEQUENCES FOR CLINICAL APPLICATION

Histoacryl® has been tested toxicologically. The systemic injection test, implantation test, intracutaneous test, cytotoxicity test and mutagenicity test did not reveal any evidence of toxicity or mutagenicity.

Numerous publications of clinical investigations confirm the efficacy and safety of Histoacryl® and of other cyanoacrylate-based adhesives in the treatment of oesophago-gastric varices. The rate of recurrence of haemorrhage can - on the basis of the results of a retrospective study - be lowered, in comparison to the general, conventional sclerotherapy from 30% to 12% by combined treatment with Histoacryl and polidocanol, thus also reducing the mortality rate.

The present animal experimental results and numerous literature reports do not reveal any evidence of a possible risk in clinical application. Application for endoscopic eradication of varices in the manner described here can be regarded as safe. The combined treatment with Histoacryl and polidocanol represents an appreciable advantage for the patient in the treatment of oesophageal and gastric fundus varices.

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9. SIGNATURE

Leipzig, 06 March 1996

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