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Endoscopic treatment of bleeding gastric varices: a single centre's experience

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Endoscopic treatment of bleeding gastric varices: a single centre´s experience

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ABREVIATIONS

CHUC: Centro Hospitalar e Universitário de Coimbra

EBL: Endoscopic Band Ligation

ECI: Endoscopic Cyanoacrylate Glue Injection

EGD: Esophagogastroduodenoscopy

GI: Gastrointestinal

GIB: Gastrointestinal Bleeding

GOV: Gastroesophageal Varices

GV: Gastric Varices

IGV: Isolated Gastric Varices

IQR: Interquartile Range

MELD: Model for End-Stage Liver Disease

NBC: N-butyl-2-cyanoacrylate

OV: Oesophageal Varices

PTH: Portal Hypertension

SB: Sengstaken-Blakemore

SD: Standard Deviation

ABSTRACT

N-butyl-2-cyanoacrylate injection is widely considered the endoscopic treatment of choice for the approach of acute gastric variceal bleeding. However, there are still some controversies concerning this technique, its safety, and long-term results. A retrospective study was conducted to analyse the safety and efficacy of cyanoacrylate injection in patients with gastric variceal bleeding. From January 1998 to February 2022, a total of 172 patients with acute gastric variceal bleeding were admitted to our department, of which 141 underwent endoscopic treatment with cyanoacrylate. Outcomes such as primary haemostasis, rebleeding rate and complications were evaluated, as well as data on patients' follow-up and mortality. Primary haemostasis was accomplished in 133 patients (94.3%), with a rebleeding rate of 14.2%. Complications occurred in 17.7% of the patients, although severe complications were rare (5.6%) and not significantly associated with the volume of cyanoacrylate injected. Mortality rate within the initial bleeding episode was 7.1%, and very early rebleeding was the strongest predictor of in-hospital mortality ($p<0.01$). These findings suggest that endoscopic injection of N-butyl-2-cyanoacrylate is a safe and effective option for treatment of gastric variceal bleeding. Although rebleeding and complications occurred in a small number of patients, they should not be overlooked.

KEYWORDS: Gastric Varices • Portal Hypertension • Gastrointestinal haemorrhage • Cyanoacrylate

RESUMO

A injeção endoscópica de N-butil-2-cianoacrilato é amplamente considerada a opção terapêutica de primeira escolha para a abordagem da hemorragia aguda varicosa gástrica. No entanto, existem ainda algumas controvérsias relativamente a esta técnica, nomeadamente no que respeita à sua segurança e resultados a longo prazo. Foi desenvolvido um estudo retrospetivo, com o objetivo de analisar a segurança e eficácia da injeção de cianoacrilato em doentes com hemorragia varicosa gástrica. Entre janeiro de 1998 e fevereiro de 2022, um total de 172 pacientes com hemorragia aguda varicosa gástrica foram admitidos no nosso departamento, dos quais 141 foram submetidos ao tratamento endoscópico com cianoacrilato. Medidas como a hemostase primária, taxa de recidiva e complicações foram avaliadas, bem como dados relativos ao seguimento e mortalidade dos pacientes. A hemostase primária foi alcançada em 133 pacientes (94,3%), com uma taxa de recidiva hemorrágica de 14,2%. Complicações ocorreram em 17,7% dos pacientes, embora as complicações severas tenham sido raras (5,6%) e não significativamente associadas ao volume de cianoacrilato injetado. A taxa de mortalidade inerente ao episódio inicial de hemorragia foi de 7,1%, e a recidiva hemorrágica muito precoce foi o preditor mais forte da mortalidade intra-hospitalar ($p<0,01$). Estes resultados sugerem que a injeção endoscópica de N-butil-2-cianoacrilato constitui uma opção segura e eficaz para o tratamento da hemorragia varicosa gástrica. Embora recidiva hemorrágica e complicações se tenham verificado num reduzido número de doentes, o risco associado à sua ocorrência não deve ser negligenciado.

PALAVRAS-CHAVE: Varizes Gástricas • Hipertensão Portal • Hemorragia Gastrointestinal • Cianoacrilato

1. INTRODUCTION

Gastric Varices (GV) are part of a complex set of vascular shunts established between the portal and the systemic circulation (1). Bleeding resulting from the rupture of such vessels is a known and severe complication of portal hypertension, determining a 20% mortality rate in cirrhotic patients (2). There is an estimated prevalence of GV that goes from 17% to 25% in patients with portal hypertension, contrasting with the much more commonly found Oesophageal Varices (OV), that are present in up to 85% of these patients (3). Studies have shown that, when compared with OV, GV bleed in significantly fewer patients (64% *vs*. 25%, respectively) (3). However, although GV are not as common as OV and don´t bleed as frequently, the haemorrhage resulting from their rupture is usually more severe and more frequently associated with higher transfusion requirements, rebleeding and mortality rates (4). In fact, it was demonstrated that such bleeding is much more critical, and the risk of mortality could go as high as 45%, being more likely in patients with GV than patients with OV (3, 5).

It has currently been established that endoscopic treatment is the initial and often definitive modality for GV bleeding (6, 7). From the numerous endoscopic treatment approaches that have risen, Endoscopic Cyanoacrylate Glue Injection (ECI) remains the most widely accepted method for controlling a GV bleeding. This technique relies on the injection of N-butyl-2-cyanoacrylate (NBC), a monomeric tissue adhesive that rapidly polymerizes when in contact with blood, leading to the formation of long solid chains, therefore obliterating the vessel (1, 8). Since it was first described in the 1980s, the GV obliteration using ECI has proved to be effective, achieving primary haemostasis in 70% to 100% of the patients (9). In addition, this method has been associated with fewer complication and rebleeding rates, when compared to other endoscopic treatment modalities (6, 10). For instance, several randomized control trials have been conducted to compare ECI and Endoscopic Band Ligation (EBL), the standardized recommended method for the approach of acute OV haemorrhage. These trials have demonstrated that the active bleeding control was achieved in approximately 80% of patients submitted to EBL and in around 94% of patients submitted to ECI (11). Other studies were conducted, comparing ECI with other treatment modalities not involving cyanoacrylate, including EBL, pharmacological treatment with propranolol and sclerotherapy with alcohol or ethanolamine. It was concluded that the use of NBC was associated with significantly lower all-cause mortality and rebleeding rate, when in comparison to the remaining therapies (12).

On that account, the use of ECI is widely considered to be the first treatment option for acute GV bleeding, as well as prevention of rebleeding episodes (13). However, and despite its widespread use, there are still some controversies in the literature concerning this technique,

its safety and long term results, mainly due to the lack of a standardized approach when it comes to the procedure (14).

The aim of this study is to retrospectively evaluate the cases of acute GV haemorrhage that were admitted to the Gastroenterology Department of the Centro Hospitalar e Universitário de Coimbra (CHUC), in order to analyse the safety and efficacy of ECI.

2. METHODS

2.1. PATIENTS

From January 1st, 1998, until February 22nd, 2022, all adult (≥18 years old) patients admitted to the Gastroenterology Department of CHUC due to GV bleeding were included (*n*= 172). Given that the main aim of the study is to examine the safety and efficacy of ECI, patients not submitted to this procedure were excluded (*n*= 31). Pregnant women were also excluded from the study. It was considered that patients had GV bleeding when there was active haemorrhage during endoscopy and/or there were stigmata of recent bleeding, such as telangiectasia, red colour signs, platelet-fibrin plug (white nipple sign) and/or red wale marking. Demographic data such as age and gender were collected, as well as data related to the admission such as date, haemoglobin and prothrombin rate, vasopressor prior to endoscopy, timing of endoscopy and endoscopic findings. Data related to patients' liver disease was collected, such as if liver disease was previously known and its aetiology. MELD (Model for End-Stage Liver Disease) score and Child-Pugh classification were determined and the second was defined as A (5 to 6 points), B (7 to 9 points) or C (10 to 15 points).

2.2. GASTRIC VARICES CLASSIFICATION

The classification of GV was based on their anatomic location as seen on endoscopy, according to the classification described by Sarin. This classification differentiates Gastroesophageal Varices (GOV) from Isolated Gastric Varices (IGV). Furthermore, GOV are subclassified into two subgroups: type 1 and type 2. GOV1 are an extension of OV below the gastroesophageal junction and can be found along the lesser curvature and cardia. GOV2 originate from the extension of OV towards the fundus of the stomach and may extend to the cardia. IGV are also divided into IGV1, when located in the gastric fundus (also called fundal varices) and IGV2, when found in other sporadic locations such as the antrum or the corpus of the stomach.

2.3. ENDOSCOPIC CYANOACRYLATE INJECTION

The endoscopic procedure that involved the injection of NBC into the gastric varices was performed according to two different protocols. Patients admitted until March of 2019 underwent endoscopic injection with a mixture of NBC and Lipiodol (Histoacryl™) at a ratio of 1:1 or 1:1.5. As to patients admitted after March of 2019, the same endoscopic procedure was

carried out using Glubran®2, a preparation of NBC added to a synthesized monomer (Methacryloxy-sulpholane), being used without any previous dilution. Prior to the procedure, the inner catheter of the injector was also filled with distilled water, in a volume corresponding to the dead space of the catheter. Once the catheter was positioned on the target varix with the help of the scope, the needle punctured the varix adjacent to the rupture point, followed immediately by the injection of the previously prepared distilled water, assuring that the entire volume of cyanoacrylate was injected. The injected volume of Hystoacryl-Lipiodol or Glubran®2 was based on the dimension and appearance of the gastric varices during endoscopic evaluation. If the bleeding failed to cease, reinjection was performed during the same procedure. Data regarding the volume of cyanoacrylate injected, total volume injected and the number of injections administered was collected. The total volume injected is higher and does not always correspond to the volume of cyanoacrylate, since it includes the Lipiodol that is present in Histoacryl™ and the distilled water injected during the procedure.

2.4. HAEMORRHAGE AND OUTCOME MEASURES

As outcome measures, several parameters were accessed, such as the primary haemostasis, rebleeding rate, new episodes of gastrointestinal bleeding (GIB) and complications related to the procedure. Primary haemostasis was defined as the absence of GV bleeding within the first 48 hours that followed the treatment and no further hemodynamic instability. Rebleeding was defined by the clinical occurrence of hematemesis or melena, if accompanied by a decrease of more than 2 g/dl of haemoglobin or by hemodynamic instability. Any new active bleeding of previously treated varices, detected in a subsequent endoscopy was, in the same way, considered as rebleeding. Rebleeding was classified as very early, when occurred within 48 to 120 hours after treatment, and early, if taken place between 120 hours and 6 weeks after the initial treatment. New episodes of GIB were considered when haemorrhage of previously treated varices occurred past 6 weeks after the initial episode. Lastly, several procedure-related complications were evaluated, such as fever, pulmonary abscess, pulmonary and cerebral embolism.

2.5. STATISTICAL ANALYSIS

Categorical data are presented as absolute frequencies and relative frequencies in percentages. Numerical data are expressed as mean ± Standard Deviation (SD) or median with range or Interquartile Range (IQR), according to histogram distribution. Categorical variables were compared using the Pearson $\chi 2$ test or the Fisher exact test. When comparing categorical and numerical variables, Student's t-test and Mann-Whitney U test were used as

appropriate. $p < 0.05$ was considered statistically significant. The statistical analysis and data interpretation was performed using the Statistical Package for Social Sciences, version 27.0 for Windows (SPSS, Inc., Chicago, IL, USA).

3. RESULTS

3.1. DEMOGRAPHICAL AND CLINICAL DATA

A total of 141 patients with GV haemorrhage were included, among which 111 were male (78.7%). The mean (± SD) age was 59.9 ± 11.4 years, ranging between 32 and 88 years old. Most patients (*n*= 122; 86.5%) had liver cirrhosis, as opposed to the 19 patients with non-cirrhotic portal hypertension (13.5%). Over the years, there has been a reduction in the number of hospital admissions due to GV bleeding. During the first decade (from 1998 to 2007), a total of 82 patients (58.2%) were admitted due to GV bleeding, whereas in the following decade, there were only 38 admissions (27%). In the last five years (from 2018 to 2022), 21 patients (14.9%) were admitted due to GV bleeding.

The mean (± SD) haemoglobin level at hospital admission was 8.6 ± 2.1 g/dl and mean prothrombin rate was 55.7 ± 14.9%. Median (IQR) packed red blood cells required for transfusion during the episode of VB was 4 (3,3) units. Previous sclerotherapy had been attempted in 34 patients (24.1%) and Sengstaken-Blakemore (SB) tube was used before endoscopic treatment in 26 patients (18.4%).

Demographic and clinical characteristics of the patients are expressed in **Table 1**.

Table 1. Demographic and clinical characteristics of patients

Characteristics		**N (%); mean ± SD; median (range)**
Male		111 (78.7%)
Age (years)		59.9 ± 11.4
Provenience	CHUC	82 (58.2%)
	Other hospital	59 (41.8%)
Aetiology of PHT		
Cirrhosis		122 (86.5%)
	Alcohol	102 (72.3%)
	Virus	10 (7.1%)
	Alcohol and Virus	5 (3.5%)
	Other	5 (3.5%)
Non-cirrhotic PTH		19 (13.5%)
GV bleeding as first manifestation of liver cirrhosis		22 (18%)
First episode of GV bleeding		57 (40.4%)
Child-Pugh classification	A	18 (14.8%)
	B	68 (55.7%)
	C	36 (29.5%)
MELD score		14 (6-26)
Clinical presentation	Hematemesis	72 (51.1%)
	Hematemesis and Melena	54 (38.3%)
	Melena	15 (10.6%)
Haemoglobin level at admission (g/dl)		8.6 ± 2.1
Prothrombin rate at admission (%)		55.7 ± 14.9%

CHUC - Centro Hospitalar e Universitário de Coimbra; GI - gastrointestinal; GV - gastric varices; MELD - model for end-stage liver disease; PTH - portal hypertension

3.2. PRE-ENDOSCOPIC PROCEDURES AND ENDOSCOPIC FINDINGS

Median (IQR) time from hospital admission until endoscopy was 15 (43.4) hours. Prior to the endoscopy, a vasoactive drug was administered to most patients (*n*= 121; 85.8%).

OV were found in 117 patients (83%), concurrently with GV. According to Sarin´s classification, GOV1 were the most common GV (*n*= 49; 34.8%), followed by GOV2 in 45 patients (31.9%), IGV1 in 39 (27.7%) and IGV2 in 8 patients (5.7%). Endoscopy showed 104 patients (73.8%) had stigmata of recent VB, whereas 37 patients (26.2%) presented active bleeding.

Pre-endoscopic procedures and endoscopic findings are expressed in **Table 2**.

Table 2. Pre-endoscopic procedures and endoscopic findings

Pre endoscopic		**N (%); median (IQR)**
Vasoactive treatment		121 (85.8%)
	Terlipressin	29 (20.6%)
	Octreotide	92 (65.2%)
Time between admission and endoscopy (hours)		15 (43.4)
Endoscopic		
Bleeding status	Recent haemorrhage	104 (73.8%)
	Active haemorrhage	37 (26.2%)
Sarin classification	GOV1	49 (34.8%)
	GOV2	45 (31.9%)
	IGV1	39 (27.7%)
	IGV2	8 (5.7%)

GOV - gastroesophageal varices; IGV - isolated gastric varices

3.3. TREATMENT EFFICACY AND SAFETY

Amongst the patients that underwent ECI, 91.5% were treated with Histoacryl™ (*n*=129) and, in the remaining cases (*n*=12), the endoscopic procedure was carried out using Glubran®2.

Primary haemostasis was achieved in 133 patients (94.3%) and the median (range; IQR) total volume injected was 2 (0.6 to 5; 1) ml, administered in 1 to 8 injections. The median (range; IQR) volume of cyanoacrylate injected was 1 (0.3 to 3; 0.5) ml. Higher volumes of cyanoacrylate injected were positively associated with achieving primary haemostasis ($p<0.01$). However, regarding the number of injections administered and the total volume injected, a significant association with primary haemostasis was not established ($p=0.55$ and $p=0.12$, respectively).

The use of SB tube after the treatment with ECI was required in 6 patients (4.3%), and the use of other sclerosant agents was necessary in 4 patients (2.8%). Furthermore, 16 patients (11.3%) required a new session of ECI within the same episode of variceal rupture.

When compared the efficacy of cyanoacrylate in patients that underwent Histoacryl™ injection to patients who underwent Glubran®2 administration, there were no significant differences found ($p=0.52$). With Histoacryl™, primary haemostasis was achieved in 94.6% and with Glubran®2 it was achieved in 91.7% of cases.

Complications after the endoscopic procedure were reported in 25 patients (17.7%), some of which registered more than one complication (*n*=8; 5.7%). Most (92%) occurred prior to March of 2019, before the Glubran®2 was introduced. The most frequent complication was fever (n=

16; 11.3%). Major complications, namely thromboembolic events, occurred in 8 patients (5.6%). Pulmonary embolism occurred in 5 cases (3.5%) and cerebral embolism took place in 3 cases (2.1%), one of which led to the death of the patient within the episode. Complications due to various other causes took place in 14 patients (9.9%). All the thromboembolic events were reported during the period when Histoacryl™ was used. There was no positive association between volume of cyanoacrylate injected, total volume injected, or the number of injections and post-treatment complications (p=0.28, p=0.29, p=0.88, respectively).

Rebleeding occurred in 20 patients (14.2%), with early rebleeding accounting for 7.8% (11 patients) and very early rebleeding taking place in 6.4% (9 patients).

Outcome measures such as primary haemostasis, rebleeding rates and complications are expressed in **Table 3**.

Table 3. Outcome measures of ECI

Parameters		**N (%)**
Primary haemostasis		133 (94.3%)
Complications		25 (17.7%)
	Fever	16 (11.3%)
	Pulmonary embolism	5 (3.5%)
	Cerebral embolism	3 (2.1%)
	Others	15 (10.6%)
Rebleeding		20 (14.2%)
	Very early	9 (6.4%)
	Early	11 (7.8%)

ECI - Endoscopic Cyanoacrylate Injection

3.4. FOLLOW-UP AND MORTALITY

Most patients maintained subsequent follow up (*n*=114; 80.9%), being the median (IQR) follow up time of 21.5 (45.3) months. A total of 11 patients (7.8%) were submitted to liver transplant at some point during their follow up period.

During follow up, new episodes of Gastrointestinal (GI) bleeding occurred in 48 cases (34%). A total of 23 of these patients required at least one additional session of ECI, due to suspected recurrent bleeding, and the majority (*n*=15; 68.2%) underwent one single additional session. There was not a significant association between Sarin's classification and the need for new ECI sessions, due to suspected recurrent bleeding (p=0.051). Nevertheless, patients with

IGV1 needed more frequently additional ECI sessions when compared to patients with GOV1, GOV2 and IGV2 (30.6% vs 12.7%, 8.3% and 0%, respectively).

The overall mortality rate during follow-up was 64.5%, and age was significantly associated with this rate ($p<0.01$). Mean (± SD) age of patients that died was 62.7 ± 13.2 years, against 56.6 ± 9.8 years who survived. A total of 10 patients died within the initial bleeding episode (in-hospital mortality rate of 7.1%) and the mortality rate within 6 weeks after this episode was 13.2%. Nevertheless, mortality within 6 weeks could not be determined in a total of 20 cases (14.2%).

Data on follow up and mortality rate are expressed in **Table 4**.

Table 4. Follow-up and mortality rate

Parameters	**N (%); median (IQR)**
Number of patients that maintained follow up	114 (80.9%)
Follow up time (months)	21.5 (45.3)
New ECI sessions	23 (16.3%)
Overall mortality rate	91 (64.5%)
In-hospital mortality rate	10 (7.1%)
Mortality rate within 6 weeks	15 (13.2%)
Liver transplant	11 (7.8%)

ECI - Endoscopic Cyanoacrylate Injection

Factors associated with in-hospital mortality ($p<0.01$) were the use of SB tube after treatment with ECI and very early rebleeding. Half of the patients that required SB tube after the endoscopic treatment and 55.6% of the cases that had very early rebleeding died within the initial bleeding episode. Child-Pugh classification was significantly associated with both in-hospital mortality and mortality within 6 weeks ($p<0.01$). Patients classified as Child-Pugh C died more frequently, when compared to patients classified as Child-Pugh A, within the initial episode and during the following 6 weeks (25% vs 5.7%; 32.3% vs 14.3%, respectively). The median MELD score was similar in patients who died within the bleeding episode when compared to those who survived ($p=0.37$). When a vasoactive drug was not administered before endoscopy, the mortality rate within the episode of VB was not significantly higher ($p=1$). Primary haemostasis not achieved after the endoscopic procedure was not significantly associated with a higher in-hospital mortality rate ($p=0.10$).

Regarding pre-procedure data, when GV bleeding was the first manifestation of liver cirrhosis, the mortality within the episode was not significantly higher ($p=0.21$). Previous episodes of GV

haemorrhage did not have a significant effect on in-hospital mortality (p=0.74). Lower levels of haemoglobin implied worse prognosis: patients with lower levels of haemoglobin died more frequently within the initial bleeding episode and during the following 6 weeks, when compared to those who survived (7.2 ± 2.7 g/dl vs 8.7 ± 2.1 g/dl, p=0.04; 7.3 ± 2.3 g/dl vs 8.7 ± 2.0 g/dl, p=0.02, respectively). Prothrombin rate at admission was also significantly lower in patients who died during the initial bleeding episode and during the subsequent 6 weeks, when compared to those who did not (42.7 ± 17.8% vs 56.7 ± 14.3%, p<0.01; 43.3 ± 15.1% vs 57.1 ± 13.8%, p<0.01, respectively).

In-hospital mortality predictors are expressed in **Table 5**.

Table 5. In-hospital mortality predictors

Predictors	**In-hospital mortality N (%); mean ± SD; median (range)**	**In-hospital survival N (%); mean ± SD; median (range)**	**p-value**
Child-Pugh classification			<0.01
A	1 (5.6%)	17 (94.4%)	
B	0	68 (100%)	
C	9 (25%)	27 (75%)	
Haemoglobin level (g/dl)	7.2 ± 2.6	8.7 ± 2.1	0.04
Prothrombin rate (%)	42.7 ± 17.8	56.7 ± 14.3	<0.01
MELD score	14 (7-26)	14 (6-25)	0.37
GV bleeding as first manifestation of liver cirrhosis	0	22 (100%)	0.21
Previous episode of GV bleeding	7 (8.3%)	77 (91.7%)	0.74
Vasoactive drug before EGD not administered	1 (5%)	19 (95%)	1
Sarin classification			0.77
GOV1	4 (8.2%)	45 (91.8%)	
GOV2	4 (8.9%)	41 (91.1%)	
IGV1	2 (5.1%)	37 (94.9%)	
IGV2	0	8 (100%)	
Primary haemostasis not achieved	2 (25%)	6 (75%)	0.10
SB tube after ECI	3 (50%)	3 (50%)	<0.01
Very early rebleeding	5 (55.6%)	4 (44.4%)	<0.01

ECI - Endoscopic Cyanoacrylate Injection; EGD - Esophagogastroduodenoscopy; GOV - gastroesophageal varices; IGV - isolated gastric varices; GV - Gastric varices; MELD - model for end-stage liver disease; SB - Sengstaken-Blakemore. The rates presented in the table refer to the number of patients that died or survived, from the various groups listed on the first column. Only p values<0.05 were considered significant.

4. DISCUSSION AND CONCLUSION

In the present study, most of the patients with GV bleeding were from CHUC's area of influence. The majority of them were male, with a mean age of 59.9 years and had liver cirrhosis, more frequently classified as Child Pugh B and clinically presented with hematemesis, which was consistent with what is described in the literature (2, 3, 15, 16). However, a high percentage of alcohol as liver cirrhosis aetiology was recorded, suggesting a high prevalence of alcohol consumption habits amongst this population and coherent with alcohol being the main aetiology of liver cirrhosis in Portugal, consistent to Silva et al. (17).

Over the years, the number of hospital admissions due to GV bleeding has been decreasing, probably due to the early diagnosis of portal hypertension and to the better understanding of the underlying mechanisms of this condition (18), allowing an assertive and individualized therapeutic approach. Besides, the latest recommendations on the use of nonselective betablockers as a primary prophylaxis strategy may have also contributed to the prevention of acute GV bleeding (1, 19).

GOV1 were the most common GV, according to Sarin classification, followed by GOV2 and IGV1 and IGV2 were the least frequently found types, which was consistent with other previous studies (3, 5). During endoscopy, a total of 104 patients (73.8%) had stigmata of recent VB, whereas only 37 patients presented with actual active bleeding. This may be explained by the fact that a vasoactive drug (either octreotide or terlipressin) was administered to most patients (85.8%) before the endoscopic procedure, having contributed to haemorrhage control.

Primary haemostasis was achieved in 94.3% of patients submitted to ECI, which was coherent with the published literature, since the success rate is described as ranging from 70 to 100% (9) and it specifically reached 94% in Qiao et al. (11). The high rate of efficacy achieved in our study may be related to the fact that most of the patients did not present with active bleeding at endoscopy, which could have facilitated the injection of cyanoacrylate adjacent to the rupture point of the varix. To the best of our knowledge, there is no information on association between volumes of cyanoacrylate injected and primary haemostasis. However, in our study, higher volumes of cyanoacrylate injected were positively associated with achieving primary haemostasis. The same association was not observed with the total number of injections administered and the total volume injected, meaning more cyanoacrylate injected translates to a more robust vessel obliteration and distilled water does not interfere in haemostasis.

Complications related to the endoscopic injection of NBC have been described in previous case reports. Although not very frequent, some of them can be life threatening, such as thromboembolic phenomena (14, 20). In the present study, complications occurred in 17.7%

of the patients, being fever the most frequent (11.3%). Pulmonary embolism was reported in 5 cases (3.5%) and cerebral embolism occurred in 3 patients (2.1%), one of which died following this event. Soehendra *et al*. reported that a large volume injection was positively associated with the occurrence of such complications (21). However, in our study, there was no significant association between the volume of cyanoacrylate injected, total volume injected, or the number of injections administered and the occurrence of post-treatment complications, maybe due to the small number of cases in which these complications occurred.

Regardless the absence of significant difference in achieving primary haemostasis using Histoacryl™ or Glubran®2, most complications, including all major complications, namely pulmonary and cerebral embolisms, occurred before March of 2019, when the use of Glubran®2 had not yet been introduced. This may be related to the use of Histoacryl™, a mixture of NBC and Lipiodol, since this last component, used as a diluter of the glue, prolongates the process of polymerization, therefore increasing the risk of embolization (14). After the introduction of Glubran®2, no further cases of systemic embolization were reported, although there must be considered that only 12 patients have been treated with this product.

Despite the success of cyanoacrylate in producing haemostatic effect, rebleeding occurred in a significant number of cases (14,2%), of which most took place during the subsequent 6 weeks post treatment (7.8%), and a few occurred within the first 120 hours after treatment (6.4%).Rebleeding rates after endoscopic treatment of GV have been previously reported to vary between 10 and 50%, associated with severe liver disease (Child-Pugh C) (22, 23). However, in the present study, such association was not found.

Over the follow-up period, a significant number of patients (16.3%) required at least one additional session of ECI, due to suspected recurrent bleeding. Although there is no information on potential association between the need of such sessions during follow-up and Sarin´s classification, our study documented that IGV1 required more additional ECI sessions, when compared to GOV1, GOV2 and IGV2. However, this difference was not statistically significant. This could be related to the fact that IGV1 have a high incidence of bleeding when compared to the other types and might require additional intervention, other than an endoscopic one, in order to achieve definitive haemostasis (3).

Overall mortality rate was 64.5%, translating the mortality occurred throughout the follow-up period and, therefore, not directly associated to this procedure. Its high value is probably related to the severity of the liver disease and the only risk factor significantly associated with it was age. Patients died at mean age of 62.7 years old.

Soehendra et al. reported an in-hospital mortality rate of 17.5%, similar to the one reported by Kind *et al*. (19.5%). However, in our study, in-hospital mortality rate was surprisingly lower

(7.1%) and was significantly associated with the severity of hepatic disease (Child-Pugh C), use of SB tube after the treatment with cyanoacrylate and very early rebleeding. From all these parameters, very early rebleeding was the strongest predictor of in-hospital mortality, since most patients with rebleeding within the first 120 hours after treatment died before hospital discharge. The low in-hospital mortality rate observed in the present study could be due to the close surveillance of patients, ensured by gastroenterologists at a Gastroenterological Intensive Care Unit, that was active during most of the study's period. Furthermore, there was a high percentage of patients (85.8%) undergoing vasopressor before endoscopy, helping with bleeding control.

Additionally, and consistently with previous studies (2), lower levels of haemoglobin and lower prothrombin rate were significantly associated with in-hospital mortality and mortality within 6 weeks, translating a more severe bleeding and more severe liver disease, respectively.

Authors have previously reported MELD score as an independent predictor of in-hospital mortality (2, 24). However, in our study, MELD score was not higher in patients who died within the bleeding episode.

The present study had several potential limitations. Its retrospective nature resulted in information not always being easily available, which sometimes lead to missing data. Particularly, data on the patient's follow-up and overall mortality was difficult to obtain since around 41.8% of the patients were followed by other hospital facilities and their clinical records were not always accessible, such as date and cause of death. Besides, due to the retrospective design of the study, we could not evaluate the size of the varix as it is not frequently and objectively reported. Varix size may influence the number of injections or volume needed to achieve haemostasis and it is a known risk factor for bleeding (25). Another factor that potentially limited the study was that data on whether patients received antibiotic prophylaxis prior the procedure or not, was not collected. Considering that the most frequent complication registered was fever, it might have been relevant to evaluate the role of antibiotic prophylaxis.

In conclusion, although highly efficient in achieving immediate haemostasis (94.3%), the risk of rebleeding after ECI should not be overlooked. Complications related to the procedure were not very frequent, and only Histoacryl™ was associated with severe complications such as pulmonary and cerebral embolism, opposite to Glubran®2, which seems to be the safest option regarding ECI. In-hospital mortality was mostly associated to very early rebleeding, highlighting the importance of achieving definitive haemostasis and closely monitoring the patients after the procedure. Taking into consideration the results obtained in the present study, it is

appropriate to consider N-butyl-2-cyanoacrylate a safe and effective option for the treatment of gastric variceal bleeding.

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