Use of non-dilutedN-Butyl-2-Cyanoacrylate for treatment of gastric varices

*Dr. Ali Ismael AL-Saedi

ABSTRACT

Objective: To study the efficacy and safety of non-diluted N-Butyl-2-Cyanoacrylate in the management of gastric varices (GV).**Design:** Prospective cohort study.**Setting:** Single tertiary care center.**Intervention:** Standardized technique of non-diluted N-Butyl-2-Cyanoacrylate (Histoacryl) injection for management of GV.**Main Outcome Measurements:** Achievement of initial hemostasis, rate of rebleeding, procedure-relatedcomplications, and mortality.
Patients and methods:In total, 25 with recent or active bleeding from the gastric varices were randomly divided into those treated with diluted N-Butyl-2-Cyanoacrylate (7 patients) and other group of non-dilutedN-Butyl-2-Cyanoacrylate (18 patients) . Patients were prospectively followed for the occurrence of bleeding and mortality in the two groups, the numbers of injections needed to abolish the varices, and the amountN-Butyl-2-Cyanoacrylate needed to obliterate thevarix.
Results: During the study period from January 2016 January 2019 ,25 patients were enrolled ,, 17 patients (69.2%) were male and 8 patients (26.2%) were female, with mean age of 53.56 and standard deviation of 16.006 , with minimum age included was 18 year and maximum age was 82 years
Limitation: small numberofpatients. **Conclusion:** non-diluted N-Butyl-2-Cyanoacrylate is safe and effective in the management of gastric variceal bleeding.

Introduction:

Gastric varices occur in 533% of patients with portal hypertension, with a reported incidence of approximately 25% in 2 years.1gastric varices located in the fundus tend to cause serious bleeding and are reported to respond less well to endoscopic treatment. Bleeding-related mortality can be as high as 45%.2 N-butyl-2-cyanoacrylate has been used successfully in many countries for the treatment of fundal variceal bleeding, with a reported initial hemostasis rate greater than 90%.38 The reported rate of rebleeding varies significantly from 0%7 to 4.4%9-10to 24% to 50% in other studies.9,10 There is also a potential risk of embolism in patients with underlying gastrorenal or gastrocaval shunts, and other serious complications such as sepsis, fistula, and adherence of the needle to the glue within the varix have also been reported. According to the authors, the problem with the current use of N-butyl-2-cyanoacrylate is the lack of a universal standardized injection technique and regimen, which may otherwise minimize complications and decrease the rebleeding rate.[3,7]

Patient and methods:

Study population and design:

This prospective cohort study was conducted The patientswith portal Hypertension(PHT)from single academic tertiary gastrointestinal tract (GIT) referral center in Baghdad (Gastrointestinal and Hepatology Teaching Hospital) attending the outpatient department or admittedto the ward with upper GIT bleeding or recent history of fundal variceal bleeding were included . The diagnosis of PHT was suspected clinicallyand confirmed by endoscopic documentation of GV. The etiology of the PHT was establishedby clinical, biochemical, and radiologic parameters, weexcluded type 1 of GV from this analysis because it could be treated by endoscopic band ligation. Informed consent were taken from all the enrolled patients.

Initial hemostasis was defined as the presence of hemodynamic stability and absence of rebleeding within 24 hours of treatment. Failure to control active bleeding, or treatment failure, was defined in accordance with Baveno III guidelines.[11]

Within the first 6 hours, failure was definedas the presence of any of the following factors: (1) transfusion of 4 units of blood or more, (2) the inability to achieve an increase in systolic blood

*CABM,CABG&H-the gastroenterology &hepatology teaching hospital

pressure of 20 mm Hg or to 70 mm Hg or more, and/or (3) a decrease in pulse rate to less than 100/min or a decrease of 20/min from the baseline pulse rate. After 6 hours, failure was defined as the presence of any of the following factors: (1) the occurrence of hematemesis, (2) a decrease in blood pressure of more than 20 mm Hg from the 6-hour point, and/or (3)an increase in the pulse rate of more than 20/min from the 6-hour point on 2 consecutive readings 1 hour apart, (4) transfusion of 2 units of blood or more (over and above the previous transfusions) required to increase the hematocrit to more than 27% or hemoglobin to more than 9 g/dL.

Rebleeding was defined as any clinically significant gastric variceal bleeding occurring at least 24 hours after the index bleed, with active bleeding or stigmata of recent bleeding over the treated varices seen during endoscopy. GV eradication was defined as firm noncollapsible varices on probing with an injector during endoscopy.

Endoscopic procedure:

Technique of variceal obliteration:

The technique of variceal obliteration was similar to that reported by Seewaldet al[7] and Hou et al where N-butyl-2-cyanoacrylate (Histoacryl; B.BraunDexon, Spangenberg,Germany) was mixed with Lipiodol (Guerbert,Roissy, France) in a ratio of 0.5 to 0.8 mL. To minimizethe risk of embolism, not more than 1.0 mL of the N-butyl-2-cyanoacrylateLipiodol mixture was injected intothe varix each time. Before injection,the dead space volume of the injection catheter was first measured and was found to be 2mL. The needle was not primed with glue before injection to prevent premature solidification of the glue at the tip ofthe needle causing blockage when dealing with acutebleeding.) The Fundal varix was punctured and 1.0 mL of the mixture was injected, followed immediately by a second injectionof 2 mL of distilled water to deliver the entire gluefrom the catheter into the varix. The needle was then retracted,followed by flushing of the needle with distilled water to keep it patent. In non-diluted method we use non-diluted N-Butyl-2-Cyanoacrylate. A sclerotherapy injector with a 23-gauge needle (Boston scientific) was first flushed with distilled water. Then non diluted N-Butyl-2-Cyanoacrylate, not mixed with lipiodol, was injected intravariceally into the GV after which 2 mL of distilled water was injected to deliver the entire glue from the injector into the varix. The needle was not primed with the glue before insertion to prevent premature solidification of the glue at the tip of the needle causing blockage. Each varix was injected with 0.5 mL to 1 mL of glue depending on the size of the varix; no more than 1 mL of N-Butyl-2-Cyanoacrylate was injected into the varix each time. After the injection, the needle was immediately withdrawn from the varix.

The endoscope was then taken out with the injector inside. The injector was cut from the proximal Luer lock end, and it was withdrawn from the tip of the endoscope to prevent blockage of channel by the glue. Repeat endoscopy was performed in the same session. Obliteration of GV was assessed by probing the injected varices with the injector for firmness. If the varices remained soft, the injection was repeated to achieve complete obliteration. Complete obliteration of all tributaries was performed in the same session to prevent rebleeding from the remaining patent varices. The maximum amount of was N-Butyl-2-Cyanoacrylate 4 mL in 1 session and 2 mL per varix.

Follow up.

After treatment, patients were monitored for the occurrence of complications of variceal obliteration by clinical assessment with signs/symptoms such as chest pain, shortness of breath, abdominal pain, fever, cough or hematemesis, and rebleeding and the development of complications of cirrhosis and mortality. Surveillance endoscopies were performed at 2 weeks, 1 month and then at 3-month intervals after the initial variceal obliteration to monitor for variceal obliteration and recurrence.

Statistical analysis:

Data were collected and analyzed using SPSS version 10.0 for windows (SPSS, Chicago, Illinois, and USA).

The significance of relationship between groups was examined by Chi squire test, the risk estimated by odds ratio.

P value < 0.05 was considered as statically significant

Result:

During the study period from January 2016January 2019 ,25 patients were enrolled ,, 17 patients (69.2%) were male and 8 patients (26.2%) were female, with mean age of 53.56 and standard deviation of 16.006 , with minimum age included was 18 year and maximum age was 82 years

The histogram below demonstrate the age distribution which shows that most cases in the study were between 40 60 years old.

Figure 1: Histogram showing the ages of the 25 cases included in the study

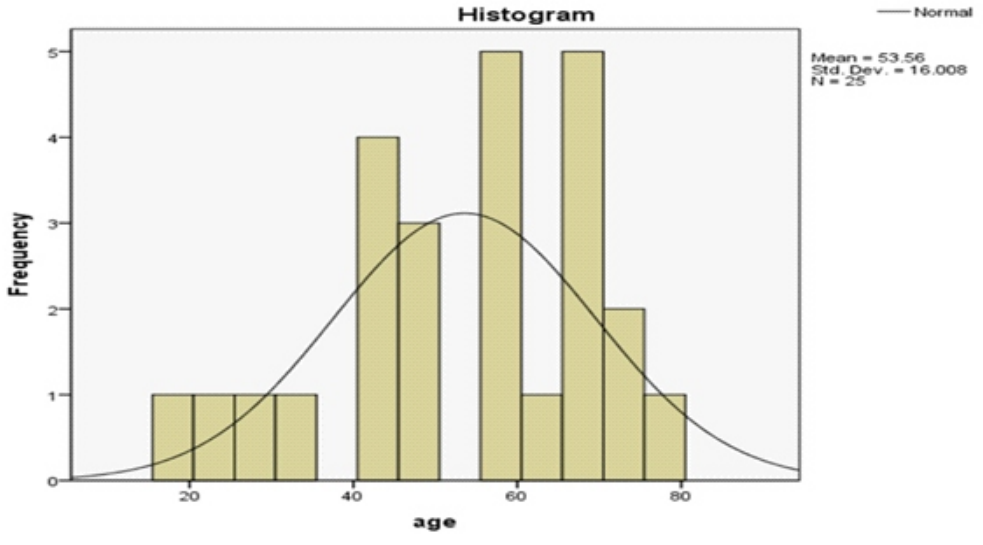
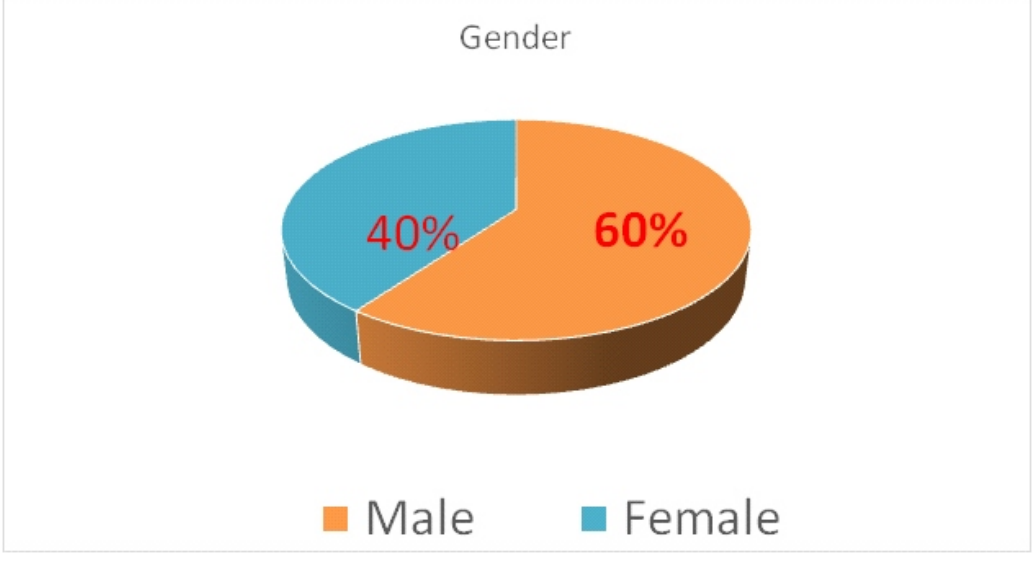


Figure 2: Relative frequency of males and females included in the study



Shows that males enrolled in the study are 60 %(15 patients) and 40 % (10 patients) were female.

Figure 3: Shows the underlying causes of gastric varices

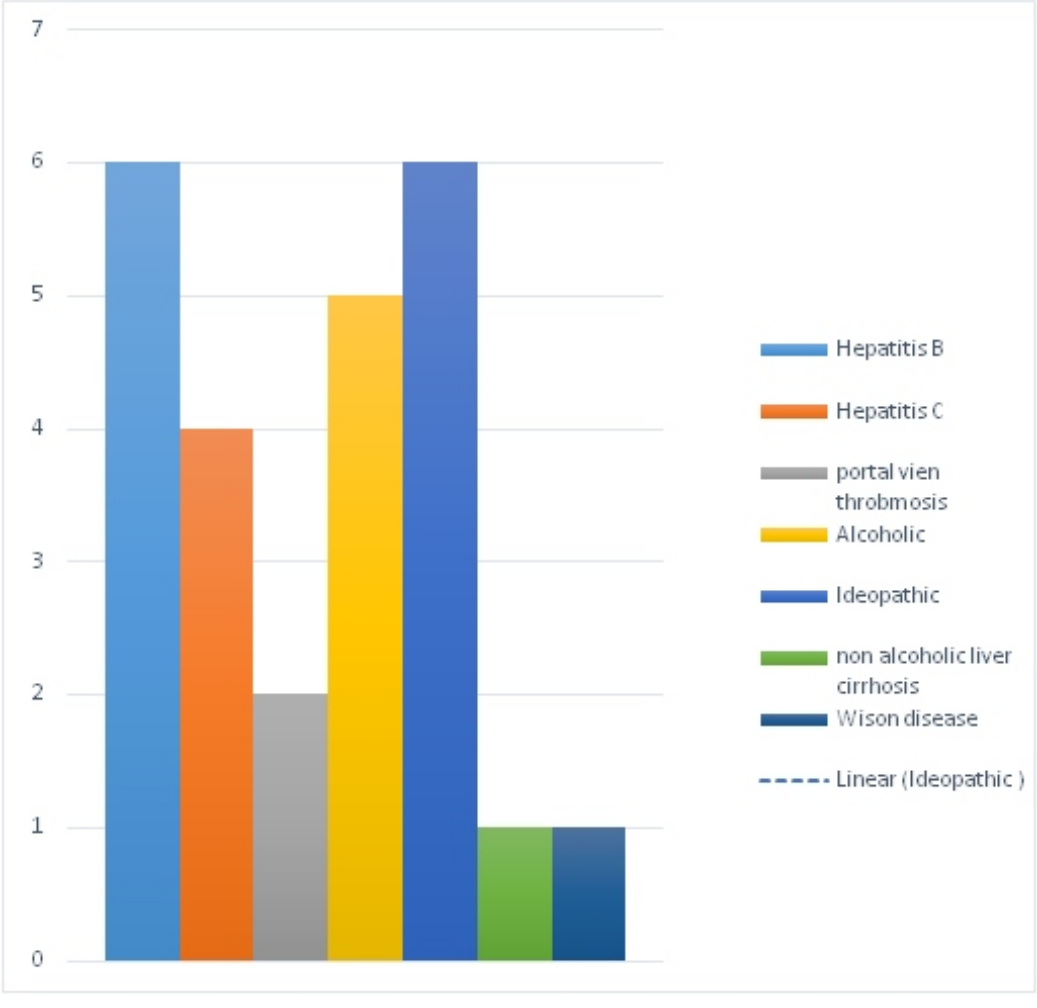


Figure 4: shows rebleeding rate in patients treated with diluted andnon-diluted N-Butyl-2-Cyanoacrylate with a P value of 1.5

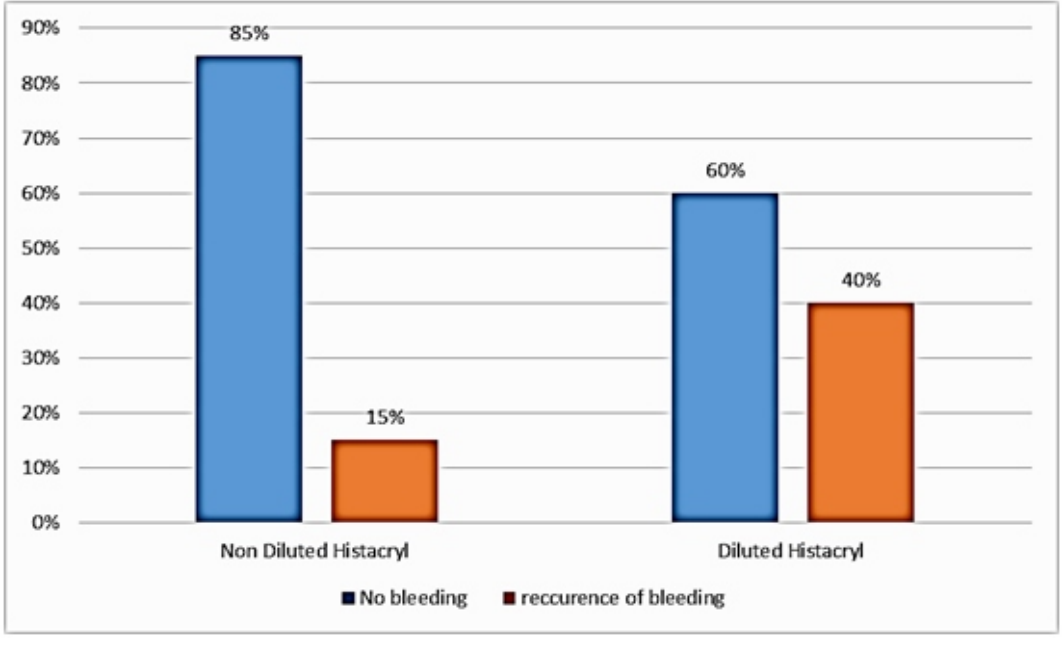
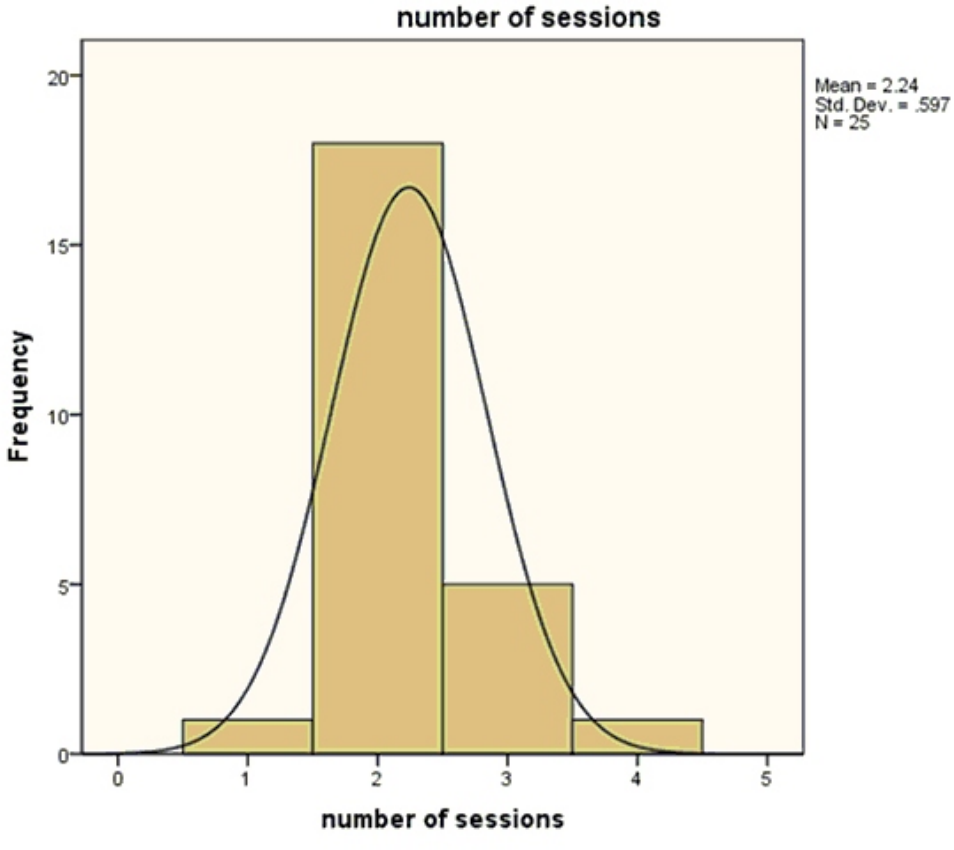


Figure 5 shows numbers of sessions needed to abolish the varix



Discussions:

The total number of patients included in our study were 25 patients, Figure 1 clearly demonstrate that the minimum age included was 18 years and maximum age included was 82 years and most of the enrolled patient age were between 40-60 years old with the mean age 49.6, while figure 2 shows that males enrolled in the study are 60 %(15 patients)compared to 40 %(10 patients) were female. Viral hepatitis B and C are 40 % (10 patients) cases which represent the most common cause of the gastric varices in the enrolled patient while idiopathic and alcoholic patient represent 24% (6 patients) and 20% (5 patients) respectively.

In total, 25 with recent or active bleeding from the gastric varices wereinitially randomly divided into those treated with diluted N-Butyl-2-Cyanoacrylate (7 patients) and other group of undiluted N-Butyl-2-Cyanoacrylate group (18 patients) , we can notice that the diluted group is much less than the non-diluted group and the reason behind that we notice early in the study that the diluted group is associated with much higher risk of rebleeding reaching to 40% of cases compared to 15% rebleeding risk in non-diluted groupas seen obviously in figure 4 .This result was expected because the lipidol dilutedN-Butyl-2-Cyanoacrylate usually take 30 seconds Before solidification which may go awayfrom the needle entry site leaving the entry site without good seal which in turn lead to delayed bleeding, Therebleeding rate of 15 % with non-dilutedgroup in this study was higher than that reported by D'Imperio et al[13] (3.7%) and Dhiman et al[14] (10.3%) butLess than to those reported by Huang et al[5] (23.3%) and Tanet al[15] (27%) and lower than reported by Lee et al[16](44.7%). It should be noted that more than half of our GVwere fundal varices, which have a higher tendency torebleed. However, most of the studies using sclerotherapywith a sclerosant other than N-Butyl-2-Cyanoacrylate found very high rebleedingrates (44%-100%), especially in patients with fundalvarices.[2,3]The bleeding was controlled in all patients by a second session of N-Butyl-2-Cyanoacrylate injection, however one case treated by diluted N-Butyl-2-Cyanoacrylate result in massive bleeding that re-endosopy was unsuccessful to control bleeding because of large blood clot was found at the gastric fundus which result in patient death 36 hours after the procedure because we have no facility oftranshepaticportosystemic shunt (TIPS)intervention.

Importantly, there were no clinically significant embolic complications noted attributed to N-Butyl-2-Cyanoacrylate injections (rate per patient, 0 [95% CI, 0-5.1%]; rate per N-Butyl-2-Cyanoacrylate injection, 0 [95% CI, 0-1.8%]), this is one of the expected benefit of using the non-diluted N-Butyl-2-Cyanoacrylate injections because it solidfy immediately after injection leaving no time for turblant flow to take the glue to a distant site.

This result was supported by similar result ofAjay Kumar et al [17]where using non dilutedN-Butyl-2-Cyanoacrylate associated with no embolic complications , in our study there was no damage to the endoscopes except damage to the outer sheeth of one endoscope.

Compared with N-Butyl-2-Cyanoacrylate, TIPS has been associated with a higher rate of long-term morbidity requiring hospitalization because of an increased incidence of encephalopathy.[7]

Cost-effective analyses comparingN-Butyl-2-Cyanoacrylateinjection with TIPS have suggested that N-Butyl-2-Cyanoacrylate is a safe and effective treatment for gastric variceal bleeding that can be provided at a significantly lower cost compared with TIPS placement.[18,19]

The usefulness of TIPS is also limited by its availability only in major centers.[20]

In our study we tried to make sure that the varix completely solidify by each session depending on the probing of the varix, we have no facility for endoscopic Doppler probe which facilitate detection of persistent flow in the varix which in turn help to assure complete variceal obliteration,We limited the maximum amount of N-Butyl-2-Cyanoacrylate per injection to 1 mL, per varix to 2 mL, and per session to 4 mL, similar to Seewald et al.[7]

The numbers of sessions depend on the varicealsize, however most of the gastric varices in our study were completely obliterated by2nd or 3rd sessions as can be seen clearly in figure 5.

Concolusions :

we conclude that, by using our technique of variceal obliteration as described, non-diluted N-Butyl-2-Cyanoacrylate was effective in achieving initial hemostasis with actively bleeding GV, , and was safe and not associated with embolic complication.

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