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Pulmonary changes associated with injection sclerotherapy of gastric fundic varices

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Abstract
Background and The study aim: Variceal bleeding remains a life-threatening emergency. Gastric fundal varices (GV) are responsible for up to 10-15% of all variceal bleeding. Endoscopic obliterative therapy with Histoacryl is now the first-choice treatment for control of gastric variceal bleeding. Pulmonary complications after injection sclerotherapy are common and range from minor asymptomatic changes to adult respiratory distress syndrome. Based on this; we tried to assess the pulmonary changes associated with endoscopic injection sclerotherapy of gastric fundic varices using undiluted N- Butyl- Cyanoacrylate.
Patients and methods: Out of 90 patients who were admitted to Tropical Medicine Department, Mansoura University Hospitals only fourty patients were inrolled in this study. Patients were grouped into; group I including 20 patients with gastric fundic varices with previous history of hematemesis and/or melena and treated with injection sclerotherapy by using undiluted N-Butyl Cyanoacrylate (NBCA) and group II including 20 patients underwent diagnostic upper GIT endoscopy for detection of varices. Patients were subjected to pulmonary function tests including Diffusion of Lung using Carbon monoxide (DLCO) the day before and one week after endoscopic procedure.
Results: The results revealed significant decrease in Forced Expiratory Volume 1 (FEV1)and Forced Vital Capacity (FVC) ($p < 0.05$) and Diffusion of Lung using Carbon monoxide (DLCO) ($p < 0.05$) while no significant change in ratio between FEV1/FVC % ($p=0.16$) in group I after procedure. There was no significant decrease in FEV1 and FVC ($p=0.3$) and DLCO was constant and no significant change in ratio between FEV1/FVC % ($p=0.3$) in group II after endoscopy. Four patients in group I developed mild pleural effusion and only one patient developed atelectitic band after procedure while no significant difference in chest X ray and CT chest in patients in group II after endoscopy.
There was significant negative correlation between age of the patient, Child score and number of NBCA ampoules injected and different respiratory function test parameters in group I after endoscopic procedure.
Conclusions: After injection of gastric fundic varices using undiluted NBCA, there was a fall in FEV1 and FVC without any change in FEV1/ FVC ratio suggesting a restrictive pattern of pulmonary function test and significant fall in DLCO suggesting diffusion defect and about 20% of patients developed mild right sided pleural effusion and about 5% of patients developed atelectitic band.

Keywords: Gastric varices, sclerotherapy, pulmonary functions test, DLCO.

Introduction
Gastric fundal varices (GV) are seen in 16-70% of patients with portal hypertension and responsible for up to 10-15% of all variceal bleeding [1]. Various treatment modalities such as pharmacological therapy, balloon tamponade, endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation have all been used for for palliative treatment of acute gastro-oesophageal variceal bleeding [2].
Although transjugular intrahepatic portosystemic shunt (TIPS) is used in many centres to treat gastric varices, endoscopic treatment with the tissue glue cyanoacrylate has been used successfully in many countries for 20 years and is considered by many clinicians to be the optimal initial treatment for bleeding gastric varices [3, 4]. Endoscopic obliterative therapy with Histoacryl is now the first-choice treatment for emergency control of acute gastric variceal bleeding [5].
Pulmonary complications after injection sclerotherapy are common and range from minor

asymptomatic changes found incidentally on routine chest radiographs to aspiration or bronchopneumonia, pleural effusions, lobar collapse or consolidation and adult respiratory distress syndrome [6, 7].

Since premedication and passage of an endoscopy may contribute to aspiration pneumonitis or hypoxaemia, the incidence of respiratory dysfunction in patients receiving injection sclerotherapy should be compared with that in patients undergoing endoscopy for other reasons [8].

Embolism is another rare but potentially serious complication of injection sclerotherapy. Emboli may go to lung [9] but systemic (arterial) embolization has also occurred [10].

Aim of the study

To evaluate pulmonary changes associated with endoscopic injection sclerotherapy of gastric fundic varices using undiluted NBCA.

Patients and methods

Study design and study population

In a cross-sectional case analysis, 90 patients were admitted to Tropical Medicine Department, Mansoura University Hospitals, Egypt between January 2012 and December 2013 for management and detection of gastro-oesophageal varices from whom fourty patients with hepatitis C virus related cirrhosis and portal hypertension were included in the study.

Patients were classified into group I including 20 patients with gastric fundic varices with previous history of hematemesis and/or melena and treated with injection sclerotherapy by using undiluted NBCA and group II including 20 patients underwent diagnostic upper GIT endoscopy for detection of varices.

Prior informed consents were taken from all the enrolled subjects. The study protocol was approved by the ethical committee of Mansoura Faculty of Medicine.

Exclusion criteria

Patients coinfected with HIV, HBV, HDV, were excluded from the study. None of the included patients had marked ascites interfering with respiration, Hepatocellular Carcinoma, cardio-respiratory diseases, fever or severe chest pain after procedure, autoimmune hepatitis, α1antitrypsin deficiency. Pregnant females, patients less than 18 years old, having a concomitant disease or alcoholic were not eligible for the present study.

All patients were subjected to:

Full history taking and physical examination.

The severity of liver disease was determined using Child – Pugh Classification.

Routine laboratory tests

CBC by automated Sysmex 800, prothrombin time and INR by-Sysmex 540 coagulation analyzer (Dad Behring), liver and kidney biochemical profile, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum total and indirect bilirubin, serum albumin, serum alpha fetoprotein, serum uric acid, urea and creatinine by Hitachi 911 Analyzer (Roche Diagnostics, Branchburg, NJ).

Serological detection of virological markers

The sera from all the study subjects were tested for routine hepatitis serological markers (HBsAg, anti-HCV, anti-HDV and anti-HIV antibodies by the Chemiluminescent Microparticle Immunoassay method (Abbott ARCHITECT® Assay (Architect i2000SR, Abbott Diagnostics; Abbott Laboratories, Chicago, IL, USA) according to the manufacturer's protocols.

Radiological investigations

- Pelvi-Abdominal Ultrasound (for detection of liver cirrhosis, portal hypertension, size of spleen, presence or absence of ascites and presence or absence of focal hepatic lesions).
- Triphasicpelvi-Abdominal CT for diagnosis of HCC.
- Chest X ray, high resolution CT chest with contrast the day before and one week after upper GIT endoscopy in both groups.

Upper GIT endoscopy

All the patients were sedated using Dormicum during procedure in a dose of 0.05 mg/kg with additional doses of 1 mg every two minutes when necessary until maximum dose (0.1mg/kg or 10 mg), and they were connected to a monitor for detection of heart rate, saturation of oxygen, blood pressure and ECG monitoring. In all patients saturation of oxygen during procedure not decreased below 90. The duration of endoscopy varied from 15 to 25 minutes in group I patients and from 7 to 9 minutes in group II patients. Some patients received 1 ampoule of NBCA and others received 2 or 3 ampoules in one session for solidification of the risky varices. All the patients were put under follow up for 24 hours post procedure to detect development of chest pain, fever or respiratory distress.

Simple Spirometry

Pulmonary function test and DLCO was performed to all patients on both groups one day before and one week after performance of upper GIT endoscopy.

Statistical Analysis

All statistical analysis of the collected data was done by using the computer program SPSS (Statistical package for social science) version 17.0 to obtain descriptive data, analytical statistics using Unpaired Student's t-test, Paired Student's t-test and chi square test (X_2-value).Pearson correlation coefficient ® test was used correlating different parameters. P value <0.05 was considered statistically significant in all analyses. The sensitivity and specificity of different respiratory functions was determined using ROC curve.

Results

This study included 40 patients with age ranging from 48 to 60 years. Table 1 and 2 showed that there was no significant difference between patients in group I and group II regarding baseline demographic factors or stage of liver cirrhosis.

Comparison of pulmonary functions pre-procedure and one week after the procedure in both groups showed that there was significant decrease in FEV1 and FVC ($p < 0.05$) and DLCO ($p < 0.05$) while no significant change in ratio between FEV1/FVC% (p=0.16) in group I after procedure.

There was no significant decrease in FEV1 and FVC (p=0.3) and DLCO was constant and no significant change in ratio between FEV1/FVC% (p=0.3) in group II after endoscopy.

Four patients in group I develop mild pleural effusion and only one patient develop atelectitic band after procedure

while no significant difference in chest x ray and CT chest in patients in group II after endoscopy.

There was significant negative correlation between number of NBCA ampoules used in injection and the different respiratory function tests in group I, with increasing age of the patient and increase Child score there was more deterioration on respiratory functions.

The sensitivity and specificity of different respiratory function tests to detect the most specific and sensitive test affected in patients underwent injection sclerotherapy of fundic varices using undiluted NBCA ampoules were as follows:

- FEV1: sensitivity was 60% and specificity was 55%.
- FVC: sensitivity was 60% and specificity was 55%.
- FEV1/FVC%: sensitivity was 55% and specificity was 60%.
- DLCO: sensitivity was 70% and specificity was 70%.

Table 1: Demographic data for the two studied groups

			Groups		P
			Group I	Group II	
age	Mean		56.35	53.2	0.8
	±SD		3.42	5.42	
gender	Male	No	13	11	0.9[b]
		%	65.0%	55.0%	
	Female	No	7	9	
		%	35.0%	45.0%	

SD: *standard deviation* ***P:*** *Probability*
Test used: *a: Unpaired –t test* ***b:*** *Qui- square test(X^2)*

Table 2: Comparison between Group (I) and Group (II) regarding to Child score

		Groups		P
		Group 1	Group 2	
score	Mean	7.10	7.3	0.97
	±SD	1.45	1.2	

SD: *standard deviation* ***P:*** *Probability* ***Test used:*** *Unpaired –t test*

Table 3: Comparison between Group (I) and Group (II) regarding to different parameters of respiratory functions and DLCO

		Groups		P
		Group I	Group II	
preFEV1 (litres)	Mean	2.27	2.27	1.00
	±SD	.48	.48	
postFEV1(litres)	Mean	2.17	2.27	0.48
	±SD	.47	.48	
preFVC(litres)	Mean	2.63	2.63	1.00
	±SD	.54	.54	
postFVC(litres)	Mean	2.46	2.63	0.3
	±SD	.50	.54	
Pre-Fvc from normal %	Mean	81.00	80.95	0.96
	±SD	3.54	3.62	
Post-Fvc from normal %	Mean	72.10	80.95	<0.001
	±SD	1.52	3.62	
PreFEV1/Fvc %	Mean	86.80	86.90	0.96
	±SD	7.92	7.75	
Post-FEV1/Fvc %	Mean	88.10	86.85	0.6
	±SD	8.31	7.72	
Pre DLCO(mmol/kpa/min.)	Mean	6.56	6.55	0.99
	±SD	2.08	2.08	
Post DLCO(mmol/kpa/min.)	Mean	4.91	6.55	0.005
	±SD	1.32	2.08	

SD: *standard deviation* ***P:*** *Probability* ***Test used:*** *Unpaired –t test*

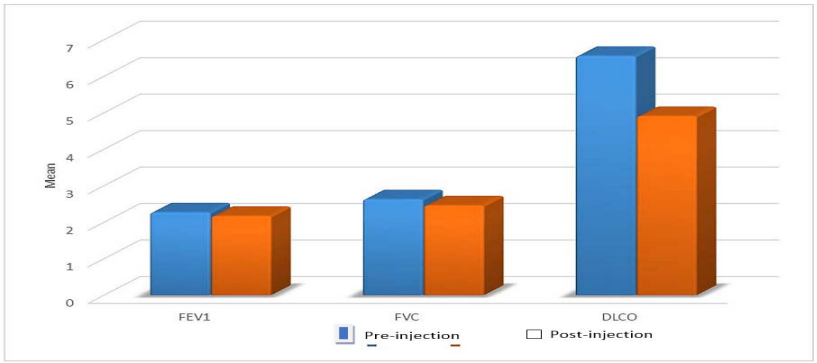


Fig 1: Comparison between pre and post procedure regarding to FEV1, FVC and DLCO in group I.

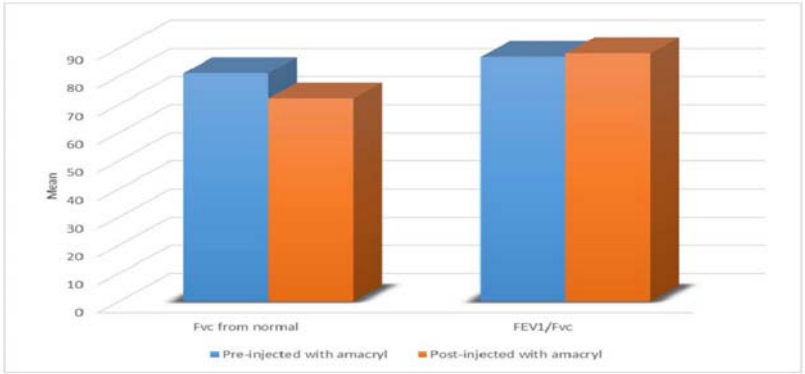


Fig 2: Comparison between pre and post procedure regarding to FVC from normal and FEV1/FVC in group 1.

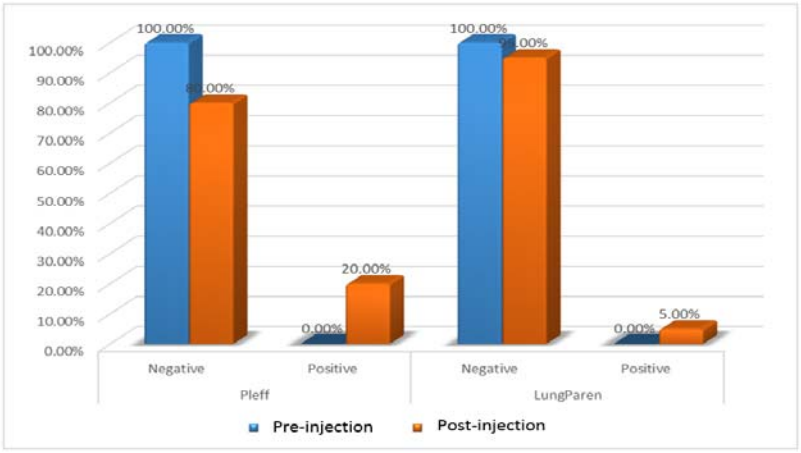


Fig 3: Comparison between pre and post procedure regarding to chest x-ray and CT chest in group 1.

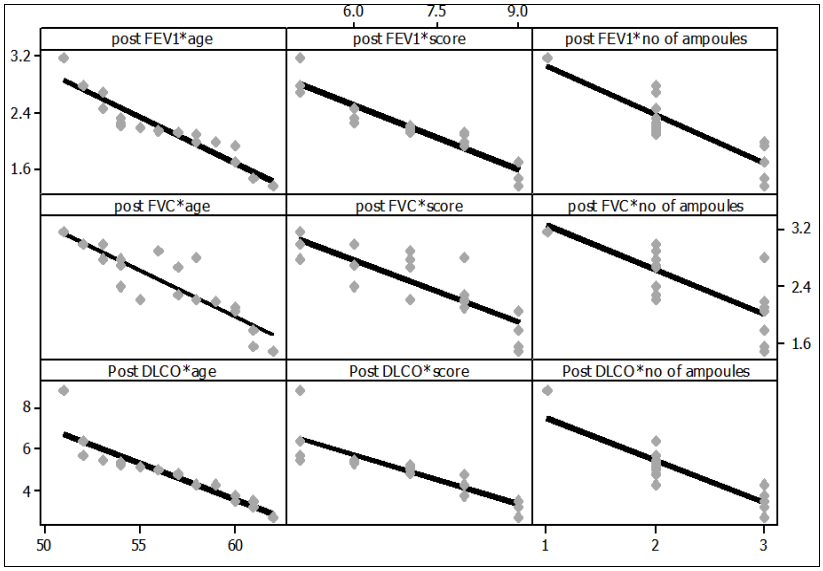
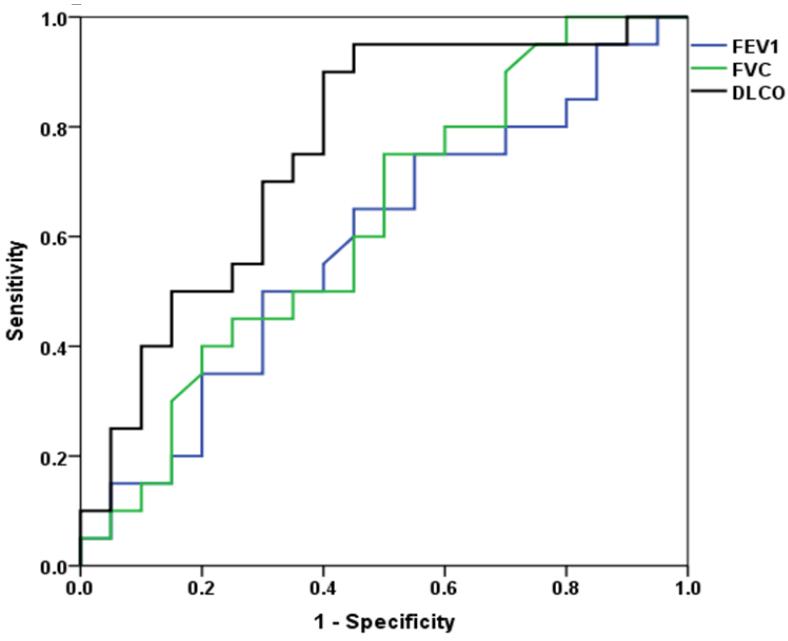


Fig 4: Correlation between age, Child score and number of ampoules and different respiratory parameters in group 1.



Roc curve to detect the most specific and sensitive test affected in patients underwent injection sclerotherapy of fundic varices using undiluted NBCA ampoules.

	Area under the curve (CI95%)	Cut off value	Sensitivity	Specificity	PPV	NPV	Accuracy
FEV1 (Litres)	0.59(0.4-0.76)	<2.195	60.0	55.0	57.1	57.9	57.5
FVC (Litres)	0.63(0.45-0.8)	<2.71	60.0	55.0	57.1	57.9	57.5
FEV1/Fvc%	0.57(0.4-0.75)	>90.5	55.0	60.0	57.9	57.1	57.5
DLCO (mmol/kpa/min.)	0.76(0.6-.91)	<5.345	70.0	70.0	70.0	70.0	70.0

Discussion

Variceal bleeding remains a life-threatening emergency. Initial management centres on resuscitation, antibiotics and terlipressin therapy. Early endoscopy is required in those suspected of variceal haemorrhage to confirm the diagnosis and direct therapy [11].

Endoscopic injection of Histoacryl® has been recommended for gastric variceal bleeding. This long-chain Cyanoacrylate glue polymerises and solidifies within seconds following contact with aqueous media such as blood within a varix. This leads to obliteration of the varix from which the cast extrudes after 2–4 weeks. Mixing the Histoacryl® with the oily agent Lipiodol delays polymerization [12]. Histoacryl®injection has reported immediate haemostasis rates of 88–100% [13].

Pulmonary complications after injection sclerotherapy are common and range from minor asymptomatic changes found incidentally on routine chest radiographs to aspiration or bronchopneumonia, pleural effusions, lobar collapse or consolidation and adult respiratory distress syndrome [14]. In this study all pulmonary complications were asymptomatic and detected only by chest X ray, high resolution CT chest and spirometry tests.

In this study injection sclerotherapy of fundic varices was done on the base of history of previous upper G.I.T bleeding (hematemesis and/or melena with no evidence of bleeding from other sources rather than gastric fundic varices and this is similar to the study done by *(Sarin et al. 2011)* [15] who evaluated the primary prophylaxis comparing Cyano-Acrylate injection versus beta-blockers versus no treatment. Significant differences were observed favouring Cyano-Acrylate injection versus no treatment in terms of prevention of bleeding and survival. But when compared with propranolol, Cyano-Acrylate injection only showed significant benefits in the prevention of rebleeding.

Cyanoacrylate injection requires careful patient selection and attention to technique for an optimal outcome. Dynamic computed tomography is recommended to determine the presence of spontaneous large splenorenal or gastrorenal shunts (GRS). These shunts are associated with the risk for systemic glue embolism [16], but in this study undiluted NBCA was used for rapid polymerization and to decrease the risk of distant embolism**.**

(Seewald et al., 2008) [16] documented that there are rare complications of Histoacryl injection include cerebral or pulmonary embolism, splenic infarcts, mediastinitis, local abscess formation, detachment of the injection needle into the varix and endoscope damage. In this study no distant embolism was recorded, no damage of endoscopy, but obliteration of injection needles were occurred in six cases as injection was done using undiluted NBCA that required change of the injection needle.

In this study, there was no significant difference in all parameters of pulmonary functions and DLCO in both groups of patients in the day before upper GIT endoscopy. All the patients also had normal chest X ray and CT chest with no evidence of pleural effusion nor lung parenchymal affection before procedure.

The pulmonary functions ingroup (I) one day before and 1 week after injection of fundic varices revealed that there was significant difference between pre FEV1 and post FEV1 ($p<0.001$), there was significant difference between pre FVC and post FVC ($p<0.001$) while no significant difference between pre FEV1/FVC ratio and post FEV1/FVC ratio ($p=0.16$). This means that there was restrictive defect in pulmonary functions after injection of fundic varices using NBCA ampoules.

The pulmonary functions in group (2) one day before and 1 week after endoscopy revealed that there was no significant difference in all respiratory function tests.

The most probable explanation for these results would be sclerosant embolisation by the paraoesophageal and azygos veins to the lung resulting in areas of alveolar exudate and consolidation with increase in lung stiffness and pulmonary shunt. There is evidence that sclerosant dissemination to the pulmonary and systemic circulation after intravariceal sclerotherapy occurs through esophagogastric collaterals and the azygous-hemiazygous systems [14].

These results are in agreement with the study done by *Pradeepta et al., 2003* [17] where they studied twenty-six patients with portal hypertension of different etiologies. Patients were subjected to variceal sclerotherapy of oesophageal varices using absolute alcohol, they found significant decline in FVC, FEV1 after sclerotherapy as compared with baseline values however FEV1/FVC ratio did not change significantly.

The results in this study are not in agreement with the study done by *Samules et al., 1994* [18] who studied pulmonary function tests in 12 patients received injection sclerotherapy of oesophageal varices using ethanolamine oleate under general anesthesia in comparison to 9 subjects had only esophagoscopy under general anesthesia. They did pulmonary function test one day after procedure to be sure of elimination of possible effect of anesthesia or sedation on pulmonary function. They found that, the vital capacity decreased by 0.39 liter ($p < 0.05$) in patients who received injection sclerotherapy but did not change in non-injected group. But this study revealed no significant changes in FVC, FEV1/FVC and PaCO2 in group I and group II before and after procedures.

These changes in respiratory function could be explained by embolization of sclerosant to the lung, but other possibilities include intravascular platelet aggregation is postulated [19].

Also there was significant difference between pre DLCO and post DLCO ($p<0.001$) and there was no significant difference between pre and post haemoglobin level as all of the patients were not in active bleeding. This means that there was diffusion defect in pulmonary functions after injection of fundic varices using NBCA ampoules.

These changes could be also explained by the presence of portosystemic anastomoses frequently occur via the umbilical and paraumbilical veins, the gastroesophageal veins, the gastrorenalsplenorenal veins, or the collateral veins through the superior or inferior mesenteric vein with embolization of sclerosant material via these portosystemic anastomoses [20].

Thus, during EIS, the opacification of unwanted collateral vessels may indicate not only the possible occlusion of

unwanted vessels but also the risk of possible pulmonary embolism. A case of pulmonary, cerebral and coronary embolism during EIS was reported, and the patient had a patent foramen ovale, so the possibility of systemic embolization during EIS via the patent foramen ovale should be considered as it occurs in 18% of the general population during routine echocardiography [20].

Entry of sclerosant into the pulmonary circulation has been demonstrated to occur by positive uptake on lung scan of technetium-99m (Tc99m)-tagged sodium morrhuate (SM) and sodiumtetradecyl sulfate (STS) solutions when injected into esophageal varices [14].

In this study, with increasing number of NBCA ampoules used in injection there was more deterioration in respiratory functions and this may be explained by embolization of the sclerosing material into the systemic circulation via collateral venous channels such as the gastrorenalsplenorenal veins, which are directly connected to the gastric varices [20].

Since some of the glue may spill out of the varix, the overall volume injected may exceed 3 mL. There are no data to support the use of smaller or larger volumes of glue outside the recommendations, which are strictly based on expert suggestions without an evidence. In fact, recent series describe volumes of injectate in excess of 2 mL/session even in patients treated for primary prophylaxis. Similarly, there is no qualified evidence that EUS-guided glue injection is superior to standard endoscopy in improvingoutcomes of therapy for gastric variceal bleeding [21]. In this study the maximum volume of NBCA injected was 3ml.

We found the older age of the patients and advanced Child-pugh score were associated with more deterioration on respiratory functions and this may explained by the severity of the cirrhosis and porto- systemic shunting of blood which occurs in decompensated cirrhosis and this results in the delivery of endotoxins directly from the gut to the systemic circulation. This can affect platelet aggregation mechanisms, coagulation and ultimately pulmonary functions [22].

Also increasing duration of endoscopy was associated with more deterioration on respiratory functions and this can be explained mainly with increasing the volume of the sclerosing material used and possibility of systemic embolization as all the patients were carefully monitored and PaO2 not decreased below 90% during and immediately after the procedure and all the patients underwent injection sclerotherapy were not in active bleeding.

Four patients (20%) in group (I) developed mild right sided pleural effusion post injection and only one patient developed atelectic band while there were no changes in chest X ray and CT chest in group (II) patients. The reported incidence of pleural effusion varies from 40% to 50% with oil-based sclerosants [17, 23]

The most probable explanation would be pleural reaction to sclerosant material. There is evidence that sclerosant dissemination to the pulmonary and systemic circulation after intravaricealsclerotherapy occurs through esophagogastric collaterals and the azygous-hemiazygous systems [14].

In the present study it was found that there was no relationship between occurrence of pleural effusion after sclerotherapy and the presence of ascites. This is in accordance with the study done by *(Bacon et al., 1985)* [24]. Most effusions are small and resolve spontaneously and this is in agreement of the study done by *(Krige et al., 2000)* [25].

In the present study there was no significant alteration in PaO2 after sclerotherapy and all patients were connected to a monitor and PaO2 not decreased below 90% during and immediately after the procedure, this in agreement with *(Korula et al., 1986*) [26] who studied 11 patients undergoing EVS and 11 controls undergoing endoscopy only and performed blood gas analysis, pulmonary function test (PFT), ventilation perfusion (V/Q) scan before and after the procedure and demonstrated no significant change in PaO2 in either group.

(Barkin et al., 1989) [27] Studied 20 patients, out of which six had a fall in O2 saturation (SaO2) of ≥4% during endoscopy. But none of these patients underwent EVS. The fall in PaO2 is probably an effect of endoscopy rather than sclerotherapy. However they recommended that larger controlled study is required to study the effect of endoscopy and sclerotherapy on PaO2.

In this study the most sensitive (70%) and specific (70%) test affected after injection sclerotherapy of gastric fundic varices was DLCO. This could be also explained by the presence of portosystemic anastomoses frequently occur via the umbilical and paraumbilical veins, the gastroesophageal veins, the gastrorenalsplenorenal veins, or the collateral veins through the superior or inferior mesenteric vein with embolization of sclerosant material via these portosystemic anastomoses [20].

Cyanoacrylate injection is a safe and effective procedure for active GV bleeding and for secondary prophylaxis [21] and also it has been used for primary prophylaxis for gastric varices [15].

All these pleuropulmonary complications occurred after treatment of gastric varices using undiluted NBCA were self-limiting and not require any medical interference, but good care and monitoring of fragile patients with cardiorespiratory diseases is require Any respiratory symptoms after injection sclerotherapy of fundic varices must be taken seriously with good monitoring of respiratory rate, radiological evaluation and pulmonary function tests to detect restrictive and diffusion defects.

Cirrhotic patients with cardiorespiratory diseases must be carefully assessed before injection sclerotherapy with good monitoring post injection sclerotherapy for detection of any deterioration which may add morbidity and mortality of those fragile patients. Risk of systemic glue embolization may be considered in patients with cardiac abnormalities and must be carefully assessed before injection sclerotherapy of fundic varices.

Conclusion

In conclusion, we showed that fall in FEV1 and FVC without any change in FEV1/ FVC ratio after injection of fundic varices using NBCA, there was suggesting a restrictive pattern of pulmonary function test and significant fall in DLCO suggesting diffusion defect. All of the pleuropulmonary abnormalities were transient and self-limiting and not clinically manifested and did not require any intervention. This work represents a single center observational study. Additional multicenter studies with a larger number of patients would be useful to confirm respiratory deterioration after injection sclerotherapy of fundic varices using undiluted NBCA.

Authors Contributions

Disclosure

All the authors of this paper report no conflicts of interest

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