Research Article

Role of addition of lidocaine to ethanolamine oleate in alleviation of chest pain after endoscopic variceal sclerotherpy

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Abstract

Background: Retrosternal chest pain after endoscopic variceal sclerotherapy (EVS) is common particularly with using ethanolamine oleate as a sclerosant. In vascular surgery, receiving lidocaine with hypertonic saline relieved vascular pain during injection of telangiectasias and reticular veins. **Aim of the Study**: Evaluation the effect of addition of lidocaine ٢٪ to ethanolamine oleate ٥٪ in alleviation of post-sclerotherapy retrosternal pain and assessment of its safety and influence on efficacy of EVS were done. **Subjects and Methods**: A prospective double-blind randomized study among ١٠٠ patients, presented with bleeding oesophageal varices, were randomly divided intto two groups :-Group A: control group receiving ethanolamine oleate ٥٪ only and GroupB: received lidocaine hydrochloride ٢٪-ethanol amine oleate ٥٪ mixture (dilution ١:٥). Clinical, routine biochemical, haematological and sonographic data were evaluated. Standard monitoring was performed throughout the procedure. Retrosternal pain scoring within ٢٤ hours after EVS, need for analgesic, safety, complication, and efficacy were recorded. Pain was scored using numeric rating scale. **Results**: Group B, compared to Group A, had significantly lower incidence of pain, pain score and need for post-endoscopic analgesia (١٦٪ vs. ٨٨٪, ٠.٣٢ ± ٠.٧٩ vs. ٥.٦ ± ١.٥, ٦٪ vs. ٤٢٪, p< ٠.٠٠١ for all respectively). Pain score had significant negative correlation with lidocaine dosage(r=-٠.٤٣٢, p=٠.٠٠٢). Neither side effects nor complications were recorded in lidocaine group. Post-sclerotherapy recorded vital signs and liver function test among Group B were comparable to those in Group A and to its corresponding pre-sclerotherapy data in lidocaine group. Efficacy and post-sclerotherapy related complications were similar in both groups (p> ٠.٠٥). **Conclusion**: lidocaine ٢٪ -ethanolamine ٥٪mixture (١:٥ dilutions) was safe and effective in alleviating post -endoscopic variceal sclerotherapy -retrosternal pain without reducing its efficacy. Increased lidocaine dose was associated with decreased pain score.

Key words: Post scelerotherapy retrosternal pain, lidocaine, ethanolamine oleate, endoscopic variceal sclerotherapy

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Introduction

Variceal bleeding is the most devastating portal hypertension related complication in patients with liver cirrhosis.[١] Several studies have shown the superiority of variceal band ligation over sclera-therapy.[٢,٣] However, endoscopic variceal sclerotherapy (EVS) is widely used and well established strategy in management of bleeding esophageal varices particularly in developing countries.[٤,٥] EVS consists of the injection of a sclerosing agent into the variceal lumen (intravariceal) or adjacent to the varix (perivariceal). EVS has many advantages: feasible, cost effective and can stop bleeding in ٨٠-٩٠٪ of patients with acute variceal bleeding. Nevertheless, it is associated with several complications.[٦]

Post-sclerotherapy retrosternal pain is commonly reported in up to ٦٥٪ of patients as either a feeling of mild discomfort that may disappears spontaneously within ٢٤ to ٤٨ hours or severe pain persists for longer periods and requires strong.[٧-٩] Also, chemical compounds in the sclerosant solution have been suggested as an etiologic factor of post sclerotherapy chest pain.

Ethanolamine oleate (٥٪) administration; the most commonly used agent in Egypt; was reported to induce chest pain more than tetradecyl sulfate.[١٠,١١]

Lidocaine succeeded in alleviating vascular pain associated with both intravenous administration of propofol and hypertonic saline, the former is an anesthetic agent and the latter is used as sclerosing agent for treatment of telangiectasias and reticular vein in vascular surgery.[١٢,١٣] Up to our knowledge, the data assess the role of lidocaine in alleviating post sclerotherapy chest pain was sparse. We hypothesize that addition of lidocaine ٢٪ to ethanolamine oleate ٪٥ can prevent post-sclerotherapy retrosternal pain. The current study was carried out to assess the role of addition of lidocaine to ethanolamine oleate in alleviating post-sclerotherapy retrosternal pain and to evaluate its safety and efficacy in EVS.

Subjects and Methods

This prospective double-blind randomized study was carried out at Gastrointestinal Endoscopy Unit, Internal Medicine Department, Minia University Hospital from May ٢٠١٢ to June ٢٠١٣. It included one – hundred cirrhotic patients (٧٦ males and ٢٤ females) with an age ranged from ٤٠ to ٦٤ years old. They were presented with bleeding esophageal varices and scheduled for EVS.

Ethical aspects: The study protocol was approved by the Institutional Ethics Committee and all patients gave informed consents to participate in this study. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice.

Exclusion criteria: Patients with fundal varices, age greater than ٦٥ years old, allergy to lidocaine, renal or cardiac problems particularly those with congestive heart failure, heart block and adam's stock attack, neurological or psychiatric disorders including those with hepatic encephalopathy, malignancy including hepatocellular carcinoma or diabetes mellitus were excluded. None of patients had current intake of drugs that enhance lidocaine toxicity such as beta blockers and ranitidine.[١٤]

Patients were randomized into two groups. Patients in Group A (fifty patients: ٤٠ males, ١٠ females) were subjected to EVS using ethanolamine oleate ٥٪ only and served as control group. Patients in Group B (٥٠ patients (٣٦ males and ١٤ females) were subjected to EVS using lidocaine ٢٪ - ethanolamine oleate ٥٪ mixture (١:٥ dilution) and called lidocaine group.

All patients of the study were subjected to thorough history taking with special attention to age, gender, medical illness and current medications. Complete physical examination including measurement of weight, abdominal examination and examination of other systems was carried out. Standard monitoring was performed throughout and after the procedure. It included electrocardiogram (ECG), vital signs, pulse oximetry, capnography and assessment of any neurological deficit such as confusion, irritability, psychosis and parasthesia. Oxygen supply, resuscitation equipment and emergency medications were available for management of any possible side effect or toxicity of lidocaine.

Sampling protocol: Before undergoing EVS, about ٨ml of venous blood sample were taken from each subject after ٨ hs overnight fasting by sterile venipuncture for routine laboratory assay according to the standard methods using fully automated clinical chemistry auto-analyzer system Konelab ٢٠. It included complete blood count, liver function test [aspartate aminotransferase (AST), alanine amino-transferase (ALT), albumin, bilirubin, and prothrombin time] and renal function (blood urea and serum creatinine).liver function tests were reassessed ٢ days after EVS procedure.

Imaging studies: Chest x ray and abdominal ultrasound were done for each patient pre and post EVS. Chest x ray was done to exclude any regional complications.

Abdominal ultrasound was performed to evaluate abdominal organs and to assess presence and severity of ascites.

Endoscopic variceal sclerotherapy (EVS): Under mild sedation "I.V. midazolam ٢-٥mg", firstly diagnostic esophago-gastro-duodenoscopy according to standard protocol was carried out for grading of esophageal varices and examination of stomach and duodenum. While only ethanol amine ٥٪ was withdrawal into a syringe in control group, lidocaine ٢٪ was added to ethanol amine ٥٪ in the same syringe immediately before EVS (dilution ١:٥) in lidocaine group. Average of used volume of lidocaine ٢٪ ranged from ١.٦ -٣.٢ml (٣٢mg-٦٤mg) per individual. In a double blind manner, combined intravariceal and perivariceal injection of oesophageal varices was done using ٢٣ gauge injector.

After EVS, each patient was questioned for retrosternal pain and need for analgesia. Assessment of retrosternal pain was done during ٢٤ hours post sclerotherapy using Numeric rating scale (NRS). In the clinical setting, the NRS is simple to use and is one of the most common approaches for quantifying pain. Patients indicate their pain intensity on a scale of ٠ to ١٠, with ٠ indicating no pain and ١٠ the worst pain imaginable. The NRS can be used at the bedside by the clinician.[١٥] We also recorded other early complication of sclerotherapy such as vomiting, fever and re-bleeding within ٥ days.

Statistical analysis:

The data of all patients were fed into IBM-compatible computer and statistical software package namely (SPSS) for windows student version ١٨.٠ was used to analyze these data. Parametric variables were expressed as mean±SD and comparison between groups using student's t-test. Non- parametric variables were expressed as numbers and percent and compared by chi-square test. Correlation between variables was analyzed using Pearson's correlation coefficient. The difference was considered significant if P value< ٠.٠٥.

Results

Patients in the present study had liver cirrhosis, ١٥ patients were Child's class B (١٥٪) and ٨٥ patients were Child's class C (٨٥٪). They had grade II to IV bleeding oesophageal varices.

Baseline characteristic of control group and lidocaine group were shown in table, (١,٣) Both groups were comparable to each other as regard age, weight, gender, vital signs (pulse rate, respiratory rate, systolic and diastolic blood pressure), studied haema-tological parameters, liver function tests and renal function. No statistically signi-ficant difference between the two groups as regard Child Pugh class, degree of ascites and endoscopic grading of oesophageal varices; the percentages of grade II, III and IV oesophageal varices were ٤٪, ٤٨٪ and ٤٨٪ in control group and ٠٪, ٦٦٪and ٣٤٪ in the lidocaine group respectively as shown in table, (١).

Role of lidocaine–ethanolamine mixture in pain relief: The number of patients who experienced post sclerotherapy retro-sternal pain was ٤٤ and ٨ in control and lidocaine group respectively. Patients in lidocaine group compared to those in control group, had significantly lower incidence of pain (١٦٪ versus ٨٨%, p<٠.٠٠١ respectively) and significantly lower pain score (٠.٣٢ ± ٠.٧٩ versus ٥.٦±١.٥١, p<٠.٠٠١ respectively). As an objective marker, the need for analgesia was significantly higher among patients in control group than those of lidocaine group (٤٢٪ versus ٦٪, p<٠.٠٠١), table ٢ figure ١ & ٢. In addition, there was significant negative correlation between pain score and volume of used lidocaine in injection sclerotherapy among lidocaine group (r=-٠.٤٣٢, p=٠.٠٠٢), figure (٣). So, increased lidocaine dosage was signifi-cantly associated with reduced pain score.

Neither cardiovascular nor neurological complication was reported in lidocaine group. No allergic reaction was reported in this study. Interestingly, when liver function (ALT, AST, serum albumin, and serum bilirubin and prothrombin time) and

recorded vital signs (heart rate, systolic and diastolic blood pressure, and respiratory rate) were compared pre and post EVS in lidocaine group, no statistically significant difference was reported. Again, when lidocaine and control group were compared to each other as regard liver function and vital signs after EVS, no statistically significant difference was reported as shown in table ٣.

Efficacy of lidocaine mixture: Two patients of lidocaine group and three patients of control group developed re-bleeding within ٥ days with no statistically significant difference between both groups (٤٪ vs. ٦٪, p=٠.٦٤ respectively), table ٣.

Table (١): Baseline Characteristic of Control and Lidocaine Groups

	Group A (Control group) (n=٥٠)	Group B (lidocaine group) (n=٥٠)	p-value
Age (years)	٥٤.٧ ± ٧.١	٥٧.٦٤ ± ٣.٥٥	٠.١٦٤
Sex n (%) **Male** **Female.**	 ٤٠ (٨٠٪) ١٠ (٢٠٪)	 ٣٦ (٧٢٪) ١٤ (٢٨٪)	٠.٣٤٩
Weight (Kg)	٨٠.١٥ ± ٦.٧٨	٧٩.٢ ± ٩.٤	٠.٥٦
Hemoglobin (gm/dl)	٩.٣٥ ± ٠.٦٤	٩.٤١ ± ٠.٨٦	٠.٦٨
Leukocyte count($١٠^{٣}$/µl)	٦.٣٩ ± ١.٤٦	٦.٤٩ ± ٢.٢٤	٠.٧٩
Platelet count ($١٠^{٣}$/µl)	٩٨.٤ ± ١١.٧٤	١٠٣.٠٦ ± ١٦.٦٢	٠.١١
Serum creatinine (mg/dl)	١.٠٦ ± ٠.٢٥	١.٠٨ ± ٠.٢٢	٠.٦٥
Blood urea (mg/dl)	٥٠.٦ ± ١٢.٠٨	٥٢.٨٤ ± ١٧.٨	٠.٤٦
Child-Pugh class: **B** **C**	 ٧(١٤٪) ٤٣ (٨٦%)	 ٨ (١٦%) ٤٢ (٨٤%)	٠.٨٨
Degree of ascites: **Mild.** **Moderate.** **Massive.**	 ٢٢ (٤٤٪) ٢٤ (٤٨٪) ٤ (٨ %)	 ٢١ (٤٢٪) ٢٧ (٥٤٪) ٢ (٤٪)	٠.٦٤
Grades of oesophageal varices: **I.** **II.** **III.** **IV.**	 ٠ (٠٪) ٠ (٠٪) ٣٣ (٦٦٪) ١٧ (٣٤٪)	 ٠ (٠٪) ٢ (٤٪) ٢٤ (٤٨٪) ٢٤ (٤٨٪)	٠.١

*Quantitative data are expressed as mean ± SD and compared students't test while qualitative variables are expressed as frequency and compared by $\chi^{٢}$ test. *: significant difference at p value < ٠.٠٥*

Table (٢): Post- Sclerotherapy Retrosternal Pain and Need for Analgesia among Control and Lidocaine Groups.

	Group A (Control group) (n=٥٠)	Group B (lidocaine group) (n=٥٠)	p-value
Presence of pain n (%) **Yes.** **No.**	 ٤٤ (٨٨٪) ٦ (١٢٪)	 ٨ (١٦٪) ٤٢ (٨٤)%	< ٠.٠٠١*
Pain score	٥.٦ ± ١.٥١	٠.٣٢ ± ٠.٧٩	< ٠.٠٠١*
Need for analgesia n (%) **Yes** **No**	 ٢١(٤٢٪) ٢٩(٥٨٪)	 ٣(٦٪) ٤٧(٩٤٪)	<٠.٠٠١*

*Quantitative data are expressed as mean ± SD and compared students 'test while qualitative variables are expressed as frequency and compared by χ^2 test. *: significant difference at p value < ٠.٠٥*

Table (٣): Pre-sclerotherapy and post-sclerotherapy vital signs and liver function tests, and post-sclerotherapy complications in control and lidocaine groups.

	Pre-EVS		Post-EVS		P Value		
Variables	**control group**	**lidocaine group**	**control group**	**lidocaine group**	**A**	**B**	**C**
Pulse (beat/minute)	٨٦.٩± ٦.٤	٨٧.٥±٥.١٢	٨٨.٣±٤.٣	٨٨.٣٢±٤.٣٧	٠.٦٠٩	٠.٨٢٩	٠.٢٠٢
SBP (mmHg)	١٠٤.١±٥.٠	١٠٣.٩±٤.٣	١٠٣.١±٥.٧	١٠٣.١±٥.٧٦	٠.٨٣٢	٠.٤٠٠	٠.٣٥٧
DBP (mmHg)	٦٤.٩ ± ٦.٤	٦٥.٢ ± ٥.٩	٦٤.١ ± ٧.٢	٦٤.١١±٧.٢٢	٠.٧٨٥	٠.٤٢١	٠.٥٦٥
Respiratory rate (breath/minute)	١٤.١±٢	١٣.٥±١.٤	١٣.٩±١.٥	١٤±١.٢	٠.٦٣	٠.٦٢٥	٠.٤٢
ALT (IU/L)	٥٥.٣±١٤.٧	٥٧.١±١١.٩	٥٥.٦±١٤.٥	٥٦.٩ ± ١٢.٠	٠.٥١٣	٠.٦١٦	٠.٩٤٠
AST (IU/L)	٦٦.٦±١٣.١	٦٧.١±١٣.٢	٦٦.٨±١٢.٩	٦٧.٤ ± ١٢.٩	٠.٨٧٣	٠.٨٠٥	٠.٨٧٢
Total protein (gm/dl)	٦.٩±٠.٣	٦.٩± ٠.٢	٦.٩ ± ٠.٣	٦.٨ ± ٠.٣	٠.٨٨٢	٠.٤٤٩	٠.٥٧٤
Serum albumin (gm/dl)	٢.٨±٠.٢	٢.٧٩± ٠.٣	٢.٨± ٠.٢	٢.٧ ± ٠.٢	٠.٥٠٨	٠.١٤٥	٠.٢٧١
Total bilirubin (mg/dl)	١.٦±٠.٧	١.٥± ٠.٦	١.٦ ± ٠.٧	١.٥ ± ٠.٦	٠.٥٢١	٠.٥٧٣	٠.٨٣٤
Prothrombin time(second	١٧.٣±١.٣	١٧.١± ١.٤	١٧.٠٢±٢.٠	١٧.٢ ± ١.١	٠.٥٠٢	٠.٥٤٤	٠.٩٤٠
٥ daysre-bleeding: **Yes.** **No.**	--------	---------	 ٣ (٦٪) ٤٧ (٩٤٪)	 ٢ (٤٪) ٤٨ (٩٦٪)	--------	٠.٦٤٦	-------
Allergic reaction	--------	---------	٠(٠٪)	٠(٠٪)	--------	١	-------
Neurological deficit **Confusion: n (%)** **Blurred vision: n (%)** **Seizure: n (%)** **Tinnitus: n (%)**	--------	---------	 ٠(٠٪) ٠(٠٪) ٠(٠٪) ٠(٠٪)	 ٠(٠٪) ٠(٠٪) ٠(٠٪) ٠(٠٪)	--------	 ١ ١ ١ ١	-------
Vomiting n (%)	--------	----------	٢(٤٪)	٣(٦٪)	--------	٠.٦٤	--------

EVS=endoscopic variceal sclerotherapy, SBP=systolic blood pressure, DBP=diastolic blood pressure, ALT= alanine aminotransferase, AST= aspartate aminotransferase .*Quantitative data are expressed as*

*mean ± SD and compared students 'test while qualitative variables are expressed as frequency and compared by χ^2 test. *: significant difference at p value <.٠٥*
A= p value when pre-sclerotherapy control group compared to pre-sclerotherapy lidocaine group
B= p value when post-sclerotherapy control group compared to post-sclerotherapy lidocaine group
C== *p value when pre-sclerotherapy lidocaine group compared to post-sclerotherapy lidocaine group*

Discussion

Retrosternal chest pain is one of the most common complications of post injection sclerotherapy.[٩] Pain is mostly elicited by irreversible endothelial and tissue injury (thrombosis, ischemia, sub mucosal edema, inflammatory cells infiltration) of the esophageal wall caused by the sclerosing agent during initial ٤٨h following EVS, this tissue injury activates nociceptors leading to its depolarization which is transmitted proximal to the spinal cord then to the higher centers.[١٦,١٧]

Lidocaine was originally described as anti-arrhythmic agent and later as a local anesthetic agent. Currently, it is an excellent effective analgesic for various painful conditions including visceral pain. It has many routes of administration including local infiltration, nerve block, intravenous regional anesthesia and systemic intravenous analgesia.[١٨] It is common in field of vascular surgery for treatment of telangiectasias and reticular leg veins, and in field of anesthesia to add lidocaine to the sclerosing agent as hypertonic saline or painful anesthetic agent as propofol respectively to relieve associated vascular pain during these procedures.[١٢,١٩] However, evaluation of addition of lidocaine to sclerosant during EVS as an attempt to alleviate retrosternal pain after this procedure was sparse done.[٢٠] This study was performed among cirrhotic patients Child class B with oesophageal varices grade II and III.

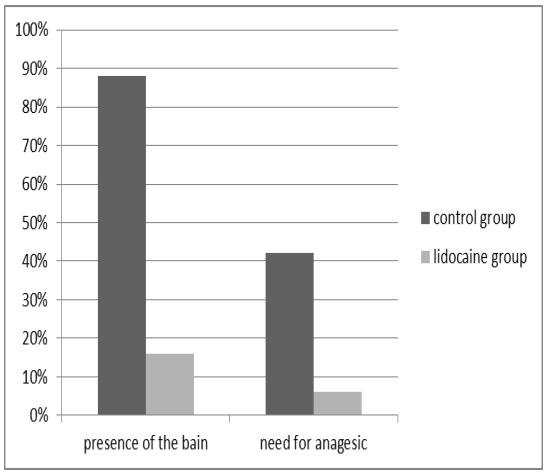

Fig. (١)

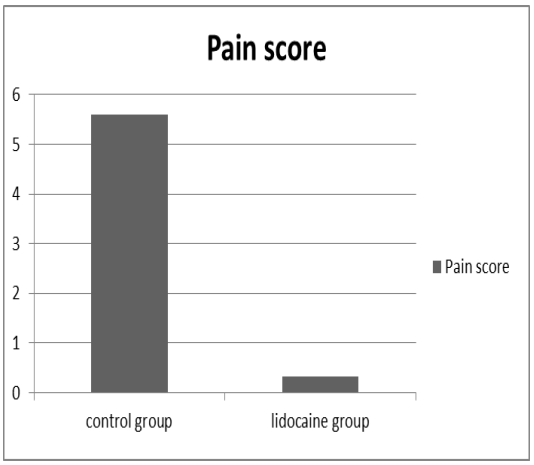

Fig. (٢)

Figure (١): Percentage of both pain and need for analgesia in control and lidocaine groups
Figure (٢): Mean of pain score in control and lidocaine group

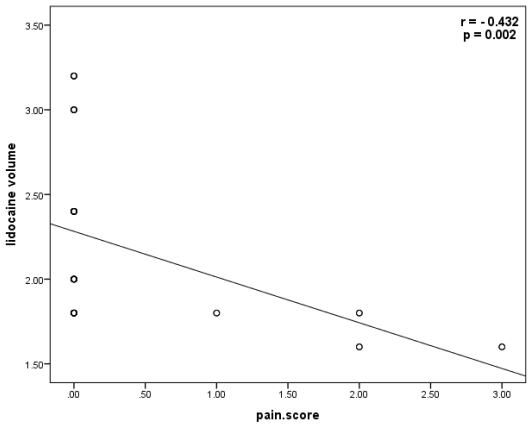

Figure (٣): Correlation between pain score and volume of used lidocaine in lidocaine group

The most important findings of this prospective double-blind randomized study were reduction in incidence and severity of post-sclerotherapy retrosternal chest pain, andreduced analgesic requirement during ٢٤h following EVS when lidocaine-ethanolamine mixture (١:٥ dilution) was used. In addition, it was safe without cardiovascular or neurological side effects.

Neither respiratory depression nor allergic reaction to lidocaine was observed. No deterioration of liver function tests was reported. Interestingly, this mixture did not reduce efficacy of EVS. Our results are valuable in clinical practice; the need to prevent retrosternal pain associated with EVS is essential not only for the pain relief but also to minimize analgesic use and subsequently analgesic-related side effects with improved quality of recovery.

Injected lidocaine with the sclerosing agent, both intravariceal and paravariceal, succeeded in pain alleviation. It was not clear how lidocaine relieving pain; possibly, intra-variceal lidocaine mixture injection may have double action; intravenous regional anesthesia and systemic intravenous (IV) analgesia. These local and systemic effects were caused by existing sclerosing substance in the variceal lumen; and its absorption and escape into systemic circulation respectively.[٢١] Intra-variceal lidocaine may reduce ischemic pain and may be efficient analgesic. In accordance, IV lidocaine reduces ischemic pain in healthy volunteers and is efficient as postoperative analgesia following laparo-scopic surgery in a meta-analysis study.[٢٢,٢٣] Peri-variceal lidocaine injection may act as local infiltration anesthesia with blocking of peripheral nerve ending.[٢٤] The mechanism of anesthetic action of IV lidocaine may be similar to its local action.[٢٥] In addition, IV lidocaine has anti-inflammatory properties and modulates the stress response following surgery.[٢٦,٢٧]

This reduction in pain scores and analgesic requirement in lidocaine group was confined to the first ٢٤ h of EVS in our study. These findings were in line with Alfert et al., ٢٠٠٣.[٢٠] Elimination half -life of lidocaine is around ٩٠-١٢٠ minutes. This prolonged duration of action in our study may be attributed to locked sclerosant in obliterated varices and prolonged elimination half-life of lidocaine among cirrhotic patients (up to٣.٥ folds among Child C) leading to delayed its meta-bolism.[٢٨,٢٩] Approximately ٩٥٪ of lidocaine is metabolized in the liver to pharmacologically-active metabolite, monoethyl glycin exylidide (MEGX). MEGX has a longer half -life than lidocaine but also is a less potent sodium channel blocker so less potent action.[٣٠] In supporting of our results, IV lidocaine during abdominal and laparoscopic surgery elicited a significant reduction in pain scores and postoperative analgesic require-ments within ٢٤ h post-operatively.[٣١,٢٣]

Analgesic requirement is a surrogate marker for pain. So, reduction of analgesia in lidocaine group indicated lidocaine is an effective analgesic adjunct with analgesic. Minimizing analgesic and its-related side were beneficial in cirrhotic patients.

Lidocaine may induce cardiovascular, neurotoxic and other complications. Initial dose of lidocaine ranges from ٠.٥-١.٥ mg/kg and may increase up to maximum ٣mg/kg which is also safe according to Emergency Cardiovascular Care ٢٠٠٥.[٣٣] In addition, no adjustment of lidocaine bolus dose (١-٢ mg/kg) for treatment of ventri-cular arrhythmia was described among patients with chronic liver disease.[٣٢] Dose of lidocaine used in our study among cirrhotic patients was varied from ٣٢ mg to ٦٤ mg (١.٦-٣.٢ml) which was considerably less than the accessible safe dose. Subsequently, neither complications nor deterioration of liver function was observed among lidocaine group. Safety of lidocaine on the liver in our study among cirrhotic patients Child class C was supported by previous clinical and experimental studies.[٢٠,٣٤] Absence of lidocaine comp-lication in our study was matched to previous meta-analysis study that involved ٨ studies (٤٨٦ patients). They reported one case suffered from cardiac side effect (arrhythmia) and no neurological side effect in the IV lidocaine group.[٢٣]

There was no difference in the effectiveness of treatments as five days re-bleeding was rare and similar in lidocaine and control groups.

We recommend that this mixture should be further studied in larger number and in various concentrations in order to come up with the most suitable formula.

In conclusion, a lidocaine ٢٪ and ethanol amine oleate ٥٪ mixture (١:٥dilution) is effective in alleviating retrosternal pain following endoscopic variceal sclerotherapy without reducing its efficacy. It is safe with no complication within this dose range in cirrhotic s patients. Increasing lidocaine dosage significantly reduced pain score.

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