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ORIGINAL ARTICLE

Transcatheter administration of buffered Lidocaine for pain relief due to transarterial chemoembolization for HCC

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KEYWORDS

Buffered Lidocaine;
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Post embolization syndrome

Abstract *Purpose:* To assess the efficacy of intra-arterial Lidocaine on post-procedural pain and on length of hospital stay in hepatocellular carcinoma (HCC) patients undergoing chemoembolization.
Materials and methods: Thirty-nine transarterial chemoembolization (TACE) procedures were carried out for 21 consecutive patients (19M, 2F, age range 52–78).This is a prospective randomized controlled study. Lidocaine was used in 20 TACE and normal saline in 19 TACE. Visual analog scoring was used to assess pain (VAS).
Results: Patients' demographic criteria, Child Pugh, tumor size and doses of chemotherapeutic emulsion and amount of used PV particles were not statistically significantly different between both groups. Average periprocedure VAS was 3.2 versus 7.4 for Lidocaine and Placebo groups, respectively ($p = 0.0001$). Postprocedure VAS in the Lidocaine group was 4.1 ± 1.6 and that for the Placebo group was 6.1 ± 1.3 ($P = 0.001$). Mean daily dose of Nalbuphine in the Lidocaine group was 8 mg versus 18 for patients in the Placebo group ($p = 0.002$). Average length of post procedure hospital stay was 3.7 and 3.8 days for Lidocaine and Placebo groups, respectively ($P = 0.36$).
Conclusions: Intra-arterial administration of buffered Lidocaine before infusing the embolization particle of TACE is safe and effective in dose as low as 50 mg for reducing peri and post-procedural pain and dosage of narcotic analgesics in patients with HCC.

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1. Introduction

Transarterial chemoembolization (TACE) is a well known technique for the management of unresectable hepatocellular carcinoma. TACE may be used as a neoadjuvant and bridging to resection or orthotopic liver transplantation (1). It is indicated as a palliative treatment and considered as the first

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line therapy for intermediate stage HCC according to the recommendation of American Association for study of liver diseases based on randomized controlled trials (2,3).

TACE is simply administration of cytotoxic drugs, with or without lipiodol, by means of a catheter directly to the hepatic artery followed by the administration of embolizing agents such as spherical gelatin or polyvinyl alcohol particles (4).

Postembolization syndrome (PES) is a common complication after embolic procedures, and it is a frequent cause of extended inpatient hospital admissions. PES is a self-limited constellation of symptoms consists of fevers, unremitting nausea, general malaise, loss of appetite, and variable abdominal pain following the procedure. Although a definite cause is unknown, this syndrome is thought to be a result of therapeutic cytotoxicity, tumor ischemia, and resulting intrahepatic and extrahepatic inflammation (5).

Intraarterial Lidocaine administration during TACE has been known not only for reduction of severity of the pain that is associated with TACE but facilitates faster recovery as well (6,7).

Lee et al. found that: transcatheter administration of Lidocaine immediately before infusion of chemotherapy had significantly better effect on pain control than after chemotherapy emulsion (8).

1.1. Purpose

To assess the efficacy of intra-arterial buffered Lidocaine on post-procedural pain and on length of hospital stay in hepatocellular carcinoma (HCC) patients undergoing chemoembolization.

2. Materials and methods

Institutional ethics committee approved this prospective randomized controlled study. Informed consent was obtained from the entire patients prior to the procedure.

All patients were subjected to thorough evaluation. HCC was diagnosed in all patients either by results of histopathological exam or typical imaging criteria of HCC with triphasic dynamic contrast study by CT or MRI in addition to High serum level of Alfa fetoprotein that is more than 400 ngm/ml. Other laboratory investigations were ordered including: Liver and renal function tests, CBC to evaluate platelets count, Prothrombine time, concentration and INR. Exclusion criteria were; uncorrected coagulopathy, Infiltrative type of HCC, tumor volume more than 50% of the liver, patients with Child C according to Child Pugh classification, extra hepatic liver metastasis of HCC that was confirmed by CT chest, abdomen and pelvis and thrombosis of main portal vein.

Conscious sedation was not provided to any of our patents. Continuous monitoring of blood pressure, pulse and cardiac electricity was provided during the entire procedure. TACE was performed after visceral angiography to evaluate arterial supply of the HCC and evaluate patency of portal vein. HCC arterial supply was accessed by selective segmental using standard 5 Fr catheter or 3 Fr coaxial technique using Renegade Hiflow microcatheter (Boston Scientific USA). Having the catheter in good position emulsion of Doxorubicin 50 mg and 50 mg Cisplatinum and 10 mg of Mitomycin C was mixed with 10 ml of water soluble contrast Urografin 76% (SCHERING-Germany) and 10 ml lipiodol (ultra-fluids Guerbet France). The total volume of the chemotherapeutic emulsion was about 22 ml. The chemotherapeutic emulsion was infused under fluoroscopy guidance till good staining of HCC was seen. The infused volume of chemotherapeutic emulsion was estimated. Five to 10 ml of buffered Lidocaine 2% was infused in patients assigned to the Lidocaine group just before of infusion of PV particles and saline was infused in patients assigned to the Placebo group. Buffered Lidocaine was prepared by adding 2 ml of Sodium Bicarbonate 8.4% to 20 ml of Lidocaine 2% for a final volume of 22. In both groups, the procedure was concluded by infusing aliquots of polyvinyl alcohol particle (PVA) size of 150–250 micron. The volume of the infused chemotherapeutic emulsion and volume of PVA vial were calculated in both groups.

Good hydration was assured for entire patients before and after procedure by IV normal saline infusion till the ability to drink. Pain was recorded using visual analog score (VAS) considering 1 is minimal discomfort and 10 is the severest pain. Pain scores were recorded 4 times per day. Pain score of 5 or more was considered as significant pain that required analgesia. Post procedure analgesia was provided by Nalbuphine IV and daily doses and total doses were recorded for each patient. Body temperature and hospital stay all were recorded for each patient in both groups. The mean dose of Nalbuphine per day and total doses were calculated for each patient. Mean of the VAS scores between the 2 groups was compared. Ondansetron hydrochloride (Zofran), 4 mg slowly IV infusion was offered to patients who had nausea.

Non contrast axial CT for the abdomen was obtained within the first week. Evaluation of serum Bilirubin, Albumin, Prothrombin time, conc., INR and ALT and AST was done within the first week of TACE and repeated after 6 weeks. Serum Alfa fetoprotein was evaluated 6 weeks after TACE only for patient who had high base line Alfa fetoprotein in addition to triphasic dynamic MRI after 6 weeks.

Statistical analyses were performed with the chi-square test and ANOVA with multiple comparisons using SPSS. P value less than 0.05 was considered significant.

3. Results

Thirty-nine transarterial chemoembolization (TACE) procedures were carried out for 21 consecutive patients (19M, 2F, age range 52–78). This is a prospective randomized controlled study; Lidocaine Group consisted of 20 TACE procedures in 10 patients at rate of 2 sessions per patient who received intra-arterial buffered Lidocaine during chemoembolization. Placebo group consists of 19 procedures in 11 patients at rate of 1.7 procedures per patient in whom Lidocaine was substituted with normal saline solution.

The patient demographic criteria, Child Pugh, tumor size and doses of chemotherapeutic emulsion and amount of PV particles used were comparable without statistically significant difference Table 1.

TACE technique was super selective or segmental for both Lidocaine and Placebo groups (Fig. 1). Three patients out of 21 patients had bilobar involvement. Each lobe was treated separately at different session. The majority of patients had right lobe lesions. Four TACE procedures were carried

out for left lobe lesions in 2 patients. There was no recorded inadvertent embolization of the gall bladder.

Good uptake of the chemotherapeutic emulsion was confirmed by CT scan (Fig. 2).

Classic anatomy of the celiac trunk was noticed in 20 patients and a single patient showed replaced right hepatic artery originated from the superior mesenteric artery Fig. 3.

There were no vascular complications during TACE procedure such as dissection or spasm of hepatic artery.

The infused dose of chemotherapeutic emulsion till tumor bed saturation ranged from 0.5 to 0.9 of the prepared chemotherapeutic emulsion for the Lidocaine group and from 0.5 to 0.8 of the emulsion in the Placebo group and the dose difference was not statistically significant and so did the volume of the embolization particles, PVA.

There were no recorded changes in blood pressure or arrhythmias in patients who received buffered Lidocaine.

Mild inter procedure pain was noticed in 65% of the Lidocaine group ($n = 13$) with VAS of 3 in the Lidocaine group compared to 42% in the Placebo group ($n = 8$).

No pain during TACE was encountered in 35% ($n = 7$) of the Lidocaine group; 5 of them had TACE twice, compared to 5% in the Placebo group ($n = 1$).

The average periprocedure pain score was less in the Lidocaine group than in the Placebo group. The average VAS was 3.2 versus 7.4 for both Lidocaine and Placebo groups respectively ($p = 0.0001$) (Table 2). Post procedure pain was significantly lower in Lidocaine group versus Placebo group. VAS for pain in the Lidocaine group was 4.1 ± 1.6 and that for the Placebo group was 6.1 ± 1.3, the difference is significant ($P = 0.001$). The frequency of analgesic demands was higher in patients who did not receive Lidocaine and mean daily dose of Nalbuphine in the Lidocaine group was 8 mg versus 18 for patients in the Placebo group ($p = 0.002$) (Table 2). It is interesting to notice that VAS and doses of nalbuphine were not statistically significant in patients who received 50 mg or 75 mg or 100 mg of Lidocaine intra arterially (Table 3).

Nausea was encountered in 95% of patients belonging to the Lidocaine group ($n = 19$) and it was 100% in those belonging to the Placebo group. The elapsed time from beginning of the procedure till the patient started to eat and drink (time to eat and drink) was close in both groups .The average duration for Lidocaine group was 15 h and ranged from 8 to 36 and that for patients in Placebo group was 13 h ranging from 9 to 33 hours. Incidence of post procedure fever was not statistically different in Lidocaine and Placebo groups. 4 mg of ondansetron hydrochloride (Zofran), was slowly offered as iv infusion to patients in 95% of TACE procedures in the Lidocaine group ($n = 19$) and repeated for more than three days in 60% of procedures ($n = 12$). Zofran was offered to the entire Placebo group patients and repeated more than three days in 79% ($n = 15$).

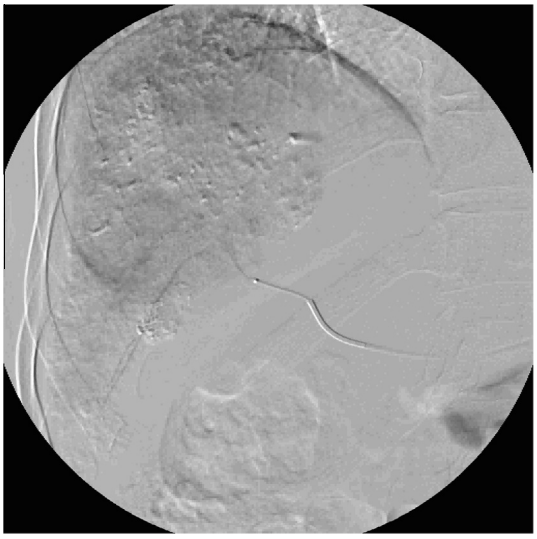

Fig. 1 62 year man who has single HCC at the right lobe, superselective segmental right hepatic angiogram showing hyper vascular HCC.

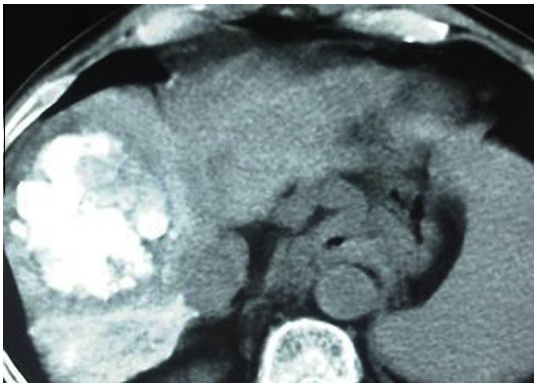

Fig. 2 62 year man who has single HCC at the right lobe. Non-contrast axial CT scan for upper abdomen 3 days after TACE showing intense uptake of the chemotherapeutic emulsion by HCC. He is same patient as mentioned in Fig. 1.

The length of patient hospitalization after TACE ranged from 15 h post procedure to 7 days for the Lidocaine group and 14 h to 8 days for the Placebo group. The average length of post procedure hospital stay was 3.7 and 3.8 days for

Table 1 Comparison between patients who received intra arterial Lidocaine versus who received Placebo.

	Lidocaine group		Placebo group		*P* value
	Mean	SD	Mean	SD	
Age in years	62.2	9.5	60.6	8.9	0.27
Child Pugh	6.3	0.9	6.4	1.0	0.47
Tumor size in cm	8.7	1.7	7.9	1.5	0.17
Chemotherapy dose	0.9	0.1	0.8	0.1	0.06
PV particles	0.8	0.2	0.8	0.2	0.50

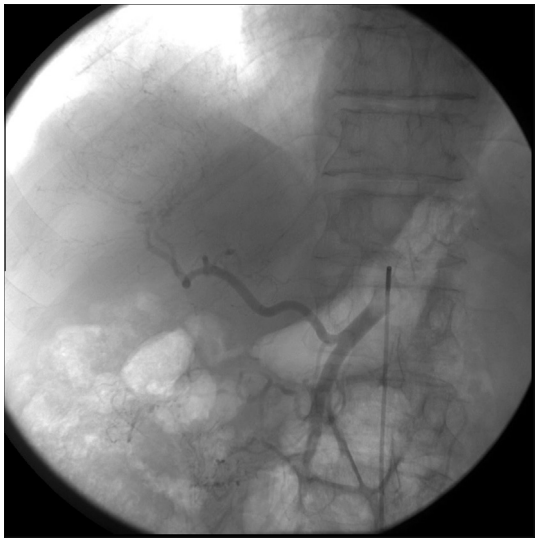

Fig. 3 73 year old man with two focal HCC at the right lobe. Superior mesenteric angiogram showed replaced right hepatic artery originating from the superior mesenteric artery.

Lidocaine and Placebo groups respectively. That difference was not statistically significant ($P = 0.36$).

4. Discussion

Postembolization syndrome (PES) is experienced after 80–90% of TACE procedures. It has widely variable manifestations but often includes pain, fever, nausea, and vomiting. PES can last from a few hours to a few days (1). Although it is a self-limiting condition, it is a major complication of hepatic TACE causing longer hospitalization (4). The large doses of intravenous narcotics needed to control the pain leads to altered mental status and respiratory depression; therefore, intensive monitoring is required. Narcotics potentiate severe post embolization nausea and vomiting (6). The exact explanation of pain component of PES in TACE is not known but many hypotheses are postulated such as ischemia and transient swelling of liver parenchyma that stretches the liver capsule or accidental embolization of the gall bladder. Severe pain during the procedure can be explained by irritant effect of the chemotherapeutic emulsion on the hepatic artery branches (6,7).

Direct irritation of the arterial wall by the chemotherapeutic emulsion is one of the theories of pain component of PES. Daniel et al. found that: pain at TACE was lower after the first session and this could be explained by lower dose of chemotherapy in the successive TACE sessions than that of the first TACE session (9). In our study 5 out of 7 patients who had no pain during the TACE were subjected to previous TACE session. In superselective TACE, the arterial system which is in contact with irritant chemotherapeutic emulsion is at minimum and the dose is lower than lobar TACE technique and carries less risk for non target embolization of the gall bladder. Inadvertently embolized gall bladder was considered as one of the theories of pain component of PES.

Contrary to Daniel et al., Patel et al. found that repetition of TACE is not a predictor of pain component of PES as their hypothesis was that: ischemic pain was the main mechanism and vascular irritation by chemotherapeutic emulsion was not the major cause for pain (10).

In a study by Coldwell et al. excellent analgesia during hepatic TACE was achieved with a celiac plexus block. However this method seems to be risky and time-consuming (11).

Lidocaine has been shown to help control the painful response to the injection of iodinated contrast material in peripheral arteries (12,13).

Molgaard et al. (6) studied the use of intraarterial Lidocaine in hepatic arterial branches prior to and during TACE. This resulted in a significant decrease in the amount of morphine required during the procedure, as well as the need for subsequent postprocedure morphine drip. It remains clear that the sequelae of pain during and after TACE, such as shallow respirations and paralytic ileus, can complicate patient management.

Table 2 Showed difference between Lidocaine and Placebo group as regard pain.

	Lidocaine group		Placebo group		*P* value
	Mean	SD	Mean	SD	
Inter procedure VAS	3.2	1.1	7.4	1.2	0.0001
Daily dose of nalbuphine	8	6.2	18.3	6.2	0.002
Total doses of nalbuphine	28.8	7.0	44	8.4	0.001
Post procedure VAS	4.1	1.5	6.9	1.4	0.05
Postprocedure fever frequency	0.7		0.6		
Length of hospital stay	3.7	1.8	3.8	1.6	0.36

VAS: visual analog scores.

Table 3 VAS for patients with different doses of intraarterial buffered Lidocain.

	[*]50 mg Lidocaine[∞]	[*]75 mg Lidocaine[©]	100 mg Lidocaine[©,∞]
VAS mean	3.5	4.4	4.6
SD	1.3	1.7	1.3

[*] *P* value = .01.
[©] *P* value = .03.
[∞] *P* value = .02.

Therefore intraarterial Lidocaine administration is recommended because it is a much easier and less time-consuming method than celiac plexus block.

The mechanism of the analgesic effect of intra-arterial Lidocaine in hepatic TACE is unclear. Hartnell et al. (7), suggested that Lidocaine has a direct local effect after diffusion into the arterial wall and liver parenchyma, and this effect will be prolonged in tumors where blood flow is occluded, preventing washout of the agent.

Unbuffered Lidocaine (pH = 6.5) is commonly employed as a local anesthetic prior to transcutaneous interventional procedures. Lidocaine administration is associated with stinging or burning pain at the injection site. The buffered anesthetic had a statistically significant reduction in the pain associated with infiltration of Lidocaine without any compromise in its therapeutic efficacy as observed on a linear visual analog scale (14). Intraarterial administration of buffered Lidocaine is less irritant to arteries and associated with less discomfort than unbuffered Lidocaine.

Lee et al. found that: patients who had received Lidocaine by intraarterial route during TACE procedure needed smaller doses of narcotic analgesics than those who had not received Lidocaine (8). These results are consistent with our results.

Different protocols for intraarterial Lidocaine administration were applied. Sharma et al. (15) used Lidocaine intermittently during the procedure. Hartnell et al. (7) injected Lidocaine at varying intervals before and during TACE up to 4 times. The dose of Lidocaine used in their study (maximum 105 mg injected over 10–20 min) was safe and effective. However Lee et al. (8) concluded that intraarterial administration of Lidocaine just before TACE was much useful than after TACE as regards pain control and post procedure requirement for narcotic.

In our study we used Lidocaine as bolus rather than infusion; we found that 50 mg of buffered Lidocaine was effective to alleviate pain during the procedure and reduced pain score and analgesic dose after the procedure. In our study we used buffered Lidocaine which may explain good control of pain during TACE. The post procedure analgesic effect was significant in terms of low pain scores and smaller doses of analgesic requirement.

In our study Lidocaine was injected after administration of the chemotherapeutic emulsion and just before embolization step of TACE by particles.

Lidocaine was administered after chemotherapeutic emulsion has partially saturated the vascular bed of the tumor and embolizing particles have led to the entrapment of Lidocaine and have prolonged its action.

Superselective embolization is better than lobar TACE as regards control of non target embolization especially inadvertent embolization of the gall bladder which in some theory is the main cause of pain component of PES (9). In our study 90% of TCAE procedures for HCC lesions were in the right hepatic lobe (n = 35). Nevertheless we did not have inadvertent embolization of gall bladder. Superselective TACE reduces the number and length of arteries exposed to irritant chemotherapeutic emulsion which is one of the theories of pain component of PES .Superselective TACE is associated with reduction in the chemotherapeutic dose infused which is another advantage of Superselective over lobar TACE technique in addition to much better tumor necrosis (16).

Lidocaine is metabolized by the liver and its half life is about 2 and 2 and ½ hours with normal liver functions. Lidocaine metabolites and unchanged drug are excreted by the kidneys. Because of the rapid rate at which Lidocaine is metabolized, any condition that affects liver function may alter Lidocaine kinetics. The half-life may be prolonged twofold or more in patients with liver dysfunction such as cirrhotic patient with HCC. Entrapment of Lidocaine in the vascular bed of liver tumor that is partially saturated by chemotherapeutic emulsion and infused embolization particle may prolong the duration of action Lidocaine but this cannot explain the extended duration of action for following few days (17).

Intraarterial administration of buffered Lidocaine may alter release of inflammatory mediators, for example histamine release from mast cells in vitro (18), Leukotriene B-4 and Interleukin-1 release from polymorphonuclear granulocytes and mononuclear cells in vitro, respectively (19). Lidocaine has a potential anti-inflammatory effect (20), however, there is still a lack of well-designed studies to support this hypothesis.

Interestingly, Kogut et al. (21) found that prophylactic intraarterial administration of steroids in TACE procedures did not affect analgesic agent use and had a minor effect on antiemetic requirements.

In our study, although periprocedure intraarterial Lidocaine administration improved pain component of PES, the length of hospital stay was not different in patients who received Lidocaine versus patients who received Placebo. This can be explained by the other component of PES nausea and vomiting. Our results agreed with those of other authors (22).

The limitation of our study was that the number of patients and procedures were small. We included patients who had first session of TACE in addition to patients who received previous TACE session; but sub grouping might affect statistical testing.

In conclusion: Intraarterial administration of buffered Lidocaine just before infusion of embolization particles in dose as low as 50 mg is sufficient for pain control during TACE procedure and helps in pain control after the procedure. Evaluation of TACE inflammatory response and the hypothesis that Lidocaine alters this response can be the topic of further investigations.

Conflict of interest

We have no conflict of interest to declare.

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