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Increasing Intra-Lesional pH with the Use of Bicarbonate Along with Doxorubicin in Trans-Arterial Chemoembolization of Hepatocellular Carcinoma: Pilot Study

Dayananda Lingegowda*; Saugata Sen; Sumit Mukhopadhyay; Argha Chatterjee; Priya Ghosh; Jeevitesh Khoda; Anisha Gehani; Aditi Chandra; Anurima Patra; Avik Som

Department of Radiology, Tata Medical Center, 14 Arterial Road, Newtown, Kolkata 700160, India.

Abstract

Introduction: Doxorubicin is a weakly basic agent and undergoes protonation below a pH of 7. The effectiveness of doxorubicin may be greatly diminished in an acidic environment, which is common in hepatocellular carcinomas during the trans arterial embolization process. We hypothesize that the efficacy of TACE can be improved by improving the potency of doxorubicin when used in combination with sodium bicarbonate by creating an alkaline environment.

Material and methods: Ten consecutive patients who consented to the study were enrolled in the trial (between August 2020 and December 2021). Enrolled patients underwent standard conventional TACE or DEB TACE. In each tumor-feeding artery that was selectively embolized, sodium bicarbonate was sandwiched with standard TACE emulsion. A maximum dose of 75 ml of 5% sodium bicarbonate was used per session. Toxicity, imaging response, and overall survival were evaluated.

Results: A total of ten patients were treated with bicarbonate-TACE (M: F-8:2, mean age 59.4 years, Child A). Three patients had portal venous thrombosis and are labelled as BCLC-C, and the rest were categorized as BCLC B. Grade 1 toxicity was seen in 2 patients; Grade 2 toxicity was found in 6 patients; Grade 3 toxicity in 2 patients; Five patients underwent additional treatment, either with RFA, TACE, or surgery, to achieve a complete response on imaging and are alive. Five patients died during follow-up.

Conclusion: Sodium bicarbonate can be safely used intra-arterially during the TACE procedure. Air pockets within the lesions are common after sodium bicarbonate TACE.

Keywords: Trans-arterial chemoembolization; Trans arterial bland embolization; Doxorubicin; and Bicarbonate TACE.

Introduction

The major guidelines, including the CIRSE, recommend the use of trans arterial chemoembolization over trans arterial bland embolization [1]. However, the superiority of the trans arterial chemoembolization over the trans arterial bland embolization has never been established conclusively in randomized control trials [2-5].The acidic tumor extracellular microenvironment is one of the probable explanations for the underperformance of the basic chemotherapeutic drugs [6]. Doxorubicin is a basic drug and protonates in an acidic extracellular tumor environment. This

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Correspondance: *Dayananda Lingegowda, Department of Radiology, Tata Medical Center, 14 Arterial Road, Newtown, Kolkata 700160, India. Email: dayanandal@gmail.com*

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results in low levels of intracellular doxorubicin, which results in physiological resistance of tumor cells to cytotoxic drugs [6]. We hypothesize that the efficacy of TACE can be improved by improving the potency of Doxorubicin when used in combination with sodium bicarbonate by creating an alkaline environment. We propose this phase 1 trial combining standard TACE with bicarbonate.

Materials & methods

This is a prospective, single-arm, single-center, phase 1 clinical trial to study the safety of using sodium bicarbonate during the standard TACE procedure. The study was approved by the institutional review board and registered with clinicaltrials.gov. Indemnity coverage in case of complications was borne by the institute.

Patients who are diagnosed as HCC based on EASL criteria/ biopsy, who are undergoing TACE procedures (Child A, BCLC A, B, C) and consenting for bicarbonate TACE, were included in the study [7]. The decision to treat the lesion with TACE was taken in MDT. Patients who had advanced liver disease (Child B or C), were less than 18 years old, and previously received TACE for lesions, systemic therapy, hepatic arterial infusion chemotherapy, or immunotherapy were excluded from the trial. All patients underwent triphasic CT or MRI of the upper abdomen or both as part of the basic initial investigation.

Procedure: Vascular access was done through the femoral route in all patients. Selective catheterization of the celiac or SMA is done with a 5F diagnostic catheter. Super selective cannulation of the feeders was done with a 2.7 F or less microcatheter. Dyna CT sections are obtained to confirm the tumor coverage and minimize the non-target embolization.

Drug preparation: For the conventional TACE procedure, contrast media was used to reconstitute the doxorubicin (50 mg) powder. Lipiodol/Doxorubicin emulsion mixture is prepared in a 2:1 ratio. A maximum of 15 ml of lipiodol is used per session. For drug-eluting beads, TACE (DEB TACE), 50 mg of doxorubicin is loaded to 100-300 microns of drug-eluting beads. Maximum 75 ml of 5% sodium bicarbonate used per patient. Maximum dose for each feeding artery is 25 ml.

Once the microcatheter is positioned satisfactorily, dyna CT is obtained to reconfirm the perfused areas. A small amount of Lipiodol doxorubicin emulsion or DEB bead-doxorubicin preparation is injected. The emulsion is flushed with a 5% sodium bicarbonate solution, followed by resumption of doxorubicin drug emulsion injection. This sandwich technique is continued till the end point is reached. If there is no stasis after the injection maximum dose of doxorubicin, the feeding artery is embolized with a gelatine sponge. The end point of CTACE is peritumoral portal vein opacification or stasis in the feeding artery. Dyna CT is taken at the end of the procedure.

Toxicity reporting done as per Common Terminology Criteria for Adverse Events (CTCAE) guidelines [8]. Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 Moderate: minimal, local, or noninvasive intervention indicated; Grade 3: Severe or medically significant but not life-threatening; hospitalization or prolongation of hospitalization indicated. Grade 4: Life-threatening consequences; urgent intervention indicated. Grade 5 Death Related to Adverse Events.

Stopping rule for trial: Any new serious complication that cannot be attributed to standard TACE is criteria for stoppage of the pilot study.

Follow up: First imaging is done after 3-4 weeks from index bicarbonate TACE. Patients will be followed for the first year every three months at their regular appointment by CT/MRI and 6-monthly CT for the second year and yearly on the 3rd year onwards. AFP/PIVKA 2 levels are obtained during the imaging for the first 2 years and 6 monthly thereafter. Stage migration principle followed during the retreatment.

Outcome measures: The primary aim of the trial is to assess the safety of treatment and adverse effects in bicarbonate TACE. The secondary aim was to assess the response and overall survival.

Response to treatment is reported using the European Association for the Study of the Liver (EASL) criteria of tumor response to treatment [9]. The targeted-tumor response to treatment was assessed 3-4 weeks after the first treatment according to EASL criteria and defined as complete response (CR-no viable tissue as evidenced by absence of enhancing tissue in the target lesion) or partial response (PR-the sum of the arterial enhancing area decreases by at least 50% as compared to pretreatment imaging). Stable disease (ST-the disease does not qualify for CR or PR, or it is progressive) and progressive disease (PD-the sum of the arterial enhancing area increases by at least 25% as compared to pretreatment imaging).

Results

A total of 10 patients underwent bicarbonate TACE (8 male, 2 females, ages ranging from 27 to 73 years, mean 59.4, median 64.5 years). 50% of patients had positive serology (HBV or HCV), and the rest were alcohol- or metabolic disease-related HCC. All patents were CHILD A. The majority of patients (7/10) were BCLC-B, and the rest (3/7) were classified as BCLC-C due to the presence of peripheral portal vein thrombus. Mean size of tumor treated is 6.7 cm (tumor size ranging from 2-13 cm). The majority of patients (9/10) presented with solitary lesions, and one had multiple lesions. CTACE is done in 6 patients, and drug-eluting TACE (DEB-TACE) is done in 4 patients. 9/10 patents showed partial response with necrosis >80%. In one patent response assessment was not done since succumbed to COVID infection within 2 weeks of TACE. 9/10 patients received additional treatment (hepatectomy, ablation, TACE, or systemic therapy). Complete response was seen on 5/10 with additional treatment. 3/10 patients progressed in target lesion and 1/10 progressed in non-target lesion. Those who achieved a complete response (5/10) were alive during the follow-up rest and died during the follow-up (Figures 1-4). Grade 1 toxicity was seen in 2 patients; Grade 1 toxicity was found in 6 patients; Grade 3 toxicity in 2 patients; no patient had grade 4 or 5 toxicity (Table 1).

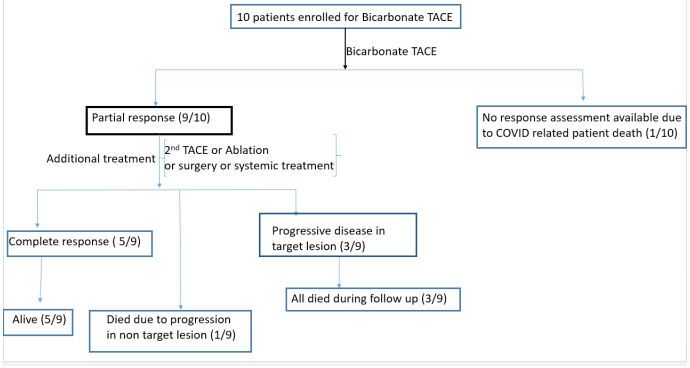

Figure 1: Flow chart of patients in the study.

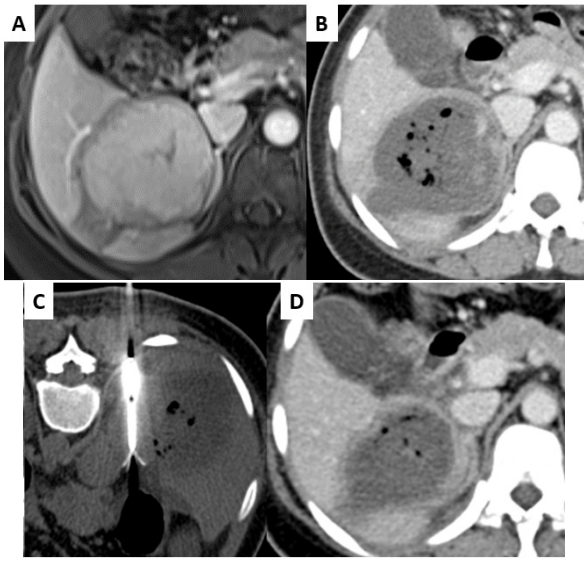

Figure 2: (A) Axial post-contrast MRI T1-weighted imaging showing enhancing large right lobe HCC. (B) Post-bicarbonate TACE, contrast CT showing significant necrosis with air pockets. Small persisting enhancement noted in medial part. This residual part of the tumor was treated with ablation **(C,D)** Follow-up CT showing complete response with persisting air pockets.

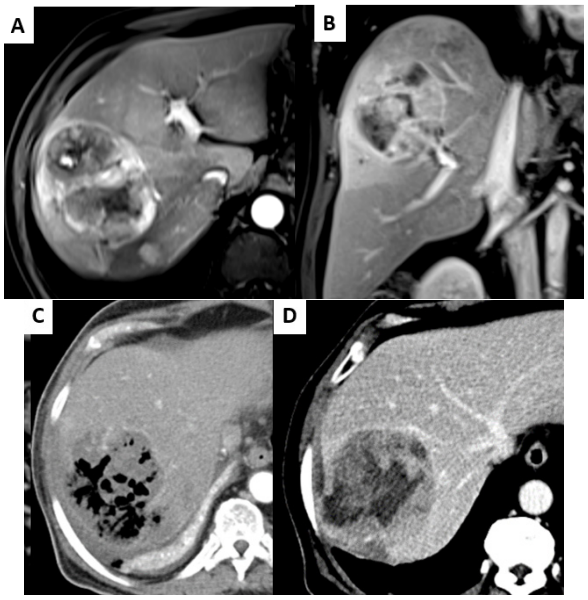

Figure 3: Axial **(A)** and coronal **(B)** post-contrast T1-weighted MRI showing the large right lobe HCC with portal vein involvement. **(C)** Post TACE contrast CT showing the extensive necrosis with air pockets. **(D)** Follow-up CT imaging showing regrowth of tumor representing progressive disease.

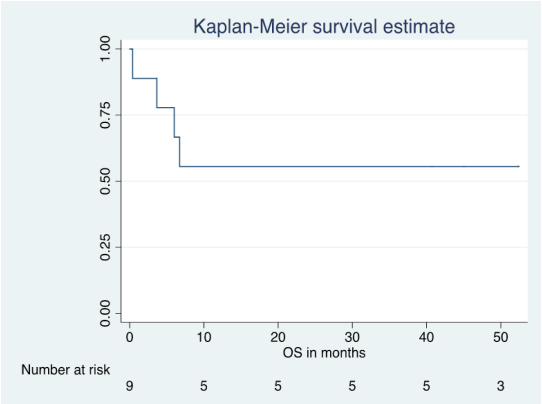

Figure 4: Kaplan-Meier curve showing the overall survival of patients. All the patients who achieved a complete response survived during the study period.

Table 1: Summary of the study.

No	Age / Sex / Comorbidity	Serology / Alcohol Abuse	Child-Pugh Score	BCLC Staging / PVT	Size of index tumour	Primary TACE	Post embolization syndrome and Complication	Imaging Response	Additional treatment for index tumour	Final response	Pre /Post AFP (IU/ml)	Follow up
1	71Y/Male/DM/HT	HCV +ve	A	C PVT- 2	7.7 cm	cTACE	Grade 2	Not available	NIL	NA	7.5/	Died after 2weeks due to COVID
2	51Y/Male	HBV +ve	A	B PVT- 0	8 cm	cTACE	Grade-1	>90% necrosis	hepetectomy	CR	135/2.7	Alive (12/08/2020 -Till date)
3	46Y/Female/DM	NIL	A	B/PVT- 0	6.1 cm	DEB TACE	Grade -1	>80% necrosis	cTACE +RFA	CR	6/3.3	13/08/2020 ALIVE
4	70Y/Male	HBC +ve	A	C/PVT-3	13 cm	DEB TACE	Grade-3, Prolonged hospital stay	>80% necrosis	DEB TACE	PR	33909/3522	Procedure 14/08/2019 - Dead- 29/02/2020
5	27Y/Male	HBV +ve	A	B/PVT-0	6.5 cm	DEB TACE	Grade-2	>90% necrosis	Ablation	CR	2/1.5	06/11/2019 ALIVE

6	73/MALE/DM/HT	NIL	A	C/PVT-2	8.1 cm	DEB TACE	Grade 3	>90% Necrosis	Systemic treatment	PD	1210/ 883	16/08/2020 Dead- 04/12/2020
7	64/MALE	HBV +ve	A	B/PVT-0	5.8 cm	cTACE	Grade 2	>90% Necrosis	MWA	CR	6.7/3.7	22/03/2021 ALIVE
8	56/FEMALE/DM	NIL	A	B/PVT- 0	6 cm	cTACE	Grade 2	>90% necrosis	MWA	CR	1.4/1.5	29/07/2021 ALIVE
9	65y/MALE/DM/ HT	NIL	A	B/PVT- 0	2 cm	cTACE	Grade 2	100% necrosis	Systemic treatment for other lesion	PD in non- index lesion	10/10	25/07/2020 Expired on expired 0 12/02/2021
10	71/male/DM/HT	NIL	A	B/PVT-0	4.2 cm	cTACE	Grade 2	>90% necrosis	MWA, RT	PD	200/76	17/12/2021 expired on 1/08/2023

Discussion

Though doxorubicin is extensively used for intra-arterial chemoembolization, it is not a popular drug for systemic treatment of HCC [10]. Even after the development of a pegylated liposomal formulation of doxorubicin, it only reduced the toxicity profile and failed to demonstrate any meaningful survival benefit when used for systemic treatment [11]. The possible reason for this lies in the changes happening to the pH tumor microenvironment [12]. Due to a combination of high metabolic rate and poor perfusion, there is significant production of lactate from glucose metabolism. The major acid load is transported to the extracellular compartment, making it more acidic while maintaining the intracellular PH. Many studies have shown that intracellular pH of solid tumors is maintained within a range of 7.0-7.2, whereas the extracellular pH is acidic [13]. An acidic extracellular microenvironment gives natural immunity from drugs that protonate in acid environments. This is the probable reason for resistance to doxorubicin [6].

The rationale for this study is based on the assumption that the result seen after chemoembolization is predominantly contributed to by the embolic effect rather than the chemotherapeutic effect. We hypothesize that the efficiency of the chemoembolization can be improved by increasing contributions from chemotherapeutic drugs [14].

Most of the patients (9/10) who underwent bicarbonate TACE showed extensive necrosis (>80% necrosis). In one patient (1/10), post-procedure evaluation could not be done since he died after two weeks of the procedure due to COVID infection. With subsequent additional procedures (partial hepatectomy, additional TACE, and ablation), we are able to achieve a complete response in 50% (5/10) of the patients. One patient has two procedures (2nd TACE and ablation) to achieve complete TACE. The second TACE was a non-bicarbonate TACE. Majority patients who achieved a complete response are alive during the follow-up. One patient had a multifocal lesion and achieved a partial response in treated lesions but died due to progressive disease in others in spite of systemic treatment. All the patients who achieved a complete response had survived during the follow-up. Patients who are partial response or have progressive disease died during the follow-up period. This finding is similar in line with other studies that showed positive survival correlation with post-TACE response [15].

As a phase 1 trial, establishing the safety of the procedure is the main aim of the study. Most patients experienced only Grade 1 or 2 complications (8/10). Grade 3 complications are seen in 2 patients who had portal vein thrombus. None of the patients experienced grade 4 and 5 complications. One patient died after 2 weeks of procedure with an established diagnosis of COVID infection, and no relation to procedure can be established. Patients who had PVT-3 developed grade 3 symptoms, which required prolonged hospital stays. All the symptoms are similar to post-embolization syndrome, and there are no unique symptoms that can be attributed to sodium bicarbonate. From this observation, patients with portal vein thrombosis are an unfavorable factor and likely develop more significant post-embolization syndrome with bicarbonate TACE.

Intratumor air is frequently seen after the bicarbonate TACE. A possible explanation is the acid-base (acidic environment reacting to sodium bicarbonate) reaction resulting in the release of the carbon dioxide [16]. This can be, at times, very extensive and can be easily misinterpreted as an infection. The clinical profile of the patient will help in differentiation. However, extensive intratumor air on the background of postembolization syndrome symptoms may pose difficulty in arriving at correct judgment. To the best of our knowledge, benign intratumoral air was never reported in literature.

On an average, 50 ml sodium bicarbonate is used (25 ml-75 ml range). Post-procedure embolization syndrome was seen in the patient with a portal vein thrombus, more severe with a higher grade of thrombus. All patients with portal vein thrombus received 25 ml of sodium bicarbonate. No significant relation seen between the post-embolization syndrome and the dose of the bicarbonate.

Rationale for bicarbonate dose is based on safe doses available from literature [17]. The maximum dose of bicarbonate used in the quoted index study was 250 ml (5% bicarbonate, 25 ml/artery) in combination with 60 ml of lipiodol. There was no adverse event reported with this dose. As per our institutional protocol, we are treating a maximum of 3 arteries per session with a maximum dose of 15 ml of lipiodol. Hence, we intend to use a maximum of 75 ml of 5% bicarbonate per session.

The limitations of the study are the lack of a control arm and the limited number of cases. It is difficult to assess the efficiency of bicarbonate due to multiple follow-up treatments. Further phase 2 prospective randomized controlled trials are required to establish the superiority of conventional TACE with bicarbonate TACE.

Conclusion

Bicarbonate TACE is safe, and it is a promising option. It may enhance the outcome of the TACE. Air pockets are commonly seen after bicarbonate TACE.

Declarations

Funding: This study was not supported by any funding

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: IRB approval was obtained

Informed consent: Informed consent it was obtained from all patients

Trial registration: Clinical Trials Registry-India (CTRI), CTRI/2020/09/028095 Presented in SIR Annual Scientific Meeting-DOI: 10.1016/j.jvir.2022.12.410

References

1. Lucatelli P, Burrel M, Guiu B, de Rubeis G, van Delden O, et al. CIRSE Standards of practice on hepatic transarterial chemoembolisation. Cardiovasc Radiol. 2021; 44: 1851-1867.

2. Tsochatzis EA, Fatourou E, O'Beirne J, Meyer T, Burroughs AK. Trans arterial chemoembolization and bland embolization for hepatocellular carcinoma. World J Gastroenterol. 2014; 20: 3069-3077.

3. Kawai S, Okamura J, Ogawa M, Ohashi Y, Tani M, et al. Prospective and randomized clinical trial for the treatment of hepatocellular carcinoma--a comparison of lipiodol-transcatheter arterial embolization with and without adriamycin (first cooperative study). The Cooperative Study Group for Liver Cancer Treatment of Japan. Cancer Chemother Pharmacal. 1992; 31: 1-6.

4. Llovet JM, Real MI, Montaña X, Planas R, Coll S, et al. Arterial embolization or chemoembolization versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: A randomised controlled trial. Lancet. 2002; 359: 1734-1739.

5. Roth GS, Benhamou M, Teyssier Y, Seigneurin A, Abousalihac M, Sengel C, et al. Comparison of trans-arterial chemoembolization and bland embolization for the treatment of hepatocellular carcinoma: A propensity score analysis. Cancers (Basel). 2021; 13: 812.

6. Swietach P, Hulikova A, Patiar S, Vaughan-Jones RD, Harris AL. Importance of intracellular pH in determining the uptake and efficacy of the weakly basic chemotherapeutic drug, doxorubicin. PLOS One. 2012; 7: 35949.

7. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018; 69: 182-236.

8. Miller TP, Fisher BT, Getz KD, Sack L, Razzaghi H, et al. Unintended consequences of evolution of the Common Terminology Criteria for Adverse Events. Paediatric Blood Cancer. 2019; 66: 27747.

9. Patella F, Pesapane F, Fumarola E, Zannoni S, Brambillasca P, et al. Assessment of the response of hepatocellular carcinoma to interventional radiology treatments. Future Oncol. 2019; 15: 1791-1804.

10. Sanduzzi-Zamparelli M, Forner A. Systemic doxorubicin and hepatocellular carcinoma: The end of an era never risen up. Lancet Gastroenterol Hepatol. 2019; 4: 418-420.

11. Kim DW, Talati C, Kim R. Hepatocellular Carcinoma (HCC): Beyond sorafenib-chemotherapy. J Gastrointest Oncol. 2017; 8: 256-265.

12. Wang S, Lv Y, Zhou Y, Ling J, Wang H, et al. Acidic extracellular pH induces autophagy to promote anoikis resistance of hepatocellular carcinoma cells via downregulation of miR-3663-3p. J Cancer. 2021; 12: 3418–3426.

13. Zhang X, Lin Y, Gillies RJ. Tumor pH and its measurement. J Nucl Med. 2010; 51: 1167-1170.

14. Hao G, Xu ZP, Li L. Manipulating extracellular tumour pH: An effective target for cancer therapy. RSC Adv. 2018; 8: 22182-22192.

15. Han G, Berhane S, Toyoda H, Bettinger D, Elshaarawy O, et al. Prediction of survival among patients receiving trans arterial chemoembolization for hepatocellular carcinoma: A response-based approach. Hepatology. 2020; 72: 198-212.

16. Davidson D. Amphoteric molecules, ions and salts. J Chem Educ. 1955; 32: 550.

17. Chao M, Wu H, Jin K, Li B, Wu J, et al. A nonrandomized cohort and a randomized study of local control of large hepatocarcinoma by targeting intratumoral lactic acidosis. Elife. 2016; 5. doi:10.7554/eLife.15691