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The Effect of "Tris-Hydroxymethyl Aminomethane" Treatment on Survival of Rats with Experimental Metabolic Acidosis Created by Intragastric Administration of Hydrochloric Acid "Tris-hydroxymethyl Aminomethane" Versus Acidosis

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Abstract

Background: Treatment of acidosis is serious health problem within emergency departments and intensive care units etc. Ingestion of household cleaning solutions (due to both suicidal and accidental reasons) is still also a serious public health problem in Turkey and the most fatal complication thereof is, severe metabolic acidosis. An effective treatment should be provided for the cases presenting to emergency departments with life-threatening metabolic acidosis.

Aim: We aimed to compare the survival rate of rats with experimental metabolic acidosis created by intragastric administration of hydrochloric acid and treated with "tris–hydroxymethyl aminomethane" or normal saline solution alone.

Study Design: This was an experimental animal study.

Methods: Following ketamine-xylazine anesthesia, internal carotid artery of fourteen female Wistar albino rat was cannulated, basal blood samples were drawn and esophagus of each was cannulated with intracath. Hydrochloric acid was subsequently poured through the cannula towards stomach. After 30 minutes, blood gas status was checked in order to see if acidosis occurred or not. The rats which developed acidosis were randomly divided into "tris-hydroxymethyl aminomethane" and "normal saline solution" groups. Later the treatment with IV tris-hydroxymethyl aminomethane or normal saline was initiated. At 30th and 60th minutes of the treatment, pH, PaO_2, HCO_3, $PaCO_2$ and base deficit parameters were checked through arterial blood gas samples to monitor the efficacy of the treatment. At the end of the second hour of the study, the experiment was finalized and the survival of rats was documented.

Results: Following the development of experimental metabolic acidosis in rats by ingestion of intragastric hydrochloric acid, four rats in tris–hydroxymethyl aminomethane and six rats in normal saline group died prior to the end of the follow-up period.

This finding was statistically significant. There was no statistically significant difference between tris–hydroxymethyl aminomethane and normal saline groups with regard to body temperature, blood pressure, heart rate, $PaCO_2$ and PaO_2. However, the comparison of two groups with respect to survival indicated a significant difference ($p<0.05$). pH at 60th minute in tris–hydroxymethyl aminomethane group was significantly lower compared to that in normal saline group ($p<0.05$), and base deficit values at 30th and 60th minutes in tris–hydroxymethyl aminomethane group were significantly higher compared to that in normal saline group ($p<0.05$).

Conclusion: In this experimental rat model, we observed that treatment with IV tris–hydroxymethyl aminomethane prolonged the survival of rats with experimental metabolic acidosis created by ingestion of hydrochloric acid compared to the treatment with normal saline solution.

Key words: Metabolic acidosis, hydrochloric acid, tris–hydroxymethyl aminomethane, sodium bicarbonate

Introduction

Treatment of the patients with acidosis is still a serious health problem within emergency departments and intensive care units etc. The main cause of acidosis may be due to different causes such as respiratory and/or metabolic causes (acute renal failure, diabetic keto-acidosis, uremic acidosis, etc.), suicidal cases (salicylate intoxication, methanol intake, ingestion of acidic solutions etc).

For cleaning of offices or houses, corrosive and acidic substances containing hydrochloric acid etc. are used frequently in daily life. Unfortunately, accidental or suicidal ingestion of these detersive and corrosive substances is still a serious health problem in many countries and as well in Turkey. Despite the presence of various precautions there against, accidental ingestion of these corrosive substances is mostly seen among children[1-5]. On the other hand, the reported adulthood cases occur a result of suicidal attempt since in Turkey, these substances are easily accessible in markets as packaged, but are stored in beverage containers in houses.

These acidic cleaners have both local destructive and systemic effects such as severe metabolic acidosis and these systemic effects are responsible for the mortality. In particular, the presence of acidosis affects the prognosis of the patient negatively[4,5]. Prompt and effective treatment should be provided for the patients admitting to emergency departments with life-threatening severe and deep metabolic ac-

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idosis clinic. Sodium bicarbonate ($NaHCO_3$) is the unique agent used to ameliorate the clinics of acidosis however; it has some side effects either such as hypernatremia or such as increased carbon dioxide (CO_2) retention etc. and the therapeutic effect of it is still doubtful [6-11].

In a study by Kazancı et al.[1] in a rat model with experimental metabolic acidosis created by ingestion of hydrochloric acid (HCl) intravenous $NaHCO_3$ treatment ended up with the shorten survival rate of rats.

In most of the studies regarding ingestion of corrosive substances, the regional damage to the gastrointestinal tract and complications related thereto as well as treatment options for such complications are discussed and emphasized.

There are only a limited number of clinical and experimental studies regarding life-threatening systemic effects brought by ingestion of acidic corrosive solutions. In such cases absorption of acid by tissue and the accumulation of lactic acid secondary to coagulation necrosis results with development of metabolic acidosis. When blood pH level declines to 7.10-7.20, myocardial muscle is suppressed and serious arrhythmias may occur[1,4]. Yanturali et al.[4] reported a case of acute ST segment elevated myocardial infarction associated with massive HCl ingestion. Severe systemic acidosis has developed and been complicated by the presence of acute myocardial infarction. In such cases, treatment specifically for increasing pH level is recommended with different alternative agents are also available for this purpose[11-17]. The absence of studies supporting treatment with $NaHCO_3$ in acidosis as well as the presence of publications showing the usefulness of alternative buffering agents like "Tris-Hydroxymethyl Aminomethane" (THAM) (Tribonat™, Fresenius, Kabi, Norway) are apparent in the literature. THAM is a biologically inert amino alcohol with a low toxicity and ability to buffer CO_2 and acids both in vivo and in vitro [6-10, 8-16, 18-23].

Here in this study, we aimed to investigate the effect of "THAM" treatment on survival of rats with experimental metabolic acidosis created by intragastric administration of HCL.

Material and Methods

The experimental protocol of the present study was approved by the Local Animal Ethics Committee of the University of Dokuz Eylül, School of Medicine, and the study was carried out in the Multidisciplinary Experimental Animal Laboratory of the Dokuz Eylül University, Medical School. It was a joint multidisciplinary study participated by the Departments of Emergency Medicine, Anesthesiology and Intensive Care, and Laboratory Animal Science of the Dokuz Eylül University, Medical School.

Animals

Fourteen female Wistar albino rats (weighing 210-250 g) with normal motor activities and 87% homogeneity from the Experimental Research Laboratory of the Dokuz Eylül University were included in the study. The subjects were kept under standard laboratory conditions (a constant lightning regimen providing a 12 hr light/dark cycle; 20-22°C room temperature; 50-60% humidity) with ad libitum access to water and food.

Anesthesia and Surgical Interventions

Rats were intraperitoneally anesthetized with 35 mg/kg ketamine (Ketalar®, Pfizer, İstanbul, Turkey) and 5 mg/kg Xylazine (Xylazine Bio®, Pana-life Bio-Chemical, China). Anesthesia was maintained by intraperitoneally injected 20 mg/kg ketamine and 5 mg/kg xylazine at 90th minute of the experiment.

Following establishment of anesthesia, dorsal tail vein of rats was cannulated with a 24 G branula (B-CAT IV Kanül; Bıçakçılar Ltd. Şti., İstanbul, Turkey). The right common carotid artery of rats was cannulated with 24 G branula (Figure 1). Esophagus was subsequently exposed in the neck dissection region, and penetrated with the 24 G branula of which the end was moved towards the stomach. The branula was fixed inside the esophagus at a position with a distance of 0.1 cm from the inlet hole from where the branula was inserted into the esophagus. To prevent acid regurgitation, the front part of the platform on which rats were immobilized was uplifted by 45° (Figure 2). During these procedures, blood pressure, heart rate (Petaş KMA 250, İstanbul), and rectal body temperature of rats were monitored (May 9404-A Small Animal Temperature Controller).

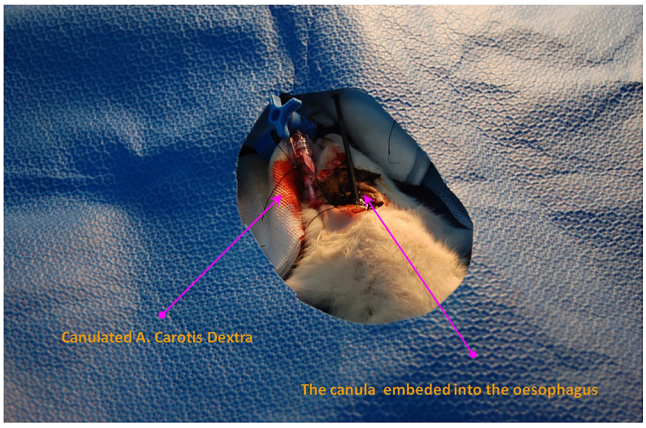

Figure 1: Rat with cannulated right common carotid artery and esophagus

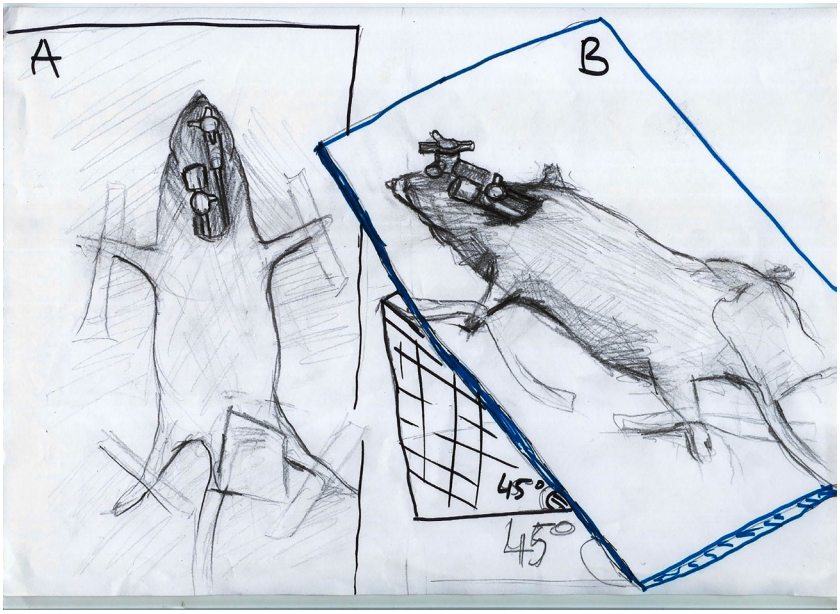

Figure 2: A) Rat with cannulated right common carotid artery and esophagus on a level surface
B) After the administration of hydrochloric acid to the esophagus, the platform was uplifted by 45° in order to prevent acid regurgitation.

Acid Model

After the completion of surgical interventions as well as monitoring procedures, 0.3 ml of blood gas was drawn from the common carotid arteries of rats to check basal blood gas values. Thereafter, 4 ml/kg (1 ml/rat) of 18% hydrochloric acid (Tuz Ruhu, Viking Temizlik ve Kozmetik Ürünleri, İzmir, Turkey) was slowly injected via an injector towards the stomach through the cannula fixed in esophagus. Afterwards, the presence of acidosis in rats was checked with blood gas values observed 30 minutes after the administration of acid (Algorithm-1). The rats with acidosis were separated into two different groups for treatment.

1. **"THAM" (Treatment Group)** (n=8):
   Eight rats in this group were treated with intravenous infusion on average of 20-25 ml THAM. The dose of THAM was calculated with the formula of: "mmol of buffer = 0.3 x kg (body weight) x base deficit (mmol of hydrogen carbonate)". The resultant value was multiplied by 2 and converted into milligrams.

2. **"Normal saline solution" (Control Group)** (n=6) (control group was considered as n=6 due to death of two rat):
   Six subjects in control groups were treated with intravenous infusion of normal saline solution (NaCl 0.9%, Eczacıbaşı-Baxter Hastane Ürünleri San. ve Tic. A.Ş., İstanbul) 30 minutes after ingestion of the acid.

Arterial Blood Gas Measurements

Prior to ingestion of acid (baseline) and at 30th, 60th and 90th minutes after administration of acid, 0.3 ml of arterial blood samples from the pre-cannulated right common carotid artery of each rat were collected, and immediately examined for the pH, HCO_3^-, PaO_2, $PaCO_2$ and base deficit parameters with "Irma TRUPOINT Blood Analysis System" (Irma Trupoint Blood Analysis System ITC Med, USA).

Timing and Method of Animal Sacrifice

At the end of the study, the surviving rats were sacrificed under high dose of halothane anesthesia.

Statistical Analysis

SPPS for Windows 15.0 was used for statistical analysis. Results were calculated as mean ± standard deviation. For inter-group comparisons, Mann-Whitney U and Chi-square tests were used. For intra-group comparisons, Wilcoxon signed-rank test was used. Statistical significance was accepted at $p<0.05$.

Results

There was no statistically significant difference between THAM and normal saline solution groups with regard to body temperature, blood pressure and heart rate (Mann Whitney U, p>0.05) (Table 1).

Table 1: Body temperature, heart rate and mean blood pressure

	THAM group	Normal Saline Solution Group
Body temperature (°C)		
Baseline	36.7 ±0.59	36.9 ±0.2
30th minute	37.0 ±0.1	36.9 ±0.2
60th minute	37.0 ±0.1	37.0 ±0.1
Mean blood pressure (mmHg)		
Baseline	76.9 ±15.2	65.3 ±13.7
30th minute	96.1 ±27.7	98.8 ±21.8
60th minute	82.1 ±18.9	81.9 ±19.0
Heart rate (beat/min)		
Baseline	194.5 ±37.7	170.0 ±33.4
30th minute	200.0 ±48.0	162.0 ±45.3
60th minute	216.6 ±26.0	189.6 ±42.7

Arterial Blood Gas Values

There was no statistically significant difference between THAM group and normal saline solution group with respect to blood pH values at baseline and at 30th minute. However, the mean pH value measured at 60th minute was significantly different (p=0.010). The mean pH values of normal saline group and THAM group at 60th minute were 6.87±0.29 and 7.18 ± 0.04, respectively (Table 2).

In comparison of mean $PaCO_2$ and PaO_2 values, no statistically significant difference was detected (Mann Whitney U, p>0.05) (Table 2).

There was no statistically significant difference between THAM group and normal saline group with respect to mean base deficit values at baseline (Mann Whitney U, p>0.05). However, at 30th and 60th minutes the difference between and normal saline groups for mean base deficit values was significant. The mean base deficit values of THAM group and normal saline group at 30th minute were 13.9±2.0 and 20.7±3.9, respectively (p=0.005). Besides, the mean base deficit values of THAM and normal saline groups at 60th minute were 9.62±0.61 and 24.6±6.8, respectively (p=0.003) (Table 2).

Survival

The survival of rats in THAM group was significantly longer compared to that of rats in control group (p=0.013) (Table 3).

Table 2: Arterial blood gas values for THAM and Normal Saline solution groups

	THAM Group	Normal Saline Solution Group
pH		
Baseline	7.36 ± 0.05	7.22 ± 0.05
30th minute	7.03 ± 0.12	7.03 ± 0.11
60th minute	7.17 ± 0.04	6.86 ± 0.28*
PaO_2 (mmHg)		
Baseline	76.6± 13.0	76.4 ±7.4
30th minute	65.1 ± 13.6	64.7 ± 10.6
60th minute	68.8± 12.8	82.5 ± 25.9
$PaCO_2$ (mmHg)		
Baseline	44.0 ±9.4	41.2±11.6
30th minute	51.5 ± 9.5	41.3±11.9
60th minute	51.0± 9.0	47.0± 19.1
Base deficit		
Baseline	3.6±2.8	2.7 ± 3.1
30th minute	13.9 ± 2.0	20.7 ± 3.9#
60th minute	9.6 ± 0.6	24.6 ± 6.8#

Table 3: Mean survival in "THAM" and Normal Saline solution groups

	THAM Group	Normal Saline Solution Group
Lifetime (in minutes)	114.5 ±30.5	67.0 ± 14.1

Discussion

In the present experimental metabolic acidosis rat model created by intragastric administration of HCL, we found that the treatment with intravenous THAM decreased the mortality rate within the first 120 minutes compared to the control group treated with normal saline solution.

There is limited number of data about the effect of THAM on survival in the literature, but the potent buffering effect thereof is commonly emphasized [6-10, 12-14, 16-20, 22, 23]. Mortality following acid ingestion may be associated with the local or systemic effects of acid ingestion, or both[1]. We have merely focused on the systemic effects, so that this is the first and only study with such a design in the literature.

In our study, we used 18% HCL as the acidic agent, since this corrosive substance is widely used as a cleaning agent in houses and offices and can be accessed in almost every store in Turkey. Unfortunately, these substances are stored under inappropriate conditions and containers in houses, and in daily practice. They can be accidently ingested due to colorless, water-like appearance thereof. The local and systemic effects of the ingested corrosive substances on patients are among the serious causes of mortality.

For successful treatment of oral acid ingestion, the systemic and deep acidosis should be eliminated rapidly. In literature, there are a number of studies mentioning about the

effects of sulfuric and hydrofluoric acid. However, there are only a limited of number of studies on the effects of hydrochloric acid [1,5,9]). Nevertheless, there are also other publications indicating the efficacy of THAM administration for treatment of acidosis brought about by any factor (diabetic ketoacidosis; acidosis during cardiopulmonary resuscitation). In a paper of Taboada et. al., mentioned that their US military experience with THAM within their combat trauma population were unable to detect worse 30 day mortality associated with THAM administration [22]. On the other hand, we could not find any study regarding the effects of intravenous THAM for the treatment of acidosis experimentally created by acid ingestion on mortality in the literature.

The present study was fictionalized on a possible daily case. Accordingly, it was supposed that an individual accidently or intentionally (for suicide) drunk a corrosive substance presented to the emergency department within 30 minutes after the incident, and following the examination of patient, THAM treatment was initiated to ameliorate acidosis. For the design of this study we have benefited from two references[1,2]. In a study regarding the effects of $NaHCO_3$ and normal saline solution on mortality in an acidosis model, Kazancı et al.[1]) found that the treatment with $NaHCO_3$ increases the mortality. In that study, arterial blood gas values at 20th, 40th and 140th minutes were checked to detect possible changes in metabolic table, and unlike the current literature, intravenous $NaHCO_3$, a known treatment method, was used for the treatment of acidosis.

Eray et al.[2] used an experimental rat model with nitric and hydrochloric acid, and showed the development of acidosis in rats 30 minutes after the administration of hydrochloric acid. Rats were followed-up for only 30 minutes and acidosis was not treated. Unlike the abovementioned studies, we planned to observe the effect of THAM treatment on rats with experimentally produced metabolic acidosis in the present study. THAM is a biologically inert amino alcohol with a low toxicity and ability to buffer CO_2 and acids both in vivo and in vitro. At 37°C, the pK (the pH value at which weak acids and bases in solutions are ionized by 50%) of THAM is 7.8, rendering it a more effective buffer than bicarbonate in the physiological range of blood pH. THAM is a proton acceptor. Stoichiometrically, each molecule captures one proton [6-7].

In our study, we observed that the pH in arterial blood gas at 60th minute in THAM group was significantly increased after acidosis. In a study carried out by Schneiderman et al.[13] with newborn piglets, THAM treatment has been shown to be effective in normalization of pH in respiratory acidosis. Also, in a study performed by Sirieix et al.[14] with albino rabbits, it was shown that THAM acts as a good buffer for correction of pH in acidosis in an isolated heart model, and a combination composed of bicarbonate and THAM gives even better results in correction of pH.

Kazancı et al.[1] didn't find any significant difference for pH values between normal saline solution and $NaHCO_3$ groups. Rehm et al.[19] showed that both $NaHCO_3$ and THAM increased the pH value in a study on comparison of $NaHCO_3$ and THAM in acidosis treatment. Similarly, Sun et al.[15] compared three different treatment approaches as HCO_3, Carbicarb and normal saline solution in a model of rats with respiratory and metabolic acidosis secondary to asphyxia, and recommended the use of Carbicarb for acidosis treatment instead of HCO_3 due to the observed insignificant increases in blood pH value in HCO_3 group. In a paper by Marfo et al.[10], it was concluded that THAM is a better buffering agent compared to $NaHCO_3$ for treating severe lactic acidosis since it generates serum bicarbonate and reduces the level of CO_2 in arterial blood.

In a study carried out in our clinic by Bolatkale et al.[11], we found that the treatment with THAM prolonged the survival of rats with metabolic acidosis created by intragastric administration of methanol compared to the treatment with $NaHCO_3$. In other words, the data obtained from our study was consistent with the present literature.

Although THAM is mentioned as an agent that have an ability to decrease blood CO_2 levels in conditions with impaired CO_2 excretion (such as acute respiratory distress syndrome and heart failure)[9-11,20], we observed a moderate increase in CO_2 levels following THAM treatment, and considered this moderate increase as mostly associated with respiratory factors given the time passing from the moment of drug administration to the moment of last observance for blood gas value. In a study regarding the effects of Carbicap, THAM and $NaHCO_3$ on dogs during cardiopulmonary resuscitation, Weinberger et al.[16] showed that THAM markedly decreased CO_2 levels. This finding is contrary to our findings. The method adopted by Bar-Joseph et al. was different from our study method, and the dogs in the study have been intubated and ventilated whereas the rats in our experiment have been allowed to breathe spontaneously. This contradiction may be the result of the abovementioned difference. According to Taboada, Tris-Hydroxymethyl Aminomethane (THAM) has been proposed as an alternative or adjunctive therapy for refractory acidosis in the setting of combat trauma. THAM is an amino alcohol that buffers carbon dioxide. It is a weak base that has been used as a buffering solution in various settings that have included respiratory failure, cardiac failure, renal tubular acidosis, brain injury, diabetic ketoacidosis, malignant hyperthermia, permissive hypercapnia, and drug intoxications [8,9,10,11,12,13]. THAM works by liberating native bicarbonate as a buffer to correct the patient's acidosis. THAM has a pH of 7.8, which makes it a more effective buffer than bicarbonate, the latter having a lower pH of 6.1[22]. In an experimental study done by Höstman et.al., of permissive hypercapnia in a porcine lung lavage model shows that intravenous infusion of THAM increased BE and bicar-

bonate concentration, normalized pH, and decreased PaCO2 during the infusion. After a prolonged infusion, however, pH decreased to values similar to those in controls owing to a rebound PaCO2 increase. Despite a similar low pH and a higher PaCO2 compared with controls, the PVR remained low in the THAM group. No major signs of augmentation of lung injury by THAM were found[23].

As a summary, we observed that the treatment with intravenous THAM decreased the mortality of rats within the first 120 minutes compared to the control treatment with normal saline solution.

Conclusion

THAM is not available in the medical market of Turkey. We supplied the vials utilised in the present study with our own means from Norway. $NaHCO_3$ has been identified as an agent increasing mortality in acidosis treatment both in a study carried out in our clinic and some others, whereas THAM has been identified as an agent with an opposite effect in our study and also in anothers.

We anticipate that, if the same or similar results are obtained from the future studies on THAM with different models, the Ministry of Health, the Emergency Medicine Associations and the Professional Chambers by referring to our study may make it possible to import THAM for Turkey to be used for the treatment of patients with metabolic acidosis.

Limitations of Our Study

1. Mortality following hydrochloric acid ingestion may be associated with the local or systemic effects of acid, or both. We have merely focused on the systemic effects. The relationship between the local effects of hydrochloric acid ingested accidently or intentionally and the mortality can be examined in a further study.
2. In our study, rats were allowed to breathe spontaneously. We could have preferred to get the respiration of rats under control by intubation, thereby excluding the role of respiration in development of acidosis.
3. We have merely focused on the systemic effects, so that this is the first and only study with such a design in the literature. The relationship between the local effects of acid ingested accidently or intentionally and the mortality can be examined in a further study.

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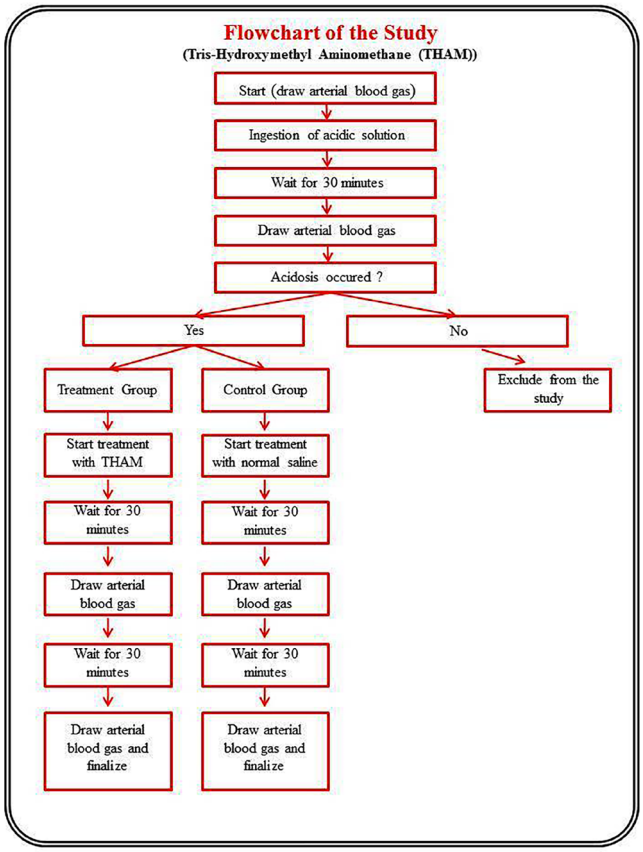

Figure 3: Flowchart of the study

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