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EFFECT OF SODIUM BICARBONATE AS A PREMEDICATION ON INCREASED CEREBRAL RESISTANCE TO ACUTE HYPOXIA

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Abstract

Background: Sodium bicarbonate injection can prevent brain trauma and serious internal problems. Since brain neuronal damage can be caused by an acute event such as hypoxia or cardio-respiratory arrest, prevention of severe acidosis can protect brain cells.

Methods: We used Mus Masculus and BALB / C mice weighing 25 -35 g, aged 8 to 12 weeks old, from the Shohada-e-Tajrish Laboratory Animal Center, Tehran, Iran. Sodium bicarbonate (SB) (4meq / kg) was injected to the mice at different times and the rate of immobility and respiratory arrest induced by acute hypoxia was measured.

Result: In the study group, we first developed acute hypoxia inside the anesthesia chamber and completed hypoxia by adding CO2. The experimental group underwent acute hypoxia, and showed slightly longer resistance than the control group. Bicarbonate (4meq / kg, IP) was injected to animals 60 min, 6 h, 12 h, and 24 h before acute hypoxia.

Conclusion: In this study, SB at doses above 4meq / kg had a significant effect on hypoxia and led increased resistance to acute hypoxia.

Keywords: Anesthesia**,** premedication, cerebral resistance, acute hypoxia, sodium bicarbonate

INTRODUCTION

Premedication before surgery and anesthesia play an important role in maintaining health, having a successful surgery and shortening the recovery time (51). For example, sodium bicarbonate injection can prevent brain trauma and serious internal problems (51). Since brain neuronal damage can be caused by an acute event such as hypoxia or cardio-respiratory arrest (52), prevention of severe acidosis can protect brain cells. Therefore, PH-dependent defense mechanisms have always been important as the primary mechanism against acute and chronic oxidative reactions to prevent brain injury (53).

Acute hypoxia is always present in a newborn, so it is advisable to take into consideration this measure 48 hours before birth (54). On the other hand, prevention of brain injury is closely related to time of bicarbonate injection (53). In this study, bicarbonate 8.4% was prescribed as a premedication 30 minutes before acute hypoxia, and it was hypothesized that longer hypoxia resistance could be achieved if an acute hypoxia event occurred and that more favorable conditions could be achieved if an anti-acidosis agent is used and evaluate the effect of bicarbonate on the resistance of mice and its consequences.

1.2 Materials and Methods:

We used Mus Masculus and BALB / C mice weighing 25 -35 g, aged 8 to 12 weeks old, from the Shohada-e-Tajrish Laboratory Animal Center, Tehran, Iran. Animals were randomly assigned to study groups. All groups were kept at a temperature of 21-23 °C for under 12 h light and 12 h. Interactions and injections were performed between 11:00 a.m. and 4:00 p.m. by a skilled person who worked with laboratory animals.

Standard conditions with maximum convenience and minimum stress and annoyance for animals equally and in compliance with the laboratory animal care guide (National institutes of health publication 80-23, rivisel 19978) and laboratory animal protection laws used in scientific projects (Directive 2010/63, EU) and approved by Guide for the Care and Use of Laboratory Animals Animal Work Guide issued by the Vice Chancellor for Research of the Ministry of Health of Iran.

2.2 Medications

The medications used in this study included sodium bicarbonate (Pharmaceutical Co. Rasht, Iran, 8.4%), L. Name- L. Argenine, (Sigma, St. Louis, Mo, USA), Ketamine, STEROP-Belgium Co., N2O, O2, CO2, and Dextros (produced in Iran). Medications with a maximum dose of 5 cc / kg were injected intraperitoneally (IP) diluted from a few days to half an hour before acute hypoxia, and the drug dose was determined based on previous studies (49-50).

2.3 Treatment

The control group received a maximum of 5 cc / kg of sterile water infusion.

Animals in all groups were randomly grouped and drugs were divided by drawing lots (55, 56). Prior to the start, we performed a tail-suspension test (TST)for each group, and excluded low-activity, sick, or very old animals that were unable to perform 50% + 1 of the test and replaced them with other animals that had a desirable ability.

Bicarbonate 8.4% was administered at the dose of 4meq / kg at 30 min, 24 h, 12 h, and 6 h before hypoxia as well as at different doses of 4, 6, 8, and 10 meq / kg 60 min before acute hypoxia (IP at a maximum of 5 cc / kg). Other medications included:

A non-selective NOS inhibitor drug, such as L.Name, at a dose of (51-52) 10 meq / kg

A selective NOS inhibitor drug such as 7.NI at a dose of 40 mg / kg (53)

A NO precursor inhibitor drug such as L.arg at a dose of 60 mg / kg (54)

An NMDA receptor inhibitor drug such as ketamine at a dose of 0.5 mg / kg (55)

Except for bicarbonate, other drugs were administrated for animal groups 60 minutes before acute hypoxia. The fluid volume of 5 cc / kg or 1% Tween 80 with sterile distilled water was selected to ensure lack of difference in the groups and control mood effects in the control group 60 min before acute hypoxia intervention.

4.2 Mood tests (Tail tests):

There are two types of mood tests: F.S.T and Tail test that assesses the animal's mood status. We chose the Tail Test in the present study and determined the mood status of the animal before and after interventions and examined the extent of stress and changes caused by acute hypoxia. This test was proposed in 1985 (14). In this test, the mouse is suspended from the tail by a hook in a container of diameter 20 cm and height 15 cm. The animal's mood status is calculated by a chronometer based on the animal's mobility and immobility in 360 seconds. The results can investigate the effects of medications, depression, behavioral disorders, and sexual arousal.

1-4-2 Anesthesia machine, Anesthesia box chamber

Anesthesia machine with vaporizer and oxygen flowmeters and N2O are connected to the Anesthesia Box or anesthesia chamber by an interface.

2-4-2- Anesthesia box chamber

Anesthesia box chamber is a container 31cm long and 31cm wide and 35cm high. The anesthesia chamber is positioned upright in front of the removable sliding wall that is used to open and close the inlet chamber of oxygen and other gases and can be opened and closed with the psoas valve. This chamber is the site of induction of anesthesia with gas or intravenous anesthesia with oxygen used in this study to induce anesthesia and acute hypoxia.

2-5 Statistical Analysis

All data obtained in this study were evaluated on average by adding and subtracting S.G.M. Specific statistical considerations of T.Test were used to evaluate the two groups. SPSS software and two-way ANOVA were used to carry out inter-group comparison and were followed and evaluated using Tukey's post-hoc test. P-values<0.05 are usually acceptable.

2-6 Acute hypoxia in animals

We introduced the animals to the anesthesia chamber based on their grouping. We first released oxygen and N2O into the anesthesia chamber at a ratio of 2:8 (80%:20%), and changed the percentage of oxygen: N2O to 8%:92% 4 minutes later.

Eight minutes after the process, the oxygen tube was separated, and 1% CO2 was added to the chamber. Time of immobility, drowsiness, and respiratory arrest were recorded for each animal. When the animal had a respiratory arrest, it was removed from the box from the sliding valve and resuscitated with pure oxygen. Recorded times were used for statistical analysis. Time to wake up from the moment of being reattached to the oxygen tube re to mild activity and movement was also recorded. After 60 minutes, we performed mood tests for each animal in each group separately. Monitoring during acute hypoxia was performed with observation of clear plastic chamber and listening to the heart and lung using a neonatal green stethoscope.

3. Results

3.1 Effect of sodium bicarbonate on time-dependent acute hypoxia and its injection in adult mice

3.1.1 Figure 1-A shows the mode changes due to injection of bicarbonate at different times. Sodium bicarbonate (SB) (4meq / kg) was injected to the mice at different times and the rate of immobility and respiratory arrest induced by acute hypoxia was measured. In the study group, we first developed acute hypoxia inside the anesthesia chamber and completed hypoxia by adding CO2. The experimental group underwent acute hypoxia, and showed slightly longer resistance than the control group. Bicarbonate (4meq / kg, IP) was injected to animals 60 min, 6 h, 12 h, and 24 h before acute hypoxia. Mice injected 24 h and 12 h before acute hypoxia showed similar reactions to the control group, with no changes in immobility and respiratory arrest status. SB injections 6 hours before acute hypoxia caused a slight change in mean resistance to acute hypoxia but was not statistically significant (Table 1).

Table 1: Animal's reaction to acute hypoxia by injecting different SB doses

F	P	Drugs
7.55 = 9.13	P<0.05*	**30 min** Bicarb 4 meq /k g
7.55 = 8.12	P> 0.05	**6h** Bicarb 4 meq /k g
7.55 = 8.04	P> 0.05	**12h** Bicarb 4 meq /k g
7.55 = 7.56	P> 0.05	**24h** Bicarb 4 meq /k g
7.55 = 7.55		Control

SB injection (4meq / kg) 60 min before acute hypoxia increased the mean duration of resistance to acute hypoxia, and the mice remained in the chamber longer until the incidence of respiratory arrest that was statistically significant (P< 0.05). In each group, 6 samples were tested.

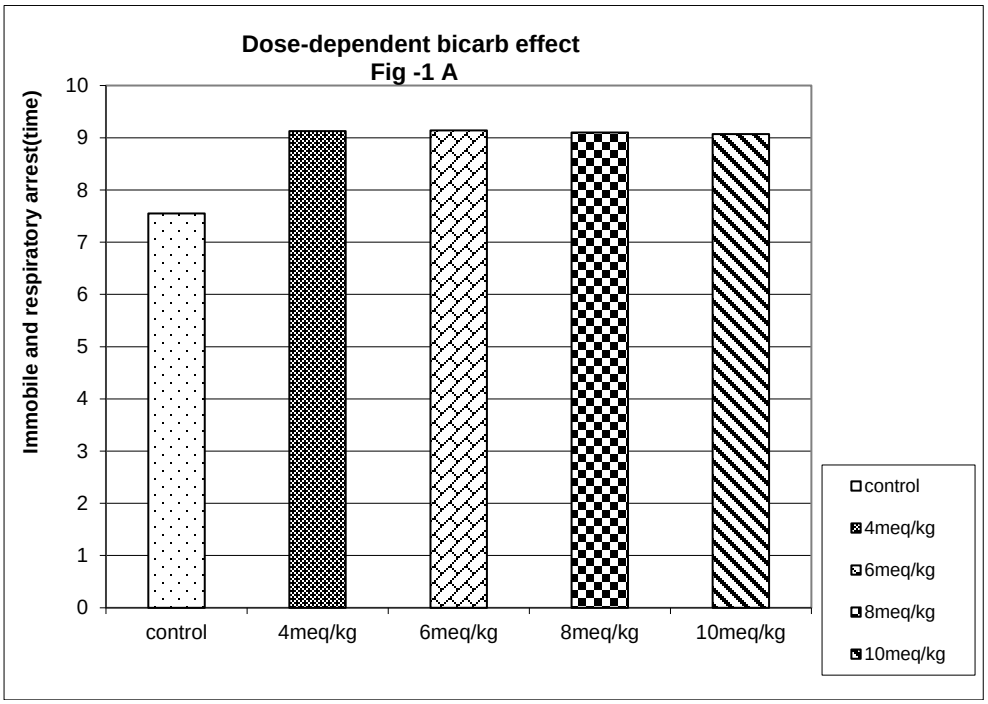

Figure 1-A: Changes in animals due to intraperitoneal SB injection at different doses

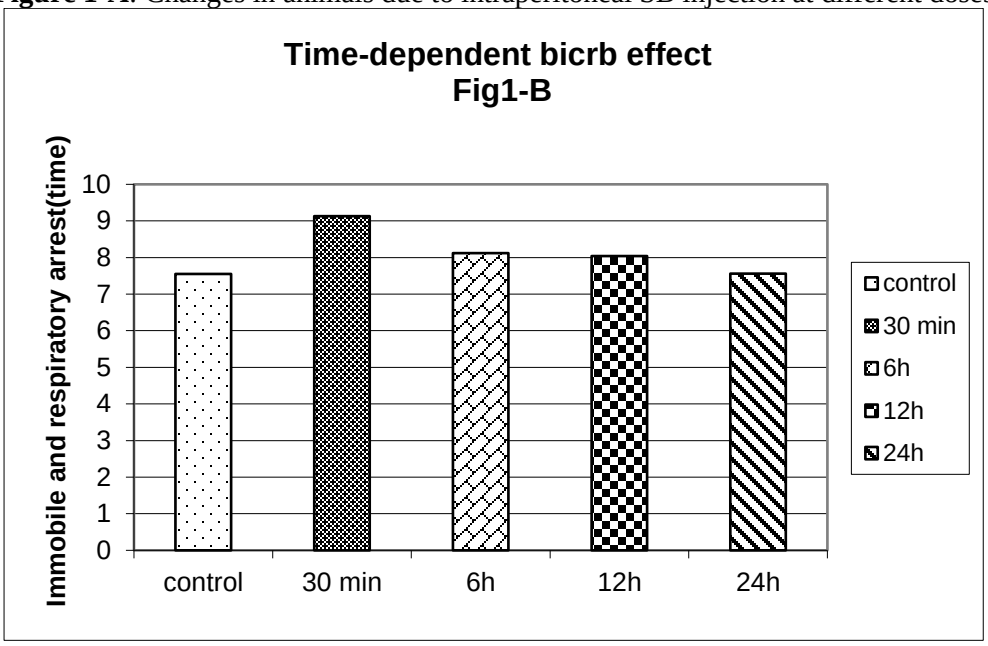

Figure 1-B shows the dose-dependent effects of SB over time when SB 4.8% was injected at

Doses of 4, 6, 8, and 10meq / kg 60 min before acute hypoxia. We can see that the resistance to acute hypoxia increased at all doses and the time to return to normal was faster and statistically better than the control group (P<0.05). The figure also showed increased activity and increased resistance under hypoxia at all doses occurred at longer time in the experimental group than control group (Table 2).

Figure 1-B: Dose-dependent effects of SB at different times

Table 2: Statistical calculation of groups in terms of P and F

F	P	Drug's

7.5 5 = 9.15	P< 0.05*	Bicarbonat 4meq/kg
7.5 5 = 9.14	P< 0.05*	Bicarbonat 6meq/kg
7.5 5 = 9.10	P< 0.05*	Bicarbonat 8meq/kg
7.55 = 9.7	P< 0.05*	Bicarbonat 10meq/kg
7.5 5 = 7.55		Control

*P <0.05 was statistically significant in all studies.

However, the thing that was statistically in significant was the fact that time deceased at high SB doses, but it was still significantly higher than the control group.

3.2.2 Interventional effect of nitric oxide system blockers

3.2.2.1 Effect of L.Name+ SB on resistance to acute hypoxia

One of the secondary methods to compensate for acute responses in the body is nitric oxide. In this study, we tested the effect of nonselective NO inhibitors such as L.Name plus bicarbonate on the adult mice resistance to acute hypoxia and plotted their effects in comparison to the control group in Figure 2. In the figure, SB (4meq / kg) and L.Name (10mg / kg) were injected to the groups 30 min before acute hypoxia and sterile saline, as the equivalent of these drugs, was also intraperitoneally administrated to the control group.

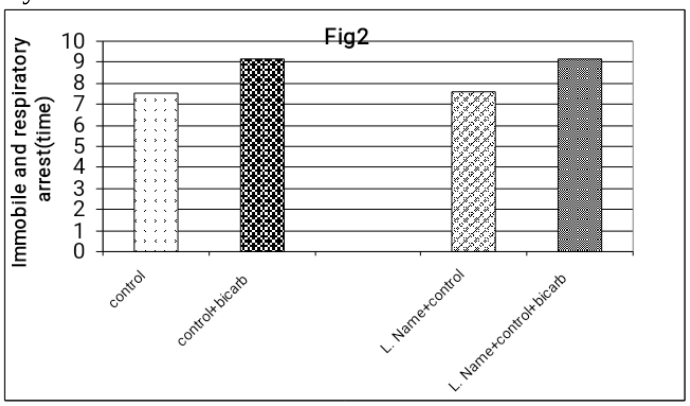

Figure 2: Effects of L.Name and bicarbonate on acute hypoxia

The figure shows that injection of SB + saline, bicarbonate, saline + L.Name (10mg / kg) had a significant effect on the resistance of mice to acute hypoxia and was statistically acceptable. SB (4meq / kg) led to an acceptable increase in the resistance (P<0.05) compared to the control group and the combination of both drugs caused increased resistance and longer negative and normal movements, which was statistically significant (P<0.001). Two-way ANOVA analysis and evaluation are shown in Table 3.

Table 3: Statistical comparison of groups in terms of P and F

F	P	Drugs
F<7.55= 9.13	P<0.05	Bicarbonat 4meq/kg
F<7.55= 7.59	p>0.05	L.Name 10mg/kg
F<7.55= 9.14	P<0.001***	Control+Bicarbonat+L.Name
7.55 = 7.55		Control

*** P <0.001 was statistically significant in all studies

3.2.2.2 Interventional effect of ketamine + SB against acute hypoxia

Ketamine is an N.M.D.A receptor blocking drug. N.M.D.A receptors have always been effective in acute reactions.

Figure 3 shows that ketamine alone has little resistance to acute hypoxia.

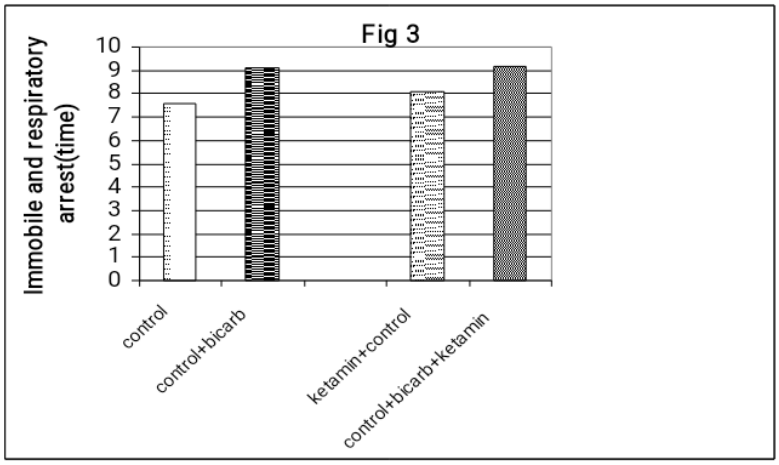

Figure 3: The effect of ketamine on acute hypoxia

Ketamine (0.5 mg / kg, IP) 60 min before hypoxia (IP) had no clear effect on anti-hypoxia resistance and was not statistically acceptable. However, ketamine + bicarbonate have a marked effect on the hypoxic resistance of mice ($P<0.01$). SB alone can induce resistance to acute hypoxia and its effects are statistically acceptable ($P<0.05$).

The two-way ANOVA analysis is shown in Table4.

Table 4: Statistical comparison of groups in terms of P and F

F	P	Drugs
F<7.55= 9.13	P<0.05*	Bicarbonat 4meq/kg
F<7.55= 8.11	P>0.05	Ketamin 0.5mg/kg
F<7.55= 9.15	p<0.01**	Control+Bicarbonat+Ketamin
7.55=7.55		Control

3.2.2.3 Interventional effect of NO precursor against acute hypoxia

As Figure 4 shows, SB (4meq / kg, IP) alone increases hypoxic resistance and is statistically acceptable. Also, accumulation of L.Arg and bicarbonate did not increase hypoxic resistance in mice.

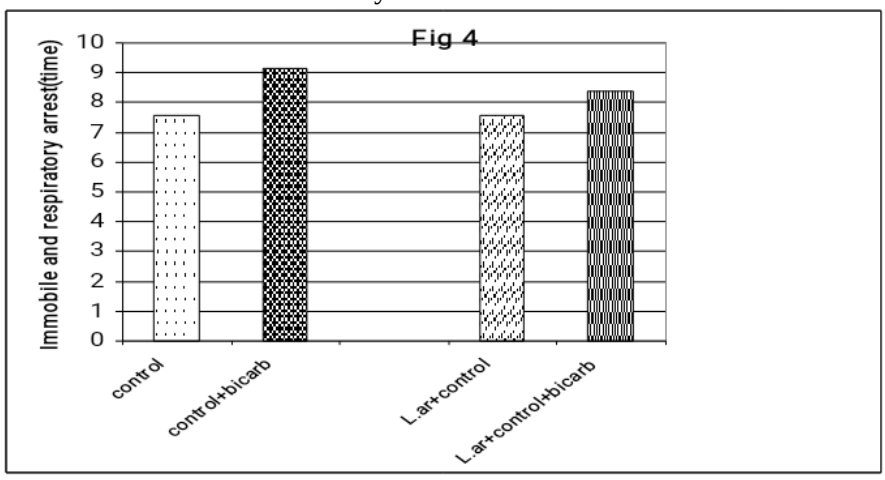

Figure 4: Effects of NO precursor on acute hypoxia

The ANOVA analysis is shown in Table 5.

Table 5: Statistical comparison of groups in terms of P and F

F	P	Drugs
F<7.55= 9.13	P<0.005*	Bicarbonat 4meq/kg
F<7.55= 7.59	P>0.05	L.Arg 60 mg/kg
F<7.55= 8.36	p>0.05	Control+Bicarbonat+L.Arg
7.55=7.55		Control

3.2.3.4 Interventional effects of 7.Ni against acute hypoxia

We tested bicarbonate interactions with a direct NO inhibitor against acute hypoxia called 7.Ni. In Figure 5 shows analysis of NO alone and NO + SB. SB alone increased resistance to acute hypoxia and increase such increase at a dose of 4meq / kg 60 minutes prior to acute hypoxia, which is statistically acceptable (P<0.05); however, SB + 7Ni (40mg / kg IP) had no statistically acceptable effect on acute hypoxia.

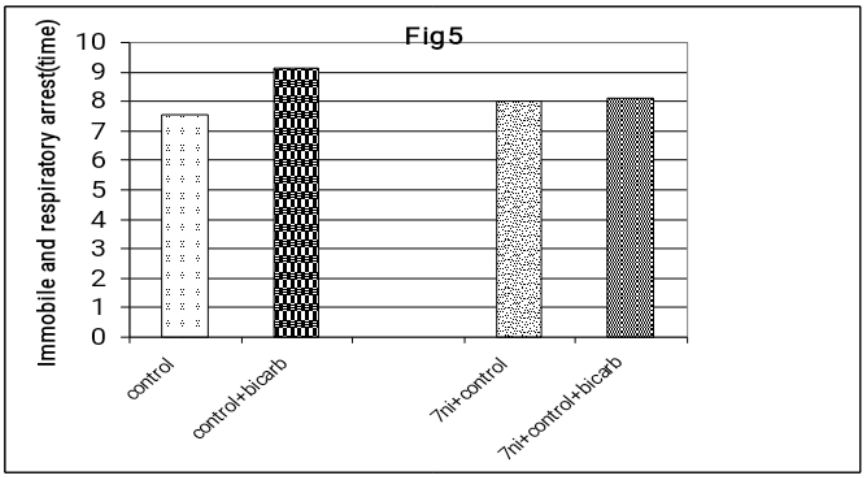

Figure 5: Interventional effect of NO on acute hypoxia

The two-way ANOVA analysis is shown in Table 6.

F	P	Drugs
F<7.55= 9.13	P<0.005*	Bicarbonat 4meq/kg
F<7.55= 8	P>0.05	7Ni 40mg/kg
F<7.55= 8.11	p>0.05	Bicarbonat+7Ni
7.55=7.55		Control

Table 6: Statistical comparison of groups in terms of P and F

DISCUSSION

Many studies have been carried out on the use of bicarbonate as an effective drug in the blood and fluid systems. Most of these studies have been conducted following an acute accident or changes based on indices of arterial gases and blood.

In a 2010 study, SB was used as an agent lowering intracranial pressure after traumatic brain injury (TBI). They used bicarbonate 8.4% without metabolic acidosis and intracranial pressure was markedly reduced and despite the increase in blood sodium nitrate, there was no change in the CO2 status of the patients (35). Another study investigated the effect of SB on the prevention of acidosis and destruction of mice's neurons after TBI and the results showed a decrease in brain tissue acidosis and a significant reduction in the destruction rate. In this study, we used SB as a premidication against acute hypoxia or any other oxidative factor that causes an acute problem in vital systems during surgery or anesthesia.

Based on previous studies, premidication was mainly used in non-cerebral patients, and there is little information about SB pretreatment in brain protection.

Inconsistent with the present study, a study showed that SB reduced metabolic acidosis in G.6.P.D and chronic kidney disease (CKD) patients (40, 41).

Previous studies proved that many factors contribute to the protection or destruction of an organ during stress, other than direct PH changes, such as NO pathways, physiologically acting NMAD receptors, and attempt to balance and protect the vital body system (21, 22, 23, 24, 25, 26, 27, 28).

Considering the above reasons, attempts were made in the present study to eliminate other intervening factors and to state that sodium bicarbonate is almost the most effective agent on PH signaling system at the time of acute hypoxia. We examined the nearly real effects of SB using direct NO inhibitors such as L.Name and NO direct inhibitors such as 7Ni, , and concluded that SB plus these inhibitors led to an increased hypoxic resistance and that mice endured longer in oxygen-free medium, which was statistically significant. The combination of SB +L.Name had a significant and positive effect on the resistance of mice to acute hypoxia.

In this study, SB at doses above 4meq / kg had a significant effect on hypoxia and led increased resistance to acute hypoxia. These results were also observed in a study by Giuseppe Pignatavo et al. who examined the effect of the same SB dose on cerebral ischemia after intraluminal middle cerebral artery occlusion (MCAO). In their study, the ischemia severity increases with time, and the cerebral ischemia rate remained nearly unchanged at the time of SB injection (42).

The present study investigated the useful time of SB injection before acute hypoxia and we injected SB (4meq / kg) 30 min, 6 h, 12 h, and 24 h before acute hypoxia and examined its effect on mice. The results of this test showed that SB (4meq / kg) 30 min before acute hypoxia had a clear and statistically significant effect on rat resistance. However, this effect did not exist or was much lower at other times. The results of our study and the study of Giuseppe et al. almost confirmed that a higher dose of SB below 3 hours had the greatest preventive effect of extensive ischemia induced by cerebral artery occlusion (42).

Caroline M. Sierra (2018) used L.Arg to treat metabolic alkalosis, which did not show a positive effect on acute hypoxia (43). The results of this study were consistent with the results of the present study and the use of SB +L.Arg couldn't increase resistance and did not increase any of the other parameters.

The present study investigated the effect of NMDA receptor antagonists such as ketamine alone and with SB on resistance to acute hypoxia. Bicarbonate alone and in combination with ketamine increased the tolerance and resistance of mice to acute hypoxia. Concurrent use of bicarbonate and ketamine has been reported in many studies, however, the aim of the present study was not to investigate prolonging the effects of each of the above agent, but to enhance resistance to hypoxia.

The function of the NMDA receptors and calcium channels stimulated the neural

pathways and NO synthesis, which acted as key regulators of NO activity in the central nervous system (CNS) (45, 46, 47).

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