Effects of Citicholine on respiration rate, Spo2, heart rate and rectal temperature during Thiopental intravenous anaesthesia in Canine model

Arash Ahmadi [1] , Soroush Mohitmafi [*,2]

[1] Faculty of Veterinary Medicine, Karaj Branch, Islamic Azad University, Karaj, Iran
[2] Department of Clinical Sciences, Faculty of Veterinary Medicine, Karaj Branch, Islamic Azad University, Karaj, Iran

*Corresponding Author: email address: smohitmafi@kiau.ac.ir, smohitmafi@yahoo.com (S.Mohitmafi)

ABSTRACT

Thiopental Sodium is an ultra short-acting barbiturate. Due to its redistribution characteristic, its first injection has a short term effect. In order to elongate its anesthesia duration, more injections are needed. As these additional injections extend the recovery length , weaken respiration and causes other dangerous effects; its repeated use is considered unsafe. Citicoline is a natural substance with neuroprotective effects. Regarding the various effects of citicoline on central nervous system which is the place where many anesthetics leave their effects, this research aims at studying the effects of citicoline on the anesthesia induced by Thiopental Sodium and also at Measuring the parameters such as heart and respiration rate,rectal temperature and SPO2. To do this,6 dogs were anesthetized by intravenous injection of 20 mg/kg of 2.5% Thiopental sodium . After the appearance of recovery signs, 250 mg of citicoline was slowly injected intravenously into the experimental dogs, and immediately the second injection of Thiopental sodium using the initial protocol was given. Before the second injection, 2ml of normal saline was intravenously injected into the dogs in the control group.Heart and respiration rate ,SPO2 and rectal temperature were then measured,recorded and statistically analyzed.Results indicated a significant increase in heart and respiration rate,an insignificant increase in SPO2 and an insignificant decrease of rectal tempreture in animals that had received citicolin before anesthesia by Thiopental Sodium.The results of this study can be used in predicting the vital signs of patients when taking these two drugs simultaneously.

Key words: Citicoline sodium; Thiopenthal sodium; Intravenous anesthesia; Heart rate; Respiration rate; SPO2; Rectal temperature; Canine model.

INTRODUCTION

Thiopental Sodium is an ultra short-acting barbiturate.Due to its great affinity for fat and muscular tissues it is quickly eliminated from the blood circulation before being metabolized by the liver. According to Redistribution phenomenon, Thiopental will gradually return to blood from the muscles while increasing its plasma level. Therefore, regarding the mentioned mechanisms, the first intravenous injection of thiopental has a short term effect after which the consciousness level of the patient quickly increases [1]. In order to extend the anesthesia duration of this drug, more injections are needed, and regarding its redistribution characteristic, its additional intravenous injections can lengthen the recovery time, weaken respiration and cause other dangerous effects thus making its repeated use unsafe [1]. Studies of Ko et al(1999),indicate the weakening effects of this drug on dogs'cardio pulmonary system[2]. Citicholine(CDP-choline) or (cytidine diphosphate choline) is a naturally occurring substance composed of two elements: choline and cytidine that are connected to each other by a diphoshate bridge. In body, this drug is converted into choline and the precursor phoshatidile choline. Choline is a vital neurotransmitter for brain intracellular communication and Phoshatidile choline is an important constituent of cellular membrane; [3,4,5].In human,this drug has been used in memory disorders, or brain ischemia caused by stroke [6,3,7,5] . Its protective effects on damage to optic nerve due to glaucoma has also been indicated [8,9].

Review of the recent literature by Hortado et al (2011), shows the protective and repairing effects of citicoline on brain[10]. Recent studies of Silveri et al also have shown that the use of this drug causes a significant increase in phosphor metabolites in cerebral cortex [11]. These studies both are an indication of neuroprotective effect of citicholine.

Baskaya et al in their animal studies have examined the neuroprotective effect of citicholine on rat model and shown a decrease both in brain edema and in blood- brain barrier breakdown after experimental traumatic brain injury (TBI) [12].

Injection of citicoline increases the secretion of surfactant in lungs[13]. Surfactant is a substance in lung that facilitates respiration. It also has a major role in improving lung functions in disorders of alveolar sacs. Although the weakening effects of thiopental in respiration has already been described[14], Ko et al have shown that the injection of thiopental alone or in combination with propofol will not have any effect on SPO2[2].

A study conducted by Hurtado et al (2005), showed that administration of citicoline will increase ATP and Glutamate in brain [15]. Another study made by Lorenzo and Secades (2006) revealed the effect of citicoline in activating biosynthesis of phospholipids in the brain neurons membrane. These two studies both indicate the effects of citicoline in increasing cerebral activities [16].

Citicoline also causes an increase in brain dopamine level which in turn can increase cerebral function [13]. Regarding the various effects of citicoline on the functions of central nervous system, the place where many anesthetics leave their effects , this research intends to study the effects of citicoline on the anesthesia induced by Thiopental Sodium and the changes occurred on the parameters such as heart rate, respiration rate, SPO2 and rectal temperature in Dogs.

MATERIALS AND METHODS

In this research, six male dogs in the age range of 2 to 4, and weight range of 22 to 28 kg were used. The dogs were all kept in individual cages, in equal conditions and had standard nutrition. All the 6 dogs were first considered control group and then, after two weeks when the drug eliminates completely, they were considered experimental group.

After transferring the dogs to the operation room and weighing them to determine the dose of the drug, an intra - venous catheter was inserted into the cephalic vein of the animals; then after a lapse of 30 minutes (in order to decrease their stress) they were anesthesized by a slow intravenous injection of 20mg/kg of 2.5% Thiopental sodium solution (Sandoz-Switzerland).

After observation of the recovery signs , in experimental group, 250 mg citicoline (Tidicholine Sodium 250 mg/2ml, Tolid-Drau Company,Tehran,Iran) was slowly injected intravenously and then immediately the second injection of thiopental sodium was performed using the initial protocol.

In control group, before the second injection of thiopental sodium, 2ml of normal saline was injected intravenously. It should be mentioned that in all phases of the experiment , the time interval between the righting reflex disappearance and its return in head and neck region was considered as the " duration of anesthesia". During the experiment, all parameters such as heart and respiration rate,rectal temperature and SPO2 in both groups were measured by a pulse-oxymeter instrument (Surgivet, USA) and recorded once every five minutes for 45 minutes. The data recorded for both experimental and control groups, were evaluated and analyzed by comparing the means (SPSS software, version 18) at a significant level of $P<0.05$.

RESULTS

The results were presented as Means ±SEM and P values in table 1. The comparison between the means of heart and respiration rate, rectal temperature and SPO2 in control and experimental groups was also shown in Graphs 1 to 4.

Table1. 1 Changes in the means of heart and respiration rate, SPO2 and rectal temperature in control and experimental groups.

Parameters	Groups	N	Mean ± SEM	P Value
Respiration Rate	Control	6	12.1167±0.30355[a*]	0.000
	Experimental	6	14.9500±0.59964[b*]	
SPO2	Control	6	85.9167±0.60706[a]	0.115
	Experimental	6	87.3500±0.66843[a]	
Heart Rate	Control	6	117.5000±2.87474[a*]	0.000
	Experimental	6	139.6167±4.53717[b*]	
Temperature	Control	6	37.4033±0.08919[a]	0.134
	Experimental	6	37.2300±0.07254[a]	

*Different words (a-b) indicating a significant difference.

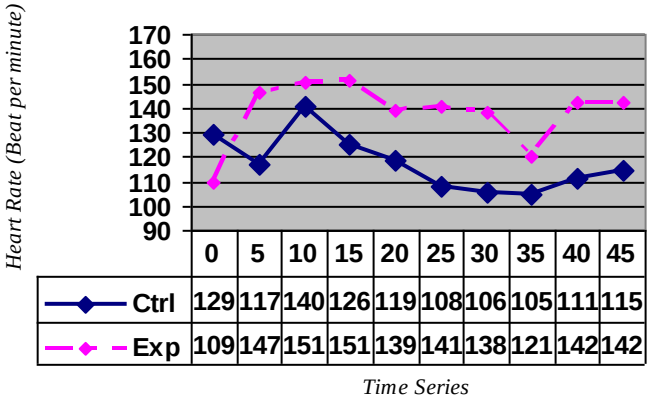

Figure 1. Changes in the means of HeartRate in control and experimental groups during the studied periods,indicating a significant difference between the two groups.

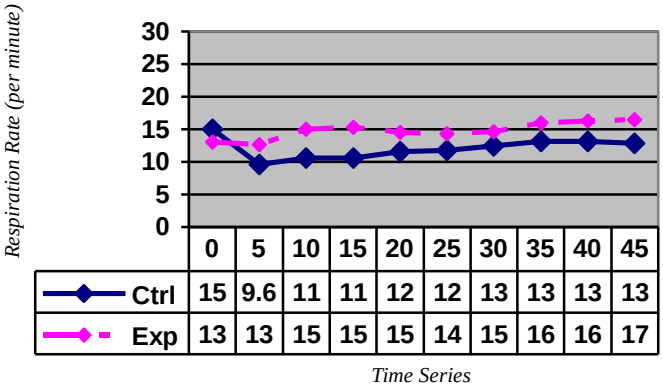

Figure 2. Changes in the mean of respiration rate in control and experimental groups during the studied periods,indicating a significant difference between the two groups (p .<0.05)

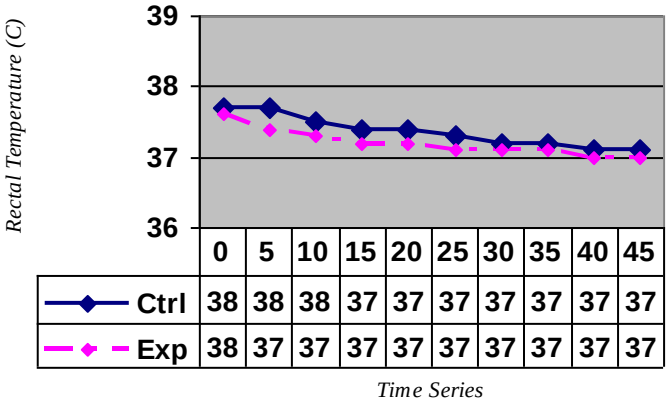

Figure 3. Changes of rectal temperature in control and experimental groups duringthe studied periods,indicating an in significant difference between the two groups.

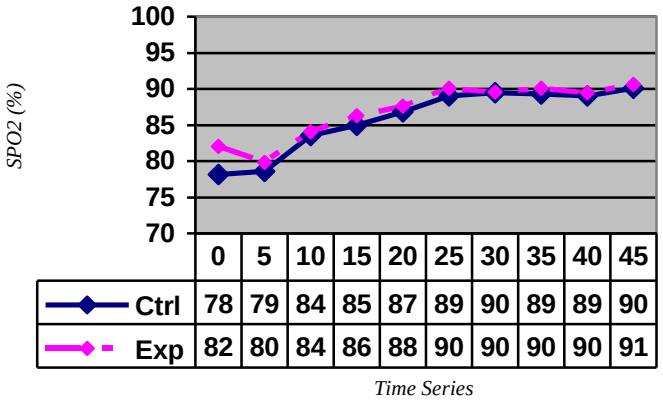

Figure 4. Changes in the SPO2 mean in control and experimental groups during the studied periods,indicating an insignificant difference between the two groups.

DISCUSSION

This research was performed to study the effects of Citicholine Sodium on the anaesthesia induced by Thiopental Sodium and the changes occurred on the parameters such as heart rate , respiration rate, Spo2 and rectal temperature. In the present study after injection of Thiopental an increase was seen in the heart rate of the dogs in control group. Haskins et al (1991) in their research on the effects of Thiopental on respiratory and cardiopulmonary systems found out that injection of thiopental can increase heart beat rate for 60 minutes after injection, but then the heart beat returns to its previous condition[13]. The findings of present research showed that an injection of Thiopental could produce similar changes in the heart beat of the dogs. In experimental group, after injection of citicoline ,a noticeable increase was seen in the heart beat.And this increase continued to escalate.Considering these results and those obtaind in research done by Jambou etal , we can attribute this type of increase to the effects of Citicoline in Adrenaline secretion[13].

The research conducted by Jambou et al (2009) proved that citicoline can increase the level of Adrenaline and Nor-Adrenaline in blood , and Dopamine in Brain[13] which are responsible for an increase in Heart beat.Some of the findings of present study confirm, to a high degree, the results of the research conducted by Jambou etal.

In 1999, Ko et al in their study on the effects of simultaneous injection of thiopental and propofol on SPO2 in dogs found out that though the weakening effect of thiopental on respiration has been proved, its injection alone,or combined by propofol , will not have any effects on Spo2[2].Similar results have been reported in a paper published by Bhutada et al(2000) [18].

In present research,after injection of thiopental into the dogs in control group, an increasing Spo2 was seen. Regarding the negative effects of thiopental on respiratory system, this increase seems to be somewhat unexpected. In experimental group, after citicoline injection, except for the first 5minutes during which Spo2 was decreasing, in the next 40 minutes it was continuously increasing.Although the level of Spo2 in experimental group was generally higher than that in control group, this difference was not statistically significant.

An intresting point in the study conducted by Jambou et al (2009) is the increase of Surfactant in lungs after administration of citicoline [13].Therefore the increase of Spo2 can probably be explained by the effect of surfactant and the increase of the volume of lung due to this effect. In the present study, however no significant change indicating an increase of Spo2 caused by citicoline injection was seen.

As mentioned before , thiopental is a drug that weakens respiration. It can cause an apnea during or immediately after injection[16].This can explain the decrease of the average number of respiration of animals studied in present research.

This decrease , however, did not have a noticeable effect on the level of Spo2.In the review of the relevant literature, no other study examining the effect of citicoline on the number of respiration was found.

The result of present studty indicated that although the process or pattern of changes of rectal temperature in both groups was almost similar, in experimental group after injection of citicolin a slight drop in the body temperature was seen though it was, when compared with the body temperature of experimental group, very trivial. These findings have not so far been reported in any scientific sources and their explanation needs more researches on the pharmacokinetics of this drug as well as an investigation into the interaction of this drug with injecting anesthetics.

Pundit's studies(2008) indicate the effect of thiopenthal in the release of histamine[14] which can lead to hypothermia[19,20]. Therefore it can be concluded that the decrease in rectal temperature of the dogs in control group has been due to the release of the histamine caused by thiopenthal injection.

CONCLUSION

The findings of this research indicate a significant increase in the heart beat and respiration rate , an insignificant increase in SPO2 and an insignificant decrease in rectal temperature of the animals that had received Citicoline sodium before anesthesia by Thiopenthal Sodium.

These results can be used in predicting the vital signs of the patients when taking these two drugs simultaneously.

REFERENCES

1.Hall LW, Clarke K W, Trim C M, Veterinary anaesthesia, 10th ed., 2001 , W B Saunders pp: 126-127.

2.Ko JC, Golder FJ,Mandsager RE,Heaton-Jones T,Mattern KL.Anesthetic and cardio respiratory effects of a 1: 1 mixture of propotol and thiopental in dogs.J Am Vet Med Assoc.1999 Nov 1;215(9):1292-6.

3.Clark WM,Warach SJ,Pettigrew LC,et al.A randomized dose-response trial of citicoline in acute ischemic stroke patients. Neurology.1997;49:671-678.

4.Clark WM,Wechsler LR,Sabounjian LA,et al. A phase ||| randomized efficacy trial of 2000 mg citicoline in acute ischemic stroke patients. Neurology 2001;57:1595-1602.

5.Davalos A,Castillo J,Alvarez-Sabin J,et al. Oral citicoline in acute ischemic stroke: an individual patient data pooling analysis of clinical trials. Stroke 2002;33:2850-2857.

6.Citicholine monograph.Altern Med Rev.2008;13:50-57

7.Conant R,Schauss AG. Therapeutic Applications of Citicoline for Stroke and Cognitive Dysfunction in the Elderly:A Review of the Literature. Altern Med Rev.2004;9:17-31.

8.Grieb P,Rejdak R. Pharmacodynamic of citicoline relevant to the treatment of glaucoma. J Neurosci Res. 2002;67:143-148.

9.Parisi V,Manni G,Golacino G,Bucci MG. Cytidin-5'-diphosphocoline (citicoline) improves retinal and cortical responses in patient with glaucoma.Ophtalmology 1999 Jun;106(6):1126-34.

10.Hurtado O,Lizasoain I,Moro MA. Neuroprotection and recovery.Recent data at the bench on citicoline.Stroke.2011;42[suppl 1]:S33-S35.

11.Silveri MM,Dikan J,RossAJ,et al. Oral citicoline supplementation significantly alters phosphorus metabolites in the anterior cingulate cortex. Poster presented at Society for Neuroscience;November 4th,2007: San Diego,Calif.

12.Baskaya K.M.,Dogan A.,Rao M.A.,Dempsey J.R. Neuroprotective effects of citicholine on brain edema and blood-brain barrier breakdown after traumatic brain injury. J Neurosurg Vol. 92 Mar. 2000 448-452.

13.Jambou R,El-Assaad F,Combes V,Emile G.G. Citicoline(CDP-choline): what role in the treatment of complications of infectious diseases.The International Journal of Biochemistrey & Cell Biology.2009;41: 1467-1470

14.Pandit J. J., Intravenous anesthetic agents, Anaesthesia and Intensive Care Medicine. 2008; Vol. 9, Issue 4, Pages 154-159

15.Hurtado O.,Maria A. Moro,Cardenas A,Sanchez V,Fernandez –Tome P, Juan C.Lenza,Lorenzo P,Julio S.Secades,Lozano R,Davalos A,Castillo J,Lizasoain I.Neuroprotection afforded by prior citicoline administration In experimental brain ischemia:effects on glutamate transport.Neuro biology of Disease.2005;18: 336-345.

16.Secades JJ, Lorenzo JL- Citicoline: pharmacological and clinical review 2006 update. Methods find exp clin Pharmacol.2006 Sep;28 Suppl B:1-56.

17.Hasking SC, Patz JD,. Cardiovascular and respiratory effects of thiopental administration in hypovolemic dogs.Am.J.Vet.Res. 1991; vol.52(4),pp.576-80.

18.Bhutada A, et al,. Randomized controlled trial of thiopental for intubations in neonates.Arch.Dis.Child: Fetal.Neonatal. 2000 Vol.82(1)F34-F37,pp.34-37.

19.Green M.D , Cox B. , Loma P. . Sites and mechanisms of action of histamine in the central thermoregulatory pathway of the rats.Neuropharmacology1976;vol.15,issue 5,pp.321-24.

20.Shaw,G.G.Hypothermia produced in mice by histamine acting on the central nervous system.J Pharmacol 1971 Jun;42(2):205-214