

Effects of Citicoline Sodium on corneal reflex, anesthesia and analgesia duration after thiopental sodium injection in dogs- A preliminary report

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ABSTRACT

Citicoline is a natural substance with neuroprotective and repairing effects. It can also increase the phosphor metabolites in cerebral cortex. Regarding the various effects of citicoline on central nervous system, this research aims at studying the effects of citicoline on the Thiopental sodium anesthesia. Six dogs were anesthetized by intravenous injection of 20 mg/kg of 2.5% Thiopental sodium. After the appearance of recovery signs, both experimental and control groups received either 250 mg citicoline or two milliliter normal saline intravenously, immediately before the second injection of Thiopental sodium. Length of anesthesia, duration of analgesia and response to corneal reflex were measured, and statistically analyzed. Results showed a significant increase in duration of analgesia and a significant decrease in the length of negative corneal reflex in experimental group. Comparison of duration of anesthesia between the two groups showed no significant difference. These findings showed that using citicoline prior to Thiopental sodium anesthesia can improve brain function by decreasing the duration of lack of response to corneal reflex and also regarding the increasing effect of Citicoline on analgesia duration, the use of citicoline as a pre-anesthetic for Thiopental Sodium can probably be considered in the future studies.

Keywords: Citicoline sodium; Thiopental sodium; Anesthesia; Analgesia; Corneal reflex.

INTRODUCTION

Thiopental Sodium is an ultra short-acting barbiturate. Due to its great affinity for fat and muscular tissues, this drug 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* , 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 diphosphate 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]. Citicoline 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 *Hurtado et al* , 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]. Although the analgesic effects of cholinergic drugs have been known for years [13] , the use of acetylcholinesterase inhibitors is limited because of its many adverse reactions [14,15]. The recent studies by *Gurun et al* and *Rowley et al* have suggested that the local and systemic injection of choline is effective in decreasing acute pains after surgery [13,16]. Injection of citicoline increases the secretion of surfactant in lungs. Surfactant is a substance in lung that facilitates respiration. It also has a major role in improving lung functions in disorders of alveolar sacs [17]. Although the weakening effects of thiopental in respiration has already been described[18], 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* ,showed that administration of citicoline will increase ATP and Glutamate in brain [19]. Another study made by Lorenzo and Secades 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 [20].

Citicoline also causes an increase in brain dopamine level which in turn can increase cerebral function [17]. 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 Corneal reflex ,Anesthesia and Analgesia duration in Dogs.

MATERIALS AND METHODS

Animals

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.

Anesthesia induction method

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 anesthetized by an intravenous injection of 20mg/kg of Thiopental sodium-2.5% solution (Sandoz-Switzerland). In experimental group, after manifestation of righting reflex as recovery sign, 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.

Method of recording anesthesia parameters

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", and the time interval from lack of response to any painful stimulus to the return of pain was referred to as the " Duration of analgesia " . Painful stimulus was produced by a hemostatic forceps pinch on the interdigital skin, between third and fourth phalanges. Examining the corneal reflex was performed by contact of a cotton swab with corneal surface. The pain and corneal reflexes were measured and recorded every five minutes all through the unconsciousness.

Data analysis

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 presented as *Means ±SEM and P values in table 1*. The comparison between the

means of anesthesia duration, analgesia duration and corneal reflex in control and experimental groups was also shown in chart 1. The results of present study showed that injection of Citicoline before Thiopental Sodium can improve brain function by decreasing the duration of lack of response to corneal reflex, P value = 0.038 (Table 1). In addition, Lack of response to mechanical pain stimulus in dogs anesthetized by thiopental had increased in duration by administration of citioline, P value = 0.012 (Table 1). The injection of citicoline was expected to shorten the anesthesia duration. However the findings of this study indicate no significant difference in anesthesia duration between the control and experimental groups, P value = 0.985 (Table 1).

Table1. Mean \pm SEM of anesthesia duration, analgesia duration and corneal reflex in control and experimental groups.

Parameters	Groups	N	Mean \pm SEM	P Value
Anesthesia Duration	Control	6	68.83 \pm 6.749	.985
	Experimental	6	68.66 \pm 5.301	
Analgesia Duration	Control	6	30.00 \pm 3.991	.012
	Experimental	6	45.00 \pm 2.366	
Negative corneal Reflex Duration	Control	6	10.00 \pm 1.825	.038
	Experimental	6	3.33 \pm 2.108	

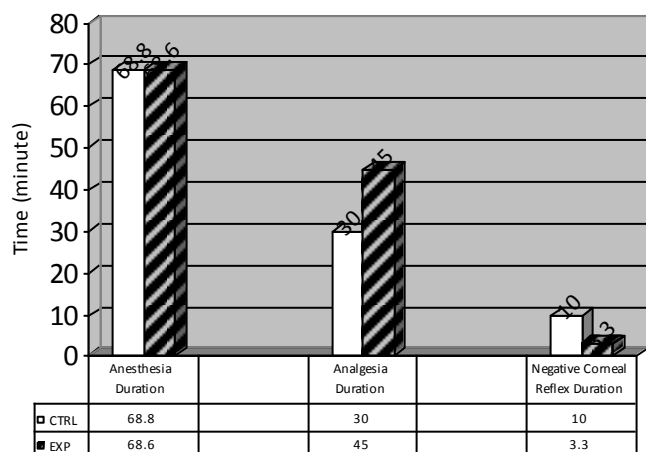


Figure 1. Comparing the means of Anesthesia duration, Analgesia duration and Corneal reflex in control and experimental groups.

DISCUSSION

This study was performed to evaluate the effects of citicoline on the anesthesia induced by Thiopental Sodium and the changes occurred on the parameters such as corneal reflex, anesthesia and analgesia duration in dogs. Duration of the response to painful stimulus in dogs receiving citicoline was significantly shorter than control group (table 1). This finding is similar to those of other researchers on the analgesic effect of citicoline on peripheral nerves. Gurun *et al* in their studies on the model of inflammation induced by chemical stimulation of rat paw, showed that administration of citicoline not only decreases inflammation and edema of the injured area but also causes an analgesic effect on the peripheral nerves in the damaged area. This study was based on the theory of the effect of citicoline in decreasing the level of inflammation precursor cytokines like TNF α [16].

Some other researchers raised some more reasons for the analgesic effect of citicoline on peripheral nerves; for example, Rowley *et al* in a study using behavioral patterns of pain feeling in rat, considered the interaction citicoline in functions of sodium and calcium channels as the causative factor of analgesic effect in peripheral nerves [13]. The results of present study, regardless of the pharmacokinetic reasons for analgesia caused by citicoline, showed that the lack of response to mechanical pain stimulus in dogs anesthetized by thiopental had increased in duration by administration of citioline. To the author's knowledge, such findings have not been reported yet, justifying the need for further studies about the effects of citicoline on other intravenous anesthetics. Thiopental Sodium, like other barbiturates, is an anesthetic with slight analgesic effect; therefore, to maintain surgical anesthesia, repeated administration is needed. On the other hand, repeating the intravenous injection of this drug will result in a longer recovery [1]. Although the findings of this study are in line with those of Gurun *et al* and Rowley *et al*, one cannot have a definitive idea about the general analgesic effect of citicoline in anesthetized dogs yet. The findings of present study showed that administration of citicoline leads to a decrease in

duration of lack of response to corneal reflex during anesthesia. In review of the literature, no other study reported similar finding; but studies on conscious rats, showed that citicoline can act as a stimulus for central nervous system. Review of literature by *Jambou et al* showed that citicoline increases dopamine in brain and leads to greater mental activities [17].

Moreover, the findings of *Baskaya et al*, indicated a decrease in edema due to a mechanical trauma to CNS in rats receiving citicoline. The doses used in this study were 100 and 400 mg/kg, and the results showed that the protective effect of citicoline on CNS, follows a dose-dependent pattern [12]. Similar studies also confirm the protective effect of citicoline on central nervous system. Findings by *Hurtado* showed that the administration of citicoline will increase the release of ATP and the amount of glutamate in brain[19].

In addition, *Lorenzo and Secades* revealed the effect of citicoline in activating the biosynthesis of phospholipids of neurons membrane. As there was no information about the dose suggested for the dogs, in review of the literature, in present study, the human dose of citicoline was used. Although in this study the probable toxic effects of this drug on different organs of dogs were not examined, no clinical evidence showing the use of overdose of the drug was seen either. Studies conducted by *Schauss et al* have reported the toxic effects of citicoline in rats at doses higher than 1000 mg/kg [21]. Although, not all aspects of the mechanism of the effects of thiopental Sodium as an intravenous anesthetic are known, this drug seems to act by increasing the response to GABA, decreasing the response to Glutamate and thereby causing a

decrease in neurons stimulation and eventually anesthesia[22].

Regarding the effect of citicoline on increasing brain metabolism [10,11,12], elevating Glutamate absorption and Dopamine release [17,19], the injection of citicoline was expected to shorten the anesthesia duration. However the findings of this study indicate no significant difference in anesthesia duration between the control and experimental groups.

CONCLUSION

Our findings indicate no significant differences in anesthesia duration, but significant differences in analgesia duration were found between experimental and control groups.

Nevertheless, any judgment about the effect of different doses of Citicoline on duration of anesthesia induced by Thiopental requires further studies. On the whole, bearing in mind the protective effects of Citicoline on brain, it seems that an injection of this drug before Thiopental Sodium can improve brain function by decreasing the duration of lack of response to corneal reflex, and also regarding the increasing effect of Citicoline on analgesia duration, the use of citicoline as a pre-anesthetic for Thiopental Sodium can probably be considered in future studies.

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