Research Article

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Clinical Assessment of Anesthesia Caused by Combinational Protocol of Acepromazine-Fentanyl-Ketamine in Dogs

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ABSTRACT

The purpose of the present study is the clinical assessment of anesthesia by adding fentanyl to ketamine and acepromazine in dogs and the clinical assessment of dogs during this anesthesia. In this study, 12 mixed-breed dogs, that weigh 20 -30 kg and are 2-3 years old, were selected and divided into two test and control groups. Anesthetizing of the test group is done by intramuscular injection of 0.2 mg of kg acepromazine; and intravenous injection of 0.1 mg kg of fentanyl and intramuscular injection of 20 mg kg of ketamine after 10 minutes. Anesthetizing of the control group is done by intramuscular injection of 0.2 mg kg of acepromazine; and intramuscular injection of 20 mg kg of ketamine after 10 minutes. One hour after anesthetizing both test and control groups, parameters such as: heart rate, respiratory rate, rectal temperature and clinical symptoms such as duration of analgesia and duration of anesthesia were assessed in 10-minute-interval periods. T independent test, ANOVA, and Tukey Post Hoc were used for the statistical analysis of the data. As the results show, the dogs' heart rate was increased in both groups without any significant difference ($P > 0.05$); however, the respiration rate in the experimental group was reduced significantly ($P < 0.05$). It has to be mentioned that two dogs suffered apnea during the injection of fentanyl and were returned to normal respiration after 2-3 minutes by CPR. A significant different ($p<0.05$) was observed in rectal temperature of the experiment group between first 10-minte-interval-period and last 10-minte-interval-period; moreover, a significant increase ($P<0.05$) was observed in the duration of analgesia and anesthesia. In this study, it was demonstrated that adding 0.1 mg kg of fentanyl to acepromazine and ketamine has a significant influence on the reduction of respiratory rate and the increase in the duration of analgesia and anesthesia; however, this addition does not have any significant influence on clinical symptoms of the dogs. Based on the results of this study, it can be suggested that this combination can be used as beneficial in the reduction of respiratory rate and the increase in the duration of analgesia and anesthesia.

KEYWORDS: Acepromazine; Dog; Fentanyl; General anesthesia; Ketamine

INTRODUCTION

Moderate anesthesia consists of soporific, relaxing and anesthetizing factors and for achieving the best result combinational protocol of multi-drug can be used. Ketamine Hcl or DL-2-Chlorophenyl 2-Metil amin Cyclohexane Hydrochloride is a unique injective anesthetizing drug which first entered human medicine in the year 1965 and was first introduced as an anesthetizing drug for cats in the year 1970. This drug is acidic, and its acidity is between 3.5 to 5.5. Immediately after the injection this drug is absorbed and distributed in all body tissues. The start of anesthetizing process is fast, but the throat reflexes will not vanish, and the rate of skeletal muscle will be increased in a way that it may be convulsive for dogs.

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This drug has a short-term and insignificant provocative effect on cardiovascular organs but sometimes it may have weakening effects on breathing. Also, it decreases vascular blood pressure in monkeys, but it increases it in dogs. In dogs it will cause increase of cardiovascular productivity and heart contraction power and decreases environmental resistance. In cats the start of anesthesia is after 3 to 5 minutes and anesthesia will last between 15 to 45 minutes and complete recovery from anesthesia will take 1 to 4 hours [1-3].

Fentanyl citrate is recognized with commercial names like Duragesic, Fundora, Instant l, Acted and Sublimize and is a derivative drug of Phenyl pyridine which is more fat-oriented that morphine [4,5]. This drug was first introduced by Paul Johnson in the year 1959 in newly established Johnson Pharmaceutical Laboratory. He performed evaluative tests on narcotic activities of patavine and succeeded to obtain the pharmaceutical structure of Fentanyl [6,7]. This drug is a complete agonist opioid with effect on Mo Kappa and Delta receivers. Anti-pain effect of Fentanyl in human is estimated as 100 times more than morphine and is considered as a drug with high level of mis consumption capability which is placed in the second pharmaceutical category [7].

Acepromazine Maleate is named structurally Acetyl promazine and is a derivative of phenothiazine and is highly used in veterinary medicine and can be applied in dogs, cats and horses according to FDA as a tranquilizer. Acepromazine is a yellowish, odorless, crystal powder drug with bitter taste. The powder of this drug will be melted in a temperature between 135 to 138 centigrade. Activities and applications of this drug is the same as its relatives, but the observing time of the symptoms is shorter in a way that tranquilizing effects can be observed in 10 minutes after consumption and 5 minutes after muscular injection [8].

Considering that today in injective anesthesia of dogs usually a combination of two or more drugs with anti-pain, anesthetizing, relaxing and tranquilizing effects simultaneously and considering that because using Fentanyl Citrate is not common among Iranian vets, thus the purpose of this study had been to evaluate the clinical characteristics of anesthesia caused by adding Fentanyl Citrate to combinational protocol of Ketamine- Acepromazine.

MATERIALS AND METHODOLOGY

Studied Animals: In this study 12 mixed-breed healthy dogs, that weighed 20-30 kg and are 2-3 years old were examined. The studied drugs in this research consisted on Acepromazine Maleate 2%, manufactured by Kelle-Belgium Company, Ketamine Hydrochloride 10% manufactured by Alfas a Company-Netherlands and 500 mgr. Fentanyl Ampoule, manufactured by boogeyman Pharmaceutical Company-Iran.

12 hours before anesthesia are dogs were on special diet and they only had water to drink. After weighing the animals were put in the surgery room for 30 minutes to become familiar with the environment and then the path of cephalic in frontal body organs of the experimental dogs were sterilized and installed at its determined placed. These dogs were first subjected to muscular injection of combined protocol of Acepromazine and ketamine and after one-week maintenance in equivalent nutritional and environmental condition they were subjected to injection of combined protocol of Acepromazine-Fentanyl-Ketamine.

Anesthesia in Control Group: Anesthesia using muscular injection of 0.2 mg for each kilogram of Acepromazine and after 10 minutes and muscular injection of Ketamine in an amount of 20 mg for each kilogram of body weight was performed. Anesthesia in Experimental Group: Anesthesia using muscular injection of 0.2 mg for each kilogram of Acepromazine and after 10 minutes and vascular injection of 100 micrograms for each kilogram of fentanyl and immediate muscular injection of 20 mg ketamine for each kilogram of body weight.

Measurement Method of the Studied Parameters: During one hour after anesthesia, in 10-minute intervals parameters such as heartbeat, breathe rate, body temperature, painful stimulation response and anesthesia duration were studied and registered. Any unexpected side effects such as convulsion, etc. (anesthesia report) were also registered in case of occurrence and the obtained data from each group were analyzed and compared. Evaluation of reacts toward painful stimulation by pressing the hand were also registered as presence or absence of any responses and pain level scaling as scaled as +1, +2 and +3 was avoided. The duration of anesthesia was also measured and registered as of the time of vanishing of head and neck writing reflexes till the time of its returning. Statistical Analysis of the Results: T test and variance analysis (ANOVA), and Tukey Post Hoc Test were used, and the meaningfulness of average differences were calculated based on $P < 0.05$.

RESULTS

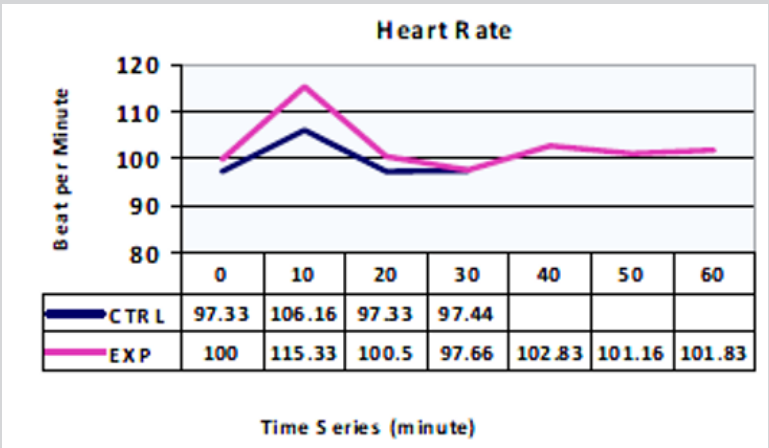

Figure 1: Heartbeat average changes in control & experimental group at studied times.

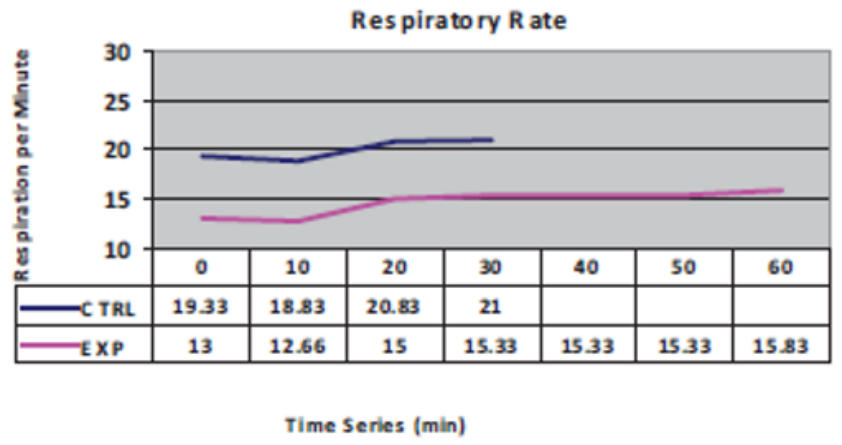

Figure 2: Breath rate average changes in control & experimental group at studied times.

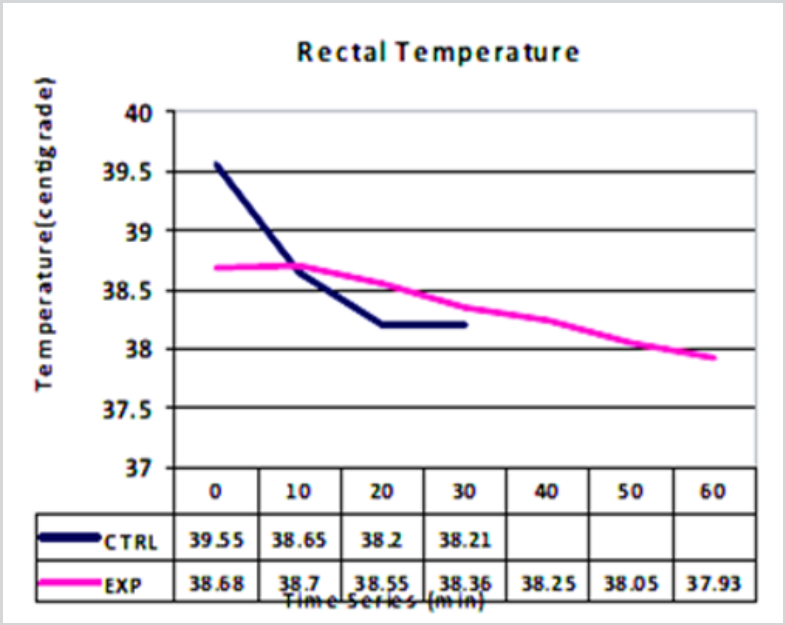

Figure 3: Rectal temperature average changes in control & experimental group at studied times.

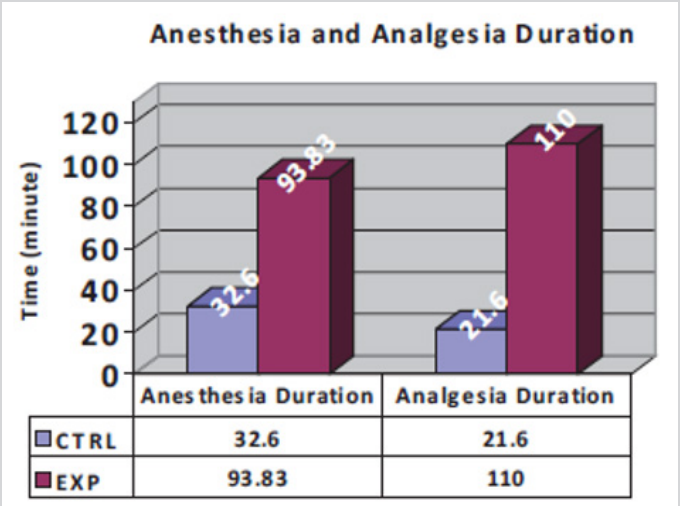

Figure 4: Comparison of anesthesia and numbness duration between control & experimental group at studied times.

Clinical results of the anesthesia caused by adding fentanyl to combination of ketamine and Acepromazine are indicated in Figures 1-4. It is worth mentioning that all of the dogs in the control group showed signs of returning from anesthesia before 40 minutes thus vital signs in this group were only measured and registered only till the 30th minute after anesthesia but in the experimental group registration and measurement of the data continued till the 60th minute after anesthesia. The process of changes in average heat beat, breath rate, body temperature, anesthesia and numbness duration and comparison of these quantities in control and experimental group at the studied times are respectively indicated in charts 1 to 4.

Statistical analysis results

The results of T statistical test for the purpose of comparing the averages of heart beat, breath rate and rectal temperature shows the meaningful difference of $P < 0.05$ in comparing the average breath rate between control and experimental groups but with respect to heart beat and rectal temperature there is no meaningful difference observed between experimental and control groups (Table 1).

Table 1: Independent T-test for the purpose of comparing the average of heartbeat, breath rate and rectal temperature between experimental and control groups.

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2 tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Heart Rate	Equal valences assumed	0.091	0.764	0.264	58	0.793	2.48413	9.40755	-16.34713	21.31538
	Equal valences not assumed			0.266	32842	0.792	2.48413	9.33104	-16.50349	21.47175
Respiratory Rate	Equal valences assumed	1.668	0.202	-3.612	58	0.001	-5.02381	1.39082	-7.80784	-2.23978
	Equal valences not assumed			-3.381	28.025	0.002	-5.02381	1.48578	-806718	-1.98044
Temperature	Equal valences assumed	3.12	0.083	-2.341	58	0.23	-43810	0.18716	-0.81274	-0.6345
	Equal valences not assumed			-1.806	20.498	0.86	-0.4381	0.24255	-0.94325	0.6706

The results of ANOVA statistical test for the purpose of studying the process of change in average heartbeat, breath rate and rectal temperature indicates a meaningful difference of $P < 0.05$ in the process of change in rectal temperature average at the studied time in the experimental group in a way that the results of Tukey Post Hoc Test shows the meaningful difference in rectal temperature at the beginning of anesthesia and 10 minutes after than with 60 minutes after anesthesia. There is no meaningful difference observed in changes in averages of heart beats and breath rate at the studied times in the experimental group (Table 2).

Table 2: Variance Analysis Statistical Test (ANOVA) and Tukey Post Hoc Test were used for analysis of the changes in average heartbeat, breath rate and rectal temperature at the studied times in the experimental group.

Descriptives								
	N	Mean	Stl. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Heart Rate Base Line	6	100	55.31004	22.58023	41.9557	158.0443	48	200
10 min	6	115.3333	50.74906	20.71822	62.0755	168.5912	68	200
20 min	6	100.5	31.0725	12.68529	67.8914	133.1086	72	140
30 min	6	97.6667	22.57137	9.21472	73.9795	121.3539	80	140
40 min	6	102.8333	24.50646	10.00472	77.1154	128.5513	76	144
50 min	6	101.1667	25.78695	10.52748	74.1049	128.2284	76	150
60 min	6	101.8333	25.20648	10.2905	75.3808	128.2859	80	150
Total	42	102.7619	33.58775	5.1827	92.2952	113.2286	48	200

Respiratory Rate Base Line	6	13	3.52136	1.43759	9.3046	16.6954	10	20
10 min	6	12.6667	6.53197	2.66667	5.8118	19.5216	6	24
20 min	6	15	6.63325	2.70801	8.0388	21.9612	10	24
30 min	6	15.3333	4.36654	1.78263	10.7509	19.9157	12	23
40 min	6	15.3333	4.58984	1.8738	10.5166	20.1501	10	23
50 min	6	15.3333	3.61478	1.47573	11.5398	19.1268	11	21
60 min	6	15.8333	3.97073	1.62104	11.6663	20.0004	11	22
Total	42	14.6429	4.67907	0.722	13.1848	16.101	6	24
Temperature Base Line	6	38.6833	0.27869	0.11377	38.3909	38.9758	38.2	38.9
10 min	6	38.7	0.28983	0.11832	38.3958	39.0042	38.2	38.9
20 min	6	38.55	0.36194	0.14776	38.1702	38.9298	38.1	38.9
30 min	6	38.3667	0.34448	0.14063	38.0052	38.7282	38	38.9
40 min	6	38.25	0.42778	0.17464	37.8011	38.6989	37.7	38.9
50 min	6	38.05	0.54314	0.22174	37.48	38.62	37.3	38.9
60 min	6	37.9333	0.55015	0.2246	37.356	38.5107	37.2	38.8
Total	42	38.3619	0.4747	0.07325	38.214	38.5098	37.2	38.9

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
Heart Rate	Between Groups	1200.952	6	200.159	0.155	0.987
	Within Groups	45052.667	35	1287.219		
	Total	46253.619	41			
Respiratory Rate	Between Groups	57.476	6	9.579	0.399	0.875
	Within Groups	840.167	35	24.005		
	Total	897.643	41			
Temperature	Between Groups	3.279	6	0.547	3.209	0.013
	Within Groups	5.96	35	0.17		
	Total	9.239	41			

The results of statistical T-test used for comparing the averages of duration of anesthesia period and numbness in control and experimental groups indicated a significant difference ($P < 0.05$) in comparison of average of anesthesia period and numbness between control and experimental groups in a way that duration of anesthesia and numbness in experimental group is significantly greater in comparison with the control group (Table 3).

Table 3: Independent T-Test for Comparing average duration of anesthesia and numbness periods between control & experimental groups.

Independent Samples Test									
	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval for Mean	
								Lower Bound	Upper Bound
Anesthesia Duration Equal variances assumed	3.888	0.077	6.253	10	0	61.16667	9.78122	39.37276	82.96058
Equal variances not assured			6.253	5.951	0.001	61.16667	9.78122	37.18499	85.14834
Analgesia Duration Equal variances assured	9.091	0.013	8.318	10	0	88.31233	10.61969	64.67119	11199547
Equal variances not assured			8.318	5.24	0	88.31233	10.61969	61.42439	11524228

DISCUSSION AND CONCLUSION

Using general anesthesia technique for different types of diagnosis and surgery methods is necessary. Although sometimes bad incidents will happen during anesthesia, but we can obtain a pre-designed guaranteed method for appropriate anesthesia depth and creating appropriate and stable conditions for the patient during anesthesia and surgery operation and easy and safe recovery [2].

HEARTBEAT RATE

Using Ketamine drug will result in an increase in cardiovascular outputs, average aorta pressure, pulmonary veins pressure, vascular central pressure and heartbeat rate because of stimulating sympatric nerves [3]. Acepromazine will also decrease blood pressure by affecting vague nerves and blocking alpha-adrenergic receiver but in continuing it is possible that the body would react in response to this change and pressure decrease [1,2]. Fentanyl will decrease the heartbeat rate by affecting the mu receivers and by stimulating the vague nerve. He time and intensity depend on the injective dose and plasma concentration of the variable matter [8].

Considering that Fentanyl is a drug with high effective power and high speed result it should have had made this effect immediately in the animal but practically by vascular injection of 500 micrograms of Fentanyl Citrate no decrease was observed in heart beat rate in experimental group dogs during the anesthesia period and no meaningful difference was created between control and experimental groups.

In the year Farer [8] studied using Acepromazine in 0.2 mg dose for each kilogram and ketamine in 10 mg dose for each kg among 13 studied dogs. The results indicated that injecting Acepromazine will meaningfully decrease the blood pressure and as a result injecting Sc ketamine will also meaningfully increase heartbeat rate. In a research made by Mendes [2] on combination of Propofol, Fentanyl, AL Fentanyl or Fentanyl for inside vascular complete anesthesia on cats, decrease of heartbeat, blood pressure, rectal temperature and breath rate were observed in all the treatments [9]. Also, Ilia performed a research on cardiovascular effects of high dose of narcotics along with low dose of anesthesia inhaling drug in comparison with inhaling drug alone in dogs. In this study when the prescribed plasmatic concentration would reach 71.7 nanograms in each ml, the quantity of MAC in loran decreased to 1.2 and heartbeat decreased meaningfully [10]. Also, during a research made by Rita in 1978 the effect of fentanyl with 5 microgram dose for each kg during the anesthesia period of Halothane gas on the heartbeat of dogs showed that using fentanyl with this dose will result in 10% decrease in heart beat rate during one hour study. Rita interpreted that approximately 90% of this state of fentanyl is because of increase in vagal efferent traffic from central neural system whereas only 10 and of it is as a result of weakening the sympathetic nerve tone [11]. Also, Loeb indicated that fentanyl can create an approximately individual activity on cardio vagal fibers which will result in change in heartbeat rate [12].

Breath rate

Comparing breath rate between control and experimental groups indicated decrease of breath rate in experimental group and meaningful difference between the two experimental and control groups. Ketamine muscular injection ordinarily does not have any effect on respiratory depression but in high doses and especially with vascular injection it is possible to observe this state in dogs [2]. Acepromazine has minor effects on breathing. Even it is possible that it may decrease the breathing rate a bit, but the volume of breathing is generally constant [2] and generally muscular injection of Acepromazine cannot create intense decrease in breathing during anesthesia. Thus, it seems that decrease in breath rate among dogs of experimental group is via direct effect of fentanyl drug on breathing control center in the brain stem which is created by being inducted on opioid receivers from mu type [1,8]. MU receivers are of two types, mu 1 receivers that will be resulted in numbness after being stimulated and m 2 which will result in an increase in vascular expansion, decrease of heart beat rate and breathing rhythm and the intensity of stimulation of this receiver and its consequent results will be subjected and dependent to the applied dose [1,8]. Thus, in the present study decrease of breathing rate in experimental group and meaningful difference between the two experimental and control groups is resulted by injection of fentanyl and its immediate effect on breathing center. During a research performed by Bailey [14] on fentanyl and its effect on dog's anesthesia in different doses of 125, 500, 750, 1000, 1500, 2000 and 3000 micrograms for each kg using unit-dose and vascular method. All the doses resulted in a significant decrease in heartbeat rate and breathing rhythm but none of the mentioned quantities resulted in producing apnea or increasing $PaCO_2$ to a level higher than 67 mm Hg [13].

Stamen studied 40 young and healthy volunteers for studying the breathing states after the effect of fentanyl and alfentanil in human with 1.5 and 3 micrograms doses of fentanyl for each kg and alfentanil of 7.5 and 15 micrograms doses for each kg and the results showed that low and high doses of fentanyl will meaningfully decrease the breathing rate respectively till 30 minutes and 80 minutes after the injection whereas no respiratory depression was created in low dose of alfentanil and only high dose of it resulted in a decrease in the breathing rate during 4 minutes after injection [14].

According to the research made by Tanaka the effect of fentanyl along with propofol on breathing rate and heartbeat in 30 women patients subjected to vertebral column surgery were studied. In this study the patients were divided into 3 groups. FP group received propofol with 0.5 mg dose for each kg along with 2 micrograms fentanyl for each kg. Group P received propofol along with normal saline and group F only received 2 micrograms fentanyl for each kg. The results achieved in FP group showed higher decrease in breath rate and CO_2 level in blood in comparison with the other 25 groups. In F and FP groups apnea production was also observed [15]. In the present study also immediate injection of fentanyl in 2 of the dogs resulted in an immediate decrease in breathing rate and apnea at the first minute that the animals automatically recovered to their ordinary breathing state by respiratory rehabilitation in approximately 2 minutes.

Rectal temperature: The results of comparing changes in temperature between the two control and experimental groups indicated that there is no meaningful difference between the two groups but in the experimental group there is a meaningful difference in temperature decrease between 0^{th} to 10^{th} minutes and the 60^{th} minute. In a research made by Limens in the year 2008 on Infusion fentanyl 5-10 micrograms for each kg per hour along with Acepromazine and Glycopyrrolate in dogs a meaningful decrease was observed in heart beat rate and body central temperature which was in conform to the obtained data from the experimental group in the present study [16].

Anesthesia duration

According to the averages achieved from the results, duration of anesthesia in experimental group was 93.83 minutes and in control group was 32.6 minutes which statistically indicates a meaningful difference between the experimental and control groups and it seems that using fentanyl drug will result in an increase in the anesthesia duration more that approximately 3 times in comparison of the control group which means that the need to anesthesia drug has meaningfully decreased.

During a research made by Ubicomp and Morrison on the effect of midazolam or fentanyl on the required dose of propofol in dogs, fentanyl significantly decreased the required dose of propofol in comparison with midazolam [6]. In the performed research by Keriado also in studying the decrease of MAC isoflurane using fentanyl and remifentanil which was performed on rats, fentanyl group with 15, 40 and 60 micrograms doses for each kg per hour and remifentanil with 60, 120 and 240 micrograms doses for each kg per hour was challenged sing continuous vascular infusion method and the quantity of MAC isoflurane in all groups similarly decreased 10% in low doses, 25% in medium doses and 60% in high doses [17].

NUMBNESS DURATION

Average period of numbness in experimental group were 110 minutes and in control group was 21.6 minutes that shows that there is a completely meaningful difference between the experimental and control groups. The results achieved from the studies made by Van Den Hogan show that in comparing numbness caused by injection of epidural and morphine, meperidine (Pethidine), Fentanyl and Fentanyl in rats show that rats that received fentanyl with 0.16 mg/kg dose had a peak consciousness time approximately between 118 to 119 minutes and numbness duration was calculated as approximately 150 minutes [18].

During the performed research made by Waterman with respect to evaluation of numbness level created by fentanyl in sheep using thermal and mechanical tests, vascular injection of 5 micrograms fentanyl created approximately 30 minutes of numbness against thermal stimulators but it did not show an appropriate numbness activity with respect to mechanical stimulators. In comparison of 10 micrograms for each kg dose of vascular injection it created 60 minutes of thermal numbness and 40 minutes of numbness against mechanical test. Moreover, in one of the sheep with 20 micrograms for each kg dose a thermal numbness of 110 minutes and mechanical numbness of 60 minutes were created that all show that the level and duration of numbness with fentanyl depends on the applied dose [19]. In the present study also by injecting 0.1 mg fentanyl for each kg, average duration of numbness of 110 minutes was achieved against mechanical stimulators.

Generally in evaluating the weak and strong points of adding fentanyl to the combined protocol of Acepromazine-Ketamine we can conclude that slow vascular injection of 0.1 mg dose for each kg in dogs had no negative and decreasing effect on the hearts muscle and created appropriate duration of numbness and anesthesia and in contrast will cause decrease of breathing rate and creation of minor hypothermia. Thus, in using this combined protocol we can have an appropriate anesthesia in dog by providing monitoring and confronting approaches for respiratory depression, apnea and hypothermia.

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