

Clinical-haemostasis assessment of anaesthesia regimens in dogs with the somatic type of pain response

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ARTICLE INFO

Article History

Received : 03.09.2021

Accepted : 06.12.2022

DOI: 10.33988/auvfd.979508

Keywords

Bone fractures

Canine

Osteosynthesis

Somatic innervation

Surgery

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How to cite this article: Rublenko S, Rublenko M, Yaremchuk A, Bakhur-Kavaliauskene T (2024): Clinical-haemostasis assessment of anaesthesia regimens in dogs with the somatic type of pain response. *Ankara Univ Vet Fak Derg*, 71 (1), 73-79. DOI: 10.33988/auvfd.979508.

ABSTRACT

The article investigates into the influence of somatic pain syndrome during osteosynthesis on dogs' clinical parameters and haemostasis. It was found, that the best variant for osteosynthesis operations in dogs is acepromazine-butorphanol-propofol-ketamine anaesthesia. This regimen has provided complete analgesia in half the time recovery of dogs without significant changes in heart rate (HR), respiratory rate (RR), blood pressure (BP), and haemoglobin saturation (SpO₂) during surgery. Acepromazine-ketamine-thiopental anaesthesia has showed pronounced analgesia with a decrease in HR and BP. Xylazine-ketamine-thiopental anaesthesia, under apparent analgesia, led to hypotension (decreased HR, BP) and hypoxia (decreased RR, SpO₂). The hypercoagulable syndrome was recorded in dogs of all experimental groups before surgery. It indicates the urgent need for its correction in the postoperative period. The data obtained will optimize the selection of drugs' combinations for dogs' anaesthesia, taking into account the type of pain response.

Introduction

Among dogs, of the total number of surgical pathologies, injuries account for about 50% (1, 29). The most common consequences of trauma are bone fractures (6, 34), accompanied by a predominantly somatic pain response (22, 24).

One of the fundamental differences in the regulation of somatic and visceral pain is their anatomical and functional organization (9, 21). Somatic pain is characterized by a clear somatotopy, the proportionality of the nociceptive stimulus' intensity feeling, and the adequate behaviour's formation and protective-adaptive reactions (14).

There is a misconception about the "universal injection" among some animal owners and veterinarians.

In their opinion, it will be effective, efficient, safe, and provide the appropriate anaesthetic effect for surgery. At the same time, the problem of anesthesiological support remains unresolved (25, 41). Modern scientific research and practical experience convincingly prove the absence of such universal drugs and methods (31).

Local anaesthesia is the simplest, most accessible and safest. However, it cannot claim the role of a universal method (19, 35). Ensuring the correct level of anaesthesia should include three main components: sleep (depression of consciousness), removal of muscle tone (muscle relaxation), and general anaesthesia (analgesia) (27, 38).

It is impossible to estimate the intensity of the pain response in animals based only on clinical indicators – manifestations of consciousness and muscle tone (12, 36,

39, 40). That is since some anaesthesia regimens suppress the dynamic function of the muscles well and cause sleep while not providing enough analgesic effect (26).

Pain is an evolutionarily formed defence reaction that occurs due to the action of pain (nociceptive) factors and the weakening of analgesic (antinociceptive) mechanisms (28, 42). Both somatic and visceral pain systems are components of the overall system of pain excitation, which determines the formation of various behavioural and autonomic manifestations of pain. It's considerable for choosing an adequate anaesthesia regimen depending on the anatomical and topographic data (15). Morphological and functional connections of nociceptive systems make it possible to link two fundamentally different types of pain perception: primary rapid and localized associated with direct effects on nerve endings and secondary (inflammatory) diffuse with negative vegetative-motor manifestations, often combined with the trauma of internal organs. Its' degree of manifestation, as well as the strength of the pain response, are directly related to the plasma systems' activity and their interaction (13, 16, 17).

Surgeons often use reduced doses of the basic anaesthetic agent in combination with various neurotropic drugs to reduce the toxicity of anaesthesia drugs. This way, doctors are also trying to prevent adverse effects and maintain a sufficiently high level of analgesia. But almost no attention is paid to the rational selection of drugs' optimal combinations taking into account the visceral and somatic components of pain (5, 10).

The recent studies' analysis indicates that currently in the issues of dogs' quality anaesthesia, there are unresolved gaps in terms of the species' sensitivity to pain and reactivity of the haemostasis system in choosing an adequate anaesthesia scheme. It became the basis for our work. The study aimed to determine the clinical and experimental justification of anaesthesia regimens in dogs with the somatic type of pain response.

Materials and Methods

The work was performed at the Department of Surgery and Diseases of Small Domestic Animals of Bila Tserkva National Agrarian University (Kyiv region, Ukraine) during 2019-2021. The research protocol of the present study was approved by the Ethics Committee of the Bila Tserkva National Agrarian University (Approval number: 23.10.2018 / №2, conclusion 5). The material for the study was clinically healthy and sick dogs admitted to the Clinic of Small Animal Diseases of the University.

Animals and study design: Studies of the somatic type of pain response were performed in dogs with bone fractures during their surgical treatment (osteosynthesis). Animals

were selected by the method of analogues. When forming groups conducted a general clinical study of basic vital signs, and studies of morphological and biochemical parameters of the blood. If necessary, instrumental examinations were performed (radiography and ultrasound examination). Dogs with fractures of the femur or humerus aged 1 to 10 years ($n = 45$), depending on the scheme of anaesthesia, were divided into three groups ($n = 15$). In group 1, 15 min before the injection of the main anaesthetic, intramuscularly 1% solution of acepromazine (0.5 mg/kg) was injected in combination with 5% ketamine (8 mg/kg) for premedication and anaesthesia. A 5% sodium thiopental solution (5 mg/kg) was used immediately before osteosynthesis intravenously slowly, and 2.5 mg/kg was used to prolong anaesthesia. In group 2, 2% xylazine (2 mg/kg) combined with 5% ketamine (8 mg/kg) was administered 15 min before the main anaesthetic injection intramuscularly for premedication and anaesthesia. Immediately before surgery, a 5% sodium thiopental (5 mg/kg) was used intravenously slowly, and 2.5 mg/kg was used to prolong anaesthesia. After premedication with acepromazine (0.5 mg/kg) immediately before surgery, animals of group 3 were intravenously administered 0.3 ml/kg of anaesthetic mixture. One ml of this mixture contained 7.5 mg of propofol and 12.5 mg of ketamine. For deepening or prolongation of anaesthesia, a mixture (1 ml of 5% ketamine solution + 3 ml of 1% propofol solution) was injected at a dose of 0.15 ml/kg.

Clinical study: The clinical study of anaesthetized animals was performed according to the following scheme. The stages of anaesthesia were determined: the beginning of anaesthesia; the stage of surgical tolerance; recovery after anaesthesia. The main criteria for their evaluation were dilation or narrowing of the pupils, age, palpebral, anal reflexes, and chewing muscle tone. Tissue perfusion was assessed by pulse oximetry or by pressing a finger on the gums, recording the time of filling the capillaries with blood (19). Clinical indicators were registered at the following stages: before, during, after anaesthesia, and in the most traumatic surgery moments. Heart rate and were determined by palpation of the heart and auscultation with a stethoscope. The frequency and depth of respiration were controlled by observing the movements of the chest and abdominal wall.

Indicators of hemodynamics and tissue perfusion were determined using a resuscitation and surgical monitor UM-300R (Yutas, Ukraine, Kyiv). Indicators such as heart rate (HR), respiratory rate (RR), blood pressure (BP), electrocardiogram (ECG), and arterial blood haemoglobin saturation with oxygen (SpO_2) were monitored.

Study of the haemostasis system: Blood samples from animals were taken before anaesthesia and during 1 hour after surgery. The functional state of the haemostasis system was determined using the coagulometer HumaClot DUO Plus (Human GmbH, Germany) on the following indicators: fibrinogen concentration, fibrin stabilizing factor activity (FXIII), soluble fibrin concentration, prothrombin time.

Statistical analysis: Statistical processing of the results was carried out using Statistica 13.3 IT Application. Multiple variance comparisons were performed using the Fisher distribution (ANOVA). Variance analysis (ANOVA) was used for determining a statistically significant effect on the factors researched. The reliability of the data was evaluated using the Fisher F-test with a $P < 0.05$ confidence level.

Results

The proposed general anaesthesia regimens were accompanied by central nervous system depression, loss of consciousness, skeletal muscle relaxation, and analgesia. In dogs with bone fractures, the onset of anaesthesia in the 1st and 2nd groups did not exceed 1 min, while in the 3rd, it was 1.38 min (Table 1). During a study of hemodynamic parameters (Table 2) in animals it was found that HR is at the upper limit of the physiological norm, decreasing during anaesthesia. The RR in the groups ranged from 20.9 to 22.0 breaths/min, which was at the upper limit of the physiological norm. During anaesthesia, it decreased in dogs of the 1st and 2nd groups by 17.2% and 35.9% ($P < 0.05$), respectively. Instead, in dogs of the 3rd group that indicator did not change significantly. Monitoring of the arterial blood haemoglobin saturation level with oxygen showed the hypoxic state development in dogs of the 2nd group during anaesthesia.

Table 1. Clinical characteristics of intravenous anaesthesia different schemes in dogs during osteosynthesis surgeries, $n=15$.

Indicators	Animal groups, anaesthesia schemes		
	1 st , acepromazine-ketamine-sodium thiopental	2 nd , xylazine-ketamine-sodium thiopental	3 rd , acepromazine-butorphanol-propofol-ketamine
Beginning of anaesthesia, min	0.50±0.04	0.46±0.07	1.38±0.06*
Duration of anaesthesia, min	29.0±0.66	32.3±0.68*	30.2±0.59
Analgesic effect	++	++	+++
Respiration effect	↑↓	↓↓	↑
Cardiovascular effect	↑↓	↓↓	↑
Recovery after anaesthesia, min	60.7±4.2	68.1±4.1	30.1±3.5*

Note: 1. Effect: ++ – expressive; +++ – absolute; 2. Impact: ↑ – increased, ↑↓ – short-term increase followed by decrease, ↓↓ – significant decrease; 3. The value of the indicator P: * – $P < 0.05$, compared with the 1st group.

Table 2. Haemodynamic and respiratory parameters in dogs for osteosynthesis and various anaesthesia regimens, $n=15$.

Animal groups, anaesthesia schemes	Period	HR, beat/min	BP systolic, mm Hg	BP diastolic, mm Hg	BP mean, mm Hg	RR, breath/min	SpO ₂ , %
1 st , acepro-mazine-ketamine-sodium thiopental	I	113.2±4.1	134.1±4.0	80.2±2.9	98.2±3.4	21.5±1.0	96.8±0.8
	II	98.4±4.2* ⁰	117.6±3.8* ⁰	69.0±3.0* ⁰	85.2±3.2* ⁰	17.8±0.9* ⁰	95.3±0.7
	III	101.7±4.3	115.3±3.7*	68.9±3.1*	84.4±3.3*	18.1±1.0*	95.8±0.7
	IV	111.8±4.0 ⁰	120.1±3.8*	77.4±3.1	91.6±3.2	19.4±1.1	97.5±0.6
2 nd , xylazine-ketamine-sodium thiopental	I	109.7±3.9	128.4±4.2	80.4±3.3	96.4±3.7	20.9±1.1	98.1±0.7
	II	71.5±3.8* ⁰	105.7±3.0* ⁰	60.3±2.2* ⁰	75.4±2.9* ⁰	13.4±0.7* ⁰	88.4±0.6* ⁰
	III	74.8±3.7*	102.5±2.9*	60.1±2.2*	74.2±2.9*	13.9±0.7*	89.3±0.7*
	IV	89.3±4.0* ⁰	107.1±3.2*	67.2±2.5* ⁰	80.5±3.1*	16.2±0.8* ⁰	94.9±0.8* ⁰
3 rd , acepro-mazine-butorphanol-propofol-ketamine	I	115.1±4.2	129.4±4.2	78.9±3.1	95.7±3.4	22.0±1.0	97.2±0.7
	II	122.4±4.6	130.7±4.1	75.8±3.0	94.1±3.3	20.4±0.9	97.0±0.7
	III	120.1±4.3	128.1±4.0	75.1±3.0	92.8±3.3	20.8±0.9	96.8±0.8
	IV	112.2±4.1	127.3±3.9	74.4±3.1	92.0±3.2	21.2±1.0	98.1±0.8

Note: 1. Periods: I – pre-anaesthesia, II – during anaesthesia, III – the most traumatic moments of the surgery, IV – after the surgery; 2. The value of the indicator p: * – $P < 0.05$, compared with pre-anaesthesia; ⁰ – $P < 0.05$, compared with the previous indicator for the group.

Table 3. The state of the blood clotting system in dogs during osteosynthesis surgeries.

Indicators	Fibrinogen, g / L	Soluble fibrin, mg%	FXIII, %	Prothrombin time, sec
Clinically healthy (n=15)	2.53±0.13	0	99.2±2.4	16.1±0.3
Pre-anaesthesia (n=45)	2.03±0.10 ⁰	45.2±2.1 ⁰	69.4±3.1 ⁰	21.7±0.4 ⁰
After the surgery, n=15				
1 st , acepromazine-ketamine-sodium thiopental	3.12±0.17*	47.7±3.2 ⁰	62.3±4.3 ⁰	22.1±0.3 ⁰
2 nd , xylazine-ketamine-sodium thiopental	2.80±0.19* ⁰	50.1±3.4 ⁰	60.1±4.1 ⁰	22.4±0.4 ⁰
3 rd , acepromazine-butorphanol-propofol-ketamine	3.05±0.21*	49.8±3.6 ⁰	64.5±4.0 ⁰	22.3±0.3 ⁰

Note: * – P<0.05, compared with pre-anaesthesia; ⁰ – P<0.05, compared with clinically healthy dogs.

Haemostasis system's activation with the formation of the hypercoagulable syndrome was detected in dogs with long tubular bones' fractures (Table 3). It was expressed in a decrease of the fibrinogen concentration by 19.8% (P<0.05) as well as in the appearance of its' metabolite (soluble fibrin) in blood plasma at a quite high concentration. In addition, the prothrombin time was prolonged by 34.8% (P<0.05), and the activity of FXIII decreased by 30.0% (P<0.05). Thus, according to haemostasiological signs, the consumption coagulopathy condition was registered in dogs with bone fractures.

Discussion and Conclusion

The somatic type of pain reaction is stipulated by injury to bones, muscles, skin, joints, tendons, and ligaments. This type of pain reaction is characterized by acute, more intense than visceral, nociceptive impulse (9, 14). Clinical-experimental substantiation of dogs anaesthesia with the somatic type pain response surgical interventions was performed on the animals with fractures of the femur or humerus. Osteosynthesis method the animals underwent depended on the anatomical and topographic location and the nature of the fracture. Particular attention in the performance of somatic pain anaesthesia was paid to the nociceptive protection of animals.. After all, it is for this type of pain response that adequate analgesia is important because the intensity of pain stimulation increases significantly.

In present studies, traditional and new anaesthesia regimens have been used for somatic pain in dogs with bone fractures (8). To improve the anaesthetic properties of the acepromazine-butorphanol-ketamine regimen and reduce the dose of the latter, we have proposed its combination with propofol. Propofol has rapid and smooth induction, pronounced hypnotic and amnestic effects, rapid recovery after anaesthesia, and rare side effects. At the same time propofol anaesthesia may be accompanied by hypotension, bradycardia and direct myocardial depression, impaired baroreflex mechanisms, nervous system depression, suppression of the nervous system (38). In contrast to propofol ketamine has a moderate

hypertensive and a pronounced analgesic effect. It stimulates the sympathetic nervous system and its general analgesic effect is 3-4 times longer than propofol (2, 4). Thus, by combining these two anaesthetics into one anaesthesia regimen, we eliminated the negative effects and complemented the positive ones (32).

Effective control of anaesthesia is important, which is currently achieved only by using inhalation anaesthetics due to their ultrashort action. But, according to the results of current studies, the combined use of short-acting (ketamine) and ultra-short-acting (propofol) anaesthetics also has made it possible to achieve adequate anaesthesia control. With the introduction of the propofol, the action of which lasts an average of 4-6 min, conditions are created to achieve good control of anaesthesia without inhalation anaesthetics.

An equally important effect achieved was the rapid recovery of dogs after anaesthesia. Other authors also testify to good anaesthesia control at the use of propofol in other drug combinations (30, 38, 43). In particular, the researchers point out that propofol ranks second after inhaled desflurane, ahead of isoflurane and sevoflurane in the rate of patients' recovery after anaesthesia.

According to the results of current studies, various combinations of neuroleptics (acepromazine, xylazine) with general anaesthetics (ketamine) provided a rapid introduction of animals into anaesthesia (0.46-1.38 minutes) with a duration of 29-32 minutes. At the same time, the successful anaesthesia of surgical care is a multifactorial process, so the duration of anaesthesia cannot be decisive.

It is known (7, 18), that anaesthetics can affect the cardiovascular system in different ways. Some of them, such as ketamine, stimulate the increase of BP in dogs, others (xylazine, acepromazine, propofol) on the contrary, cause hypotension. For the surgery process, it is important how these drugs affect the cardiovascular system when they are used in anaesthesia regimens that combine antihypertensive and hypertensive preparations. According to the results of the current research, the peculiarities of their interaction were established. Using acepromazine with ketamine, the latter neutralizes the

hypotensive effect of acepromazine. In the case of a combination of xylazine with ketamine, the hypotensive properties of the former outweigh the hypertensive ability of the latter. Therefore, dogs with impaired or cardiovascular insufficiency should be closely monitored: the use of xylazine-ketamine in dogs during surgery led to the depression of the respiratory system and could cause it to stop.

Nociceptive stimulation with insufficient analgesia during the most traumatic moments of the operation briefly accelerates RR, while with its' sufficient adequacy it remains stable.

A significant decrease in HR and BP in dogs after anaesthesia showed that xylazine-ketamine-thiopental anaesthesia creates a risk of haemodynamic disorders. That is especially important in animals with cardiovascular failure and significant blood loss. In contrast, acepromazine-butorphanol-propofol-ketamine anaesthesia has no significant adverse effect on dogs' haemodynamics during osteosynthesis.

Under acepromazine-ketamine-thiopental anaesthesia, ketamine counteracts the hypotensive effect of acepromazine and sodium thiopental and is therefore accompanied by a moderate effect on haemodynamics.

We found that xylazine-ketamine-thiopental anaesthesia developed a hypoxic state during osteosynthesis that can lead to respiratory arrest. Instead, acepromazine-butorphanol-propofol-ketamine or acepromazine-ketamine-thiopental anaesthesia had no significant effect on the respiratory system.

Only a few studies are devoted to the research of the anaesthetics effect on the haemostasis system (3, 23). In these studies, acepromazine or xylazine-thiopental anaesthesia without surgery had no haemocoagulation changes. Abdominal pathology in dogs causes the development of a hypercoagulation state (11, 20, 33, 37). Comprehensive data on the state of haemostasis in dogs during osteosynthesis have not been published. According to the present study results of the haemostasis system, repeated bone injury, caused by osteosynthesis, with adequate analgesia provokes moderate hyperfibrinogenemia and thrombinemia with a deficiency of plasma coagulation factors, deepens the hypercoagulable state without significant effect on its components.

Summing up, the study results showed that the neurohumoral mechanisms of pain regulation and modern schemes of anaesthesia are justified. The combination of acepromazine-butorphanol-propofol-ketamine provides complete analgesia with twice faster recovery of dogs from anaesthesia without significant changes in HR, RR, BP, and SpO₂ during surgery. Acepromazine-ketamine-thiopental anaesthesia is accompanied by pronounced analgesia with a decrease in HR and BP. At the same time, xylazine-ketamine-thiopental anaesthesia in severe

analgesia leads to hypotensive and hypoxic conditions. Further research could usefully explore the effect of different anaesthesia regimens on the clinical-haemostasis condition of dogs in abdominal surgery, with a visceral type of pain response. Taken together, the optimal option for osteosynthesis in dogs is a combination of acepromazine-butorphanol-propofol-ketamine. However, like others, this anaesthesia regimen requires correction of the hypercoagulative syndrome in the postoperative period.

Acknowledgments

The author's team expresses its gratitude to the Clinic's of Small Animal Diseases staff of Bila Tserkva National Agrarian University for their support and assistance in conducting experimental research.

Financial Support

This research received no grant from any funding agency/sector.

Conflict of Interest

The authors declared that there is no conflict of interest.

Author Contributions

SR, MR, AY and TB-K conceived and planned the experiments. SR and MR carried out the experiments. SR, MR, and AY contributed to sample preparation. SR, AY and TB-K contributed to the interpretation of the results. TB-K took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Data Availability Statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Ethical Statement

This study was approved by the Ethics Committee of the Bila Tserkva National Agrarian University (Approval number: 23.10.2018 / №2, conclusion 5).

Animal Welfare

The authors confirm that they have adhered to ARRIVE Guidelines to protect animals used for scientific purposes.

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