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Evaluation of Sumianxin II-Pentobarbital, Ketamine-Pentobarbital and Sumianxin II-Ketamine Anesthesia in a Minipig Periodontitis Model

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Abstract

Objectives: In this study, we assessed in a minipig periodontitis model the effects of sumianxin II-pentobarbital, ketamine-pentobarbital, and sumianxin II- ketamine anesthetic combinations.

Methods and materials: Thirty minipigs were divided into three groups and anesthetized intramuscularly (neck) with sumianxin II (1 mg/kg) and pentobarbital (20 mg/kg; Group S-P); ketamine (5 mg/kg) and pentobarbital (20 mg/kg; Group K-P); or ketamine (5 mg/kg) combined with sumianxin II (1 mg/kg; Group K-S). Body weight, body length, experimental period, induction time, maintenance time, and recovery time were recorded. Heart rate, respiration, mean arterial pressure, and rectal temperature were analyzed pre-anesthesia (T_0), after induction (T_1), 30 min after surgery (T_2), 60 min after surgery (T_3), and at the end of anesthesia (resuscitation, T_4). Effectiveness of anesthesia was assessed and classified by respiratory rate, ocular signs, pain stimuli, cardiovascular function, and muscle tone.

Results: There were no significant differences in body weight, length, or experimental period between minipigs in the three treatment groups. The induction times of groups K-P and K-S (2-3 min) were significantly shorter than that of group S-P (7.4 ± 1.1 min). The maintenance time of group K-P (136 ± 11.4 min) was significantly different from the maintenance times of groups S-P and K-S (230-240 min). The recovery time of group K-S was 4 ± 1.0 min, compared with 9 ± 0.6 min in group S-P and 10 ± 1.5 min in group K-P. The heart rates and respiration of animals in group K-S decreased at T_2 and T_3 compared with the heart rates of group S-P and K-P; there were no differences in heart rate and respiration between groups S-P and K-P. There were no differences in rectal temperature or mean arterial pressure in the three treatment groups. Ninety percent of minipigs in group K-S were assessed as having class I effectiveness of anesthetic induction, whereas 30% and 10% in group S-P and K-P had class I. One hundred percent of minipigs in group K-S were evaluated as having class I effectiveness of anesthetic maintenance, in contrast to 40% and 60% in group S-P and K-P. All minipigs in group K-S were stable during the experiment. One pig in group S-P and K-P died from anesthetic- induced respiratory and cardiac arrest.

Conclusions: Intramuscular injection of ketamine-sumianxin II was the best anesthesia in a minipig periodontitis model because of short induction and recovery times, long maintenance time, and good effectiveness.

Keywords: Minipig; Anesthesia; Pentobarbital; Sumianxin II; Ketamine

Introduction

Minipigs are used widely in experimental research because of their small size, and because they have physiological and biochemical attributes similar to humans [1]. In addition, similar structures and positions of periodontal tissue make the minipig a useful experimental model for the study of periodontal diseases [1,2]. Usually, to minimize interference by extremity movement, minipigs are anesthetized before experiments. Anesthesia must be safe and reliable with minimal side effects during experiments. However, a single anesthetic drug is usually insufficient to have all the desired properties, such as strong analgesia, deep hypnosis, and muscle relaxation. In addition, high anesthesia doses may cause deep anesthesia and even death, whereas low doses may not eliminate painful stimuli [3]. Thus, careful selection of anesthetic drugs is important.

Ketamine, pentobarbital, and sumianxin II are often used in animal experiments. Ketamine, a non-barbiturate anesthetic, has the advantages of intense analgesia, sympathetic nervous system stimulation, and cardiovascular-stimulating effects of increasing heart rate and blood pressure. However, when used alone, ketamine has the disadvantages of short anesthetic duration and muscular rigidity [4,5]. Pentobarbital is a moderate sedative used at doses from 30 mg/kg to 100 mg/kg of body weight in animal experiments; the depressive

action of pentobarbital, especially cardio depressive effects, is dose-dependent [6,7]. Pentobarbital does not have an analgesic effect at usual doses; thus, it must be combined with other analgesics to prevent pain [6]. Sumianxin II consists of dihydroetorphine, 2,4-xylylamine triazole and haloperidol. Because of the strong analgesic effect of dihydroetorphine and the stabilization, sedation, and muscle relaxation effect of haloperidol and 2,4-xylylamine triazole, sumianxin II not only enhances the effect of each single drug, but also reduces the adverse effects of each single drug, especially inhibition of respiration. However, sumianxin II has a long, unsatisfactory induction time [8,9].

The opposing properties of ketamine, pentobarbital, and sumianxin II may make their combined use more suitable than single drugs. In addition, by combining the drugs, the doses of each are reduced to levels at which side effects may be avoided [4]. So far, there have not been any studies to assess the effects of sumianxin II-pentobarbital, ketamine-pentobarbital, and ketamine-sumianxin II combinations in a minipig periodontitis model. Thus, we compared drug combinations to identify the safest, most effective and reliable mix.

Methods

Animals

Thirty healthy minipigs (weighing 35-45 kg, 15 male, 15 female, 24-months-old) were supplied by Chengdu experimental animal breeding center (Chengdu, China). These minipigs received humane care in normal light-dark cycles at room temperature, and they had free access to food and water in accordance with the Guide for the Care and Use of Laboratory Animals [10]. All of the animal experimental procedures were approved by the Ethics Committees of Xi'an Jiaotong University and were executed in accordance with the Guidelines of Animal Care and Use Committee of Xi'an Jiaotong University.

Anesthesia

Sumianxin II was purchased from Changchun Veterinary Research Reagent Factory (Changchun, China). Pentobarbital was purchased from Beijing Suolaibao Reagent Company (Beijing, China). Ketamine was purchased from Fujian Gutian Pharmaceutical Company (Fujian, China).

Experimental design

The thirty minipigs were divided into three groups and fasted for 12 h before anesthesia. Anesthetics were introduced as follows: Group S-P, sumianxin II (1 mg/kg) and pentobarbital (20 mg/kg); Group K-P, ketamine (5 mg/kg) and pentobarbital (20 mg/kg); Group K-S, ketamine (5 mg/kg) and sumianxin II (1 mg/kg). All animals were premedicated with diazepam 0.4 mg/kg and atropine 0.04 mg/kg, and then injected in neck muscles caudal to the base of the ear (splenius and brachiocephalic muscles). No more than 10 mL was injected at any one site to avoid tissue irritation.

Experimental procedure

All animals were anesthetized and transferred to the operating room table, immobilized in a supine position, and monitored by electrocardiogram (ECG, GE Medical Systems Information Technologies, Wisconsin, USA). An arterial catheter with a pressure transducer was placed in the left carotid artery (Model PM-2B; Honeywell, Minneapolis, MN) for monitoring mean arterial pressure and respiration. Rectal temperature was continuously monitored.

An established protocol in Generation of a Periodontitis Model was used in this study [11]. Briefly, a mucoperiosteal flap was raised and the alveolar bone was surgically drilled in the buccal region of root furcation of the first molars to create experimental periodontal defects. A 5×6×5 mm^3 alveolar bone defect was created in the root surface. Four weeks after the creation of the periodontal lessons, clinical assessment and X-ray evaluation were performed. After all the experiments, animals were euthanized with intravenous 500 mg/kg pentobarbital.

Physiological parameters

We measured body weight, body length, experimental period, heart rate, respiratory rate, rectal temperature, and mean arterial pressure. The parameters for heart rate, respiratory rate, rectal temperature and mean arterial pressure were assessed at pre-anesthesia (T_0), 10 min after induction (T_1), 30 min after surgery (T_2), 60 min after surgery (T_3), and at the end of anesthesia (resuscitation, T_4).

The following variables were also recorded: the time of anesthetic induction, maintenance, and recovery. Briefly, after drug injection, the minipigs were placed in a dorsal recumbent position every minute or until the righting reflex was lost and the animals remained recumbent for at least 30s. Then, animals were observed until they regained the righting reflex. Elapsed time from drug injection to loss and regaining of the righting reflex was recorded and considered as the onset and end of anesthesia. Induction time was the time from drug injection to loss of the righting reflex. Maintenance time was defined as the time from complete loss of the righting reflex to the regaining of the righting reflex. Recovery time was the time from the regaining of the righting reflex to the time at which the animal could stand and start walking [12].

Anesthesia assessment

Effectiveness of anesthesia was assessed by respiratory rate, ocular signs, pain stimuli, cardiovascular function, and muscle tone. The classification was defined as follows.

Class I: During induction, minipigs were well tranquillized. Breath was regular. The palpebral and corneal reflexes disappeared. During surgery, deep anesthesia was maintained with good muscular relaxation. Surgical stimuli didn't produce any response, and there was no cardiopulmonary distress. During recovery phase, pigs were completely awake and had regained full muscle strength and spontaneous breathing.

Class II: During induction, minipigs were slightly restless. Respiration was frequently irregular. During surgery, muscular relaxation was poor, and extremity movement occurred slightly with surgical stimuli. During recovery phase, the minipigs showed some restlessness.

Class III: During induction, pigs were obviously restless. Respiration and cardiac arrest occurred rapidly. During surgery, muscular relaxation was poor, and extremity movement occurred frequently with surgical stimuli. During recovery phase, anesthesia was prolonged, and the peripheral circulation was poor with a falling mean arterial pressure, and apnoea occurred occasionally.

Statistical analysis

Data analysis was performed with SPSS 19.0 software (SPSS Inc., Chicago, IL, USA), and the data were expressed as mean ± SEM. Statistical significance was measured using Fisher's exact test. After confirming the data for normal distribution, differences between two groups were analyzed by Student's *t* test, and one-way ANOVA with Tukey's test was applied for analyses of more than two groups. A value

of P <0.05 indicated that the results were statistically significant.

Results

General experimental data

Table 1 shows the general experimental data. There were no significant differences in body weight, body length, or experimental period between the three groups (P>0.05).

Induction time, maintenance time, recovery time

The induction time of group S-P was 7.4 ± 1.1 min. The induction times of group K-P and K-S were 2-3 min, greatly shorter than that of group S-P. The maintenance time of group K-P was 136 ± 11.4 min, which was significantly different from the maintenance times of groups S-P (234 ± 11.4 min) and K-S (232 ± 17.8 min). The recovery time of group K-S was 4 ± 1.0 min, compared with 9 ± 0.6 min in group S-P and 10 ± 1.5 min in group K-P (Table 2).

Heart rate, respiration, rectal temperature, and mean arterial pressure

Table 3 presents heart rate, respiration, rectal temperature, and mean arterial pressure of the three groups. The heart rate and respiration of minipigs in group K-S were decreased at T_2 (30 min after surgery) and T_3 (60 min after surgery) compared with groups S-P and K-P; there were no significant differences in heart rates and respiration between groups S-P and K-P. In addition, we did not observe any differences in rectal temperature or mean arterial pressure between the three treatment groups.

Anesthesia assessment

Ninety percent of minipigs in group K-S had Class I effectiveness of anesthetic induction, whereas 30% and 10% in group S-P and K-P had class I. However, there were no significant differences between the three treatment groups. In addition, one hundred percent of minipigs in group K-S were evaluated as having class I effectiveness of anesthetic maintenance, in contrast to 40% and 60% in group S-P and K-P (P<0.05). All minipigs in group K-S were stable during the experiment. One pig each in group S-P and K-P died from anesthetic-induced respiratory and cardiac arrest (Table 4).

Table 1: The general experimental data of minipigs.

Groups	Quantity	Body weight (kg)	Body length (cm)	Experimental period (min)
Group S	6	35 ± 2.4	78.34 ± 2.46	180 ± 11
Group P	6	35 ± 3.8	78.34 ± 3.55	178 ± 12
Group K	6	36 ± 1.8	77.34 ± 3.42	182 ± 10
Group S-P	6	36 ± 3.4	79.34 ± 1.23	176 ± 13
Group K-P	6	34 ± 4.4	78.26 ± 1.14	185 ± 16
Group K-S	6	35 ± 3.8	77.35 ± 1.38	187 ± 18
P		0.9274	0.5744	0.884

Table 2: Effects of three anesthetic treatments.

Methods	Induction time (min)	Maintenance time (min)	Recovery time (min)
Group S-P	7.4 ± 1.1	234 ± 11.4	9 ± 0.6
Group K-P	2.2 ± 0.5	136 ± 11.4	10 ± 1.5
Group K-S	2.4 ± 0.3	232 ± 17.8	4 ± 1.0
P	0.0040*	0.0038*	0.0180*
S-PvsK-P	*P*<0.05*	*P*<0.05*	*P*>0.05
S-PvsK-S	*P*<0.05*	*P*>0.05	*P*<0.05*
K-PvsK-S	*P*>0.05	*P*<0.05*	*P*<0.05*

Discussion

The ideal anesthetic drug should have full anesthesia properties: deep hypnosis, strong analgesia, muscular relaxation, and low cardiovascular stress. Most drugs couldn't fulfill all these criteria; thus, they should be used in combination. Furthermore, reducing drug dose by combination may avoid the side effects of any one drug [4]. Sumianxin II, ketamine, and pentobarbital are used widely in animal experiments. Sumianxin II has strong analgesic, sedation, and muscle relaxation properties; however, a long induction time makes sumianxin an unsatisfactory choice when used alone [13]. Ketamine produces strong analgesic and minimal circulation effects, but it has a short maintenance time [14,15]. Pentobarbital has hypnotic and muscular relaxation effects, but dose-dependent toxicity; pentobarbital overdose may cause cardiac and respiratory depression and even death [16]. Thus, in the present study, we measured the effects of sumianxin II-pentobarbital, ketamine-pentobarbital, and ketamine-sumianxin II combinations in a minipig periodontitis model. To assess anesthesia, we selected the doses of sumianxin II, ketamine, and pentobarbital and measured three important indexes, namely, induction, maintenance, and recovery times [9,17-19]. The results indicated that injection of minipigs with ketamine-sumianxin II was the best approach because of the short induction and recovery times and a long maintenance time.

We also measured heart rate, respiration, rectal temperature, and mean arterial pressure. The heart rate and respiration in group K-S were greatly decreased at T_2 and T_3 compared with those parameters for groups K-P and S-P. These results suggested that the minipigs in group K-S had deep anesthesia to safely undergo periodontal surgery [20]. The rectal temperature of most animals continuously decreased during anesthesia because of reduction in metabolic rate, inhibition of the temperature regulation center, and cessation of skeletal muscle activity [21]. The rectal temperatures in all three groups declined, and we observed an upward trend in temperature at the end of anesthesia. However, there were no significant differences in rectal temperature and mean arterial pressure between the three treatment groups.

The depth of anesthesia for minipigs is difficult to assess accurately - because there is no single method that is reliable for all anesthetic drugs. Nevertheless, In the present study, we conducted a simple method to assess anesthetic effectiveness by observing the activities of respiratory, eye-related, cardiovascular, and muscular systems. The ratio of minipigs that gained good effectiveness during anesthetic induction and maintenance was both higher in group K-S than in either group S-P or K-P. In addition, one pig each died in group K-P and S-P from anesthetic-induced respiratory and cardiac arrest, which emphasized that caution, should be taken when considering pentobarbital in minipigs.

In summary, we demonstrated that intramuscular injection of ketamine-sumianxin II was a highly efficacious anesthesia therapy in a minipig periodontitis model. Advantages of this protocol include short induction and recovery times, a long maintenance time, and good anesthesia effectiveness. However, we did not investigate the

Table 3: Heart rate, respiration, rectal temperature, and mean arterial pressure of pigs treated with three different anesthetics.

Parameters	Groups	T_0	T_1	T_2	T_3	T_4
Heart rates (beats/ min)	S-P	83 ± 6	73 ± 9	69 ± 5	75 ± 4	80 ± 6
	K-P	94 ± 11	70 ± 8	67 ± 4	78 ± 3	83 ± 5
	K-S	86 ± 9	63 ± 9	46 ± 5	58 ± 4	77 ± 6
	P	0.6479	0.7204	0.0234*	0.0177*	0.7676
	S-P vs K-P			*P*>0.05	*P*>0.05	
	S-P vs K-S			*P*<0.05*	*P*<0.05*	
	K-P vs K-S			*P*<0.05*	*P*<0.05*	
Respiration (times/ min)	S-P	27 ± 4	23 ± 6	22 ± 4	20 ± 3	22 ± 4
	K-P	33 ± 7	22 ± 7	23 ± 3	20 ± 4	24 ± 3
	K-S	28 ± 6	20 ± 5	11 ± 3	10 ± 2	20 ± 5
	P	0.8956	0.9875	0.0254	0.0136	0.9739
	S-P *vs* K-P			P>0.05	P>0.05	
	S-P *vs* K-S			P<0.05*	P<0.05*	
	K-P *vs* K-S			P<0.05*	P<0.05*	
Rectal temperature (°C)	S-P	37.1 ± 0.7	36.1 ± 0.5	36.1 ± 0.8	36.6 ± 0.5	37.0 ± 0.8
	K-P	37.3 ± 0.9	36.6 ± 0.6	35.9 ± 0.7	36.8 ± 0.8	37.1 ± 0.7
	K-S	37.2 ± 0.6	36.2 ± 0.4	36.0 ± 0.8	36.8 ± 0.6	37.2 ± 0.8
	P	0.9823	0.7743	0.9834	0.9693	0.9831
Mean arterial pressure (mmHg)	S-P	115 ± 6	95 ± 8	70 ± 8	90 ± 7	98 ± 8
	K-P	120 ± 9	98 ± 7	78 ± 6	95 ± 9	102 ± 5
	K-S	112 ± 8	102 ± 5	76 ± 9	98 ± 8	106 ± 7
	P	0.7727	0.7707	0.7640	0.7840	0.7168

Table 4: Complications and assessment of anaesthesia.

Characteristics	Group S-P(n=10)	Group KP(n=10)	Group K-S(n=10)
Assessment of anaesthetic induction			
Class I	3	1	1
Class II, III	7	9	9
p	0.4095		
Assessment of anaesthetic maintenance			
Class I	4	6	0
Class II, III	6	4	10
p	0.0106*		
S-P vs K-P	*P<0.05*		
S-P vs K-S	*P>0.05*		
K-P vs K-S	*P>0.05*		
Mortality	1	1	0
p	0.6120		

specific mechanisms of action of ketamine-sumianxin II; thus, further investigation is needed to expand on our findings.

Conclusion

The intramuscular injection of ketamine-sumianxin II was a highly efficacious anesthesia therapy in minipigs periodontitis model. Advantages of this protocol include short induction and recovery times, a long maintain time, and good anesthesia effectiveness.

Declarations

Ethics Approval and Consent to Participate all of the animal experimental procedures were approved by the Ethics Committees of Xi'an Jiaotong University and were executed in accordance with the Guidelines of Animal Care and Use Committee of Xi'an Jiaotong University.

Consent for Publish

All Authors have agreed to publish the manuscript in Journal of Medicinal Chemistry and Drug Design.

Competing Interests

The Authors declare that no conflict of interest exists.

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Authors' Contributions

This study is a product of the intellectual efforts of entire team; all members have contributed to various degrees. The contributions of each author are listed as follows: Mingqing Kou (study design, data acquisition and analysis, statistical analysis, manuscript draft); Xiaolong Chen (study design, data acquisition and analysis, statistical analysis, manuscript revision for important intellectual content); Minggang Huang (data acquisition and analysis, statistical analysis); Kai Lu (study conception and design, final approval of the article, obtained funding, overall supervision). All authors read and approved the final manuscript.

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