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Research Article

Comparison of Anaesthetic Effects of Intravenous Emulsified Isoflurane and Inhaled Isoflurane in Dogs

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Abstract

To compare anaesthetic effects between emulsified isoflurane (EI) through intravenous route and inhaled isoflurane in dogs, 16 healthy adult non-purebred dogs were randomly divided into intravenous anaesthesia groups with 8% EI (EI group) and an induction anaesthesia group (IA group) with vapor isoflurane. The anaesthetic effect was assessed by observing dog's reaction, obvious side effects and baseline physiological parameters, including of Mean Arterial Pressure (MAP), Respiratory Rate (RR), Diastolic Arterial Pressure (DAP), Heart Rate (HR), Systolic Arterial Pressure (SAP), Oxygen saturation (SpO_2) were recorded at 0, 5, 10, 20, 30, 40, 50, 60, 70 and 80 min after administered anaesthetic agents. The results revealed that no conspicuous differences were discovered between the groups during anaesthesia. This study showed that there is a good prospect for using EI intravenously in dog anaesthesia.

Keywords: *Isoflurane, Emulsified isoflurane, Anaesthetic effects, Dog*

Köpeklerde İntravenöz Emülsifiye İzofluran ve İnhale İzofluranın Anestetik Etkilerinin Karşılaştırılması

Öz

İntravenöz yoldan verilen emülsifiye izofluran (EI) ile inhale izofluran arasındaki anestezik etkileri karşılaştırmak için, sağlıklı yetişkin safkan olmayan 16 köpek rastgele %8 EI intravenöz anestezi grubu (EI grup) ve inhale izofluran anestezi grubu (IA grup) olarak iki deneme grubuna ayrıldı. Anestezik etki, köpeğin reaksiyonu, belirgin yan etkiler ve Ortalama Arteriyel Basınç (MAP), Solunum Hızı (RR), Diyastolik Arteriyel Basınç (DAP), Kalp Hızı (HR), Sistolik Arteriyel Basınç (DAS), Sistolik Arteriyel Basınç (SAP), Oksijen doygunluğu ($Sp0_2$), anestezik ajanların uygulanmasından sonraki 0, 5, 10, 20, 30, 40, 50, 60, 70 ve 80. dakikalarda kaydedildi. Sonuçlar, anestezi sırasında gruplar arasında belirgin bir fark bulunmadığını ortaya koydu. They all play a good role in dogs, as time goes on, these parameters are slightly reduced, and there are also physiological acceptable limits. Bu çalışma, köpek anestezisinde intravenöz olarak EI kullanımının iyi bir seçenek oluşturduğunu gösterdi.

Anahtar sözcükler: *Isoflurane, Emülsifiye isoflurane, Anestezik etki, Köpek*

INTRODUCTION

Anaesthesia is currently used for transportation and experimental work in many animal species, especially in surgical operation aspects. Considering economic, technological and even legal constraints, volatile anesthetics, such as, isoflurane, sevoflurane or halothane, cannot be used in some states. Intravenous (I/V) injection of volatile anesthetics can cause organism damage, such as changing hemodynamic variables and pulmonary function [1]. However, several preliminary investigations have confirmed to a certain extent that intravenous injection of emulsified halothane or isoflurane has no harmful effects on animals [2,3]. Over the years, emulsified isoflurane was appeared frequently to our laboratory's (The Key Laboratory of Zoonosis of Liaoning Province, College of Animal Science &Veterinary Medicine, Shenyang Agricultural University) investigations, but it has not been used all over the world, in sharp contrast to inhalational isoflurane. Emulsified isoflurane is a special lipid emulsion state of isoflurane, and one component content of the preparation is 30% Intralipid (Libang Pharmaceutical Co, Ltd., Xi'an, China), a

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bacterium-free, non-pyrogenic axunge emulsion provided for I/V administration. Compared with the traditional route of inhalation, apply for emulsified isoflurane demands for changes in dosage of estimate, but they are handy and fast acting to apply I/V, and also does not need additional volatilizing equipments. So it could be used in the areas with complex natural environments. Recent studies already put forward that emulsified isoflurane emerged good anaesthesia after I/V injection and provided certain advantages [4]. The main objective of this research was to compare anaesthetic effects between intravenous EI and inhaled isoflurane in dogs.

MATERIAL and METHODS

Animals

With the permission of the Animal Care and Use Committee of Shenyang Agricultural University (201604-001), 16 healthy adult non-purebred dogs were applied for this study, included 8 females and 8 males, with body weights 5.2±0.4 kg and ages 15±3 months. The dogs were housed individually and fed the same kinds and equal amounts of dry food twice a day and water adequate and casual for 15 days. Before the formal experiment, basic examination (including biochemical profile, electrocardiography, and complete blood count) was performed. The results stated clearly that all dogs were apparently healthy without significant changes of clinical disease.

Materials

Emulsified isoflurane (EI) was set up on the basis of use an aseptic technique as described before [1,5]. Briefly, taking 0.8 mL liquid isoflurane (Heilongjiang Key Laboratory of Anesthesiology and Intensive Care Research, Harbin, China) and 9.2 mL 30% intralipid (Libang) to a 10 mL glass ampoule, and then, the ampoule was conserved after seal hermetically by an alcohol blowtorch. Shake ampoules with a vibrator forcefully, maintain for 15 min, to dissolve isoflurane into the lipid emulsion. Stored at room temperature for six months, there were no lipid droplets be found in liquid isoflurane, and the concentration of lipid droplets remained unchanged.

Study Design

Organized 16 dogs into the intravenous anaesthesia group with 8% EI (EI group) or the inhalation anaesthesia group with isoflurane vapor randomly (IA group). Before operation apiece begun, fasting with no food for 12 h, and no drinking water for 3 h, intravenous catheter (26 G, Jinhuan Medical Products Co., Ltd., Shanghai, China) was placed on brachiocephalic vein of each dog for 2 h.

Dogs were arranged for a sternal recumbency on a limitative holder. Dogs were put on an obedient respiratory mask which link up together with an anaesthesia machine (Excel 210 SE; Datex-Ohmeda, Madison, USA) contain an isoflurane atomizer and dogs primary breathed 100% oxygen before foggy EI or isoflurane was administered. In EI group, atropine sulfate (0.03 mg/kg, Qilu Animal Health Products Co., Ltd, Jinan, China) was administered by intramuscular injection before anaesthesia, after 15 min every dog recepted 1 mL/kg of emulsified isoflurane in 20 sec by intravenous push, then they were intravenous pushed 8 mL/kg·h^{-1} of EI by intravenous infusion. As soon as intravenous infusion of drugs for anaesthesia, timing notes were jot down. After 60 min of pushing drugs, the intravenous anesthetic was stopped. But recording the time was continued until 80 min. In IA group, atropine sulfate (0.03 mg/kg) was administered by intramuscular injection before anaesthesia, after 15 min each dog received 5 mg/kg of propofol (Libang) by intravenous push, and the dogs were intubated after induction of general anaesthesia. 3% isoflurane was inhaled at fast rate for 3 min through anaesthesia machine. Then 1.5% isoflurane was maintained for 60 min. As soon as inhalation of 3% isoflurane, time notes were recorded again. After 60 min of drugs intervention, inhalation of anesthetic was stopped. But recording the time was continued until 80 min.

Physiological Monitoring

Physiological indicators and anaesthesia grades were assessed at time nodes, which were 0, 5, 10, 20, 30, 40, 50, 60, 70 and 80 min, and observed the side effects such as excitement, conjunctival flushing, convulsions, poisoning, vomiting and so on, until the dog can stand or even walk. Recording baseline physiological parameters, which was comprised of Mean Arterial Pressure (MAP), Respiration Rate (RR), Diastolic Arterial Pressure (DAP), Heart Rate (HR), Systolic Arterial Pressure (SAP), Oxygen saturation (SpO_2). Experimental animals were instrumented through the non-invasive patient monitor (S/5TM; Datex-Ohmeda Drive, Madison, Wisconsin, USA) for calculate SpO_2 and RT. Only when the pulse rate obtained by the pulse oximeter matched the heart rate calculated by the stethoscope can the parameter of SpO_2 be acceptable. MAP was surveyed with "non-invasive" by the same monitor. Rectal temperature was surveyed an electronic temperature surveying instrument and it was assessed by the number displayed on the instrument. HR was determined through a stethoscope placed at the left lower lateral pleural wall by counting heartbeats for 1 min. RR was reckoned by naked eye observation or hand exploration of the number of pleural ripple cycles for 1 min.

Anaesthesia Scores Determination

Time taken for the palpebral reflex, pedal reflex and tail clamp reflex to disappeared, which was taken notes after administered anesthetic agents. The tail clamp reflexes were as similar as the reflex disappeared to nipped interphalangeal skin of a limb and the tail during 3 sec using Kocher's forceps. Resumed times to head exercise, standing and walking were written down either.

Assessment of anaesthesia refer to the proposed scoring methods *(Table 1)* [5]. Total score was the sum of posture score, sedation score, analgesia score, jaw & tongue relaxation score and auricular response score.

Statistical Analysis

Every dog should have an independent anaesthesia note. Data are exhibited in the form of mean ± standard deviation (SD) and were analyzed using: two-way analyses of variance (ANOVA) for data of several measures for HR, RR, SpO_2, MAP, SAP, DAP; the Student-Newman-Keuls or Bonferroni's test to determine overall differences at each time point in each anaesthesia group. Compared with anaesthesia groups of the score of assessment at the same time point, utilized the Fisher's Least Significant Difference test. Statistic differences were considered statistically significantly as $P<0.05$. Statistical software SPSS v 23.0 for Windows was used to summarize and analyze all test data.

RESULTS

Scores of analgesia, sedative effects, muscular flaccidity as well as posture were recordedfor each time interval. As given in the second sequence *Table 2,* in terms of total scores, conspicuous changes came up on account of two treatments, monitoring period, dog's posture, sedation, ear reaction in IA group revealed a good state of anaesthesia at 5th min of induction, and adequate muscle relaxation at 10th min of anaesthesia. But there was a lack in analgesia, determined by clamping interphalangeal skin for 3 seconds using Kocher's forceps, 75% of dogs reacted in varying degrees. In EI group, there were no apparent reactions in the dog's posture, sedative and analgesic effects 5 min after induction of anaesthesia, except a few dogs showed mild reactions (head movement) when clamping interphalangeal skin 3 sec using Kocher's forceps

Table 2. *Anaesthesia score table in total (X±SD, n=8)*

Time (min)	IA group	EI group
0	0.00±0.00	0.00±0.00
5	10.63±1.^{6}8a	13.63±1.40^{b}
10	11.13±1.35^{a}	15.25±1.40^{b}
20	14.50±0.92	15.38±1.06
30	14.13±1.30	15.50±1.31
40	14.38±0.92	16.00±1.60
50	14.50±1.30	16.00±2.50
60	14.63±1.19	16.00±2.39
70	5.75±1.28	6.50±0.93
80	0.00±0.00	0.00±1.68

The contrast between the two groups, shoulder subscript letters indicate significant difference (P<0.05)

Table 1. *Criteria used to score after injected one of two groups anaesthetic agents*

Criteria	Score	Observation
Posture score	0	Normal
	1	Ataxic, but able to walk
	2	Completely prone, unable to walk,but able to crawl
	3	Lateral recumbency, but able to move the tail or paw
	4	Complete lateral recumbency without movement
Sedation score	0	Normal
	1	sternal recumbency, head movement, blinking
	2	recumbent, head down, moderate eyelid reflex, bulbus oculi enstrophe
	3	no movement, palpebral reflex disappeared, even mydriasis
Ear reaction (beat the desktop next to the ear using Kocher's forceps)	0	Normal response
	1	Unresponsive, head move with body move
	2	The body does not move but the eyes move
	3	No response reflex
Analgesic scores (Clamp Interphalangeal skin 3s using Kocher's forceps)	0	Normal response
	1	Reduced response
	2	Faint response
	3	No reflex
Muscle relaxation score (open the mouth)	0	Normal resistance to open the mouth
	1	The jaw can be opened, but there is still some resistance
	2	Little resistance to open the mouth and obvious muscle relaxation
	3	No resistance

Table 3. *Cardiopulmonary parameters of IA group and EI group (n=8, X±SD)*

Time (min)	HR (beats/min)		RR (/min)		SpO_2 (%)		SAP (mmHg)		DAP (mmHg)		MAP (mmHg)	
	IA Group	EI Group	IA Group	EI Group	IA Group (%)	EI Group (%)	IA Group	EI Group	IA Group	EI Group	IA Group	EI Group
0	120.38±9.31	118.13±11.43^{A}	22.13±0.61	23.88±0.89^{A}	98.25±1.08	97.75±0.91^{A}	127.38±3.75	128.63±4.02^{A}	75.75±3.55	73.50±4.02^{A}	96.25±4.98	94.13±6.75^{A}
5	132.50±10.24*	126.25±9.05*^{A}	20.00±0.00	25.25±1.01^{B}	98.88±0.98	96.88±0.86^{A}	131.63±4.98	128.75±3.82^{B}	78.63±2.13	74.00±2.10^{A}	98.75±6.89	94.38±3.89^{A}
10	122.25±7.87	120.00±8.32^{A}	20.00±0.00	24.13±1.78^{B}	97.75±0.98	95.75±0.79^{A}	123.25±4.29	124.13±5.09^{A}	74.38±2.09	72.88±3.64^{A}	94.38±7.53	90.25±7.26^{A}
20	118.75±6.54	118.25±7.68^{A}	20.00±0.00	20.75±0.98^{A}	98.25±0.82	95.88±0.74^{A}	120.50±3.74*	120.25±3.28^{A}	72.25±1.99	70.50±3.21^{A}	92.13±4.62	89.75±4.81^{A}
30	117.38±5.87	117.00±8.16^{A}	20.00±0.00	18.88±0.79*^{A}	99.00±0.79	95.13±0.83^{A}	116.88±5.12*	118.50±4.65*^{A}	69.88±3.72*	67.88±2.78^{A}	88.88±5.39*	88.50±5.26^{A}
40	115.50±6.42	115.88±7.36^{A}	20.00±0.00	19.00±0.63*^{A}	98.38±0.83	95.38±0.89^{A}	116.75±4.02*	115.38±3.77*^{A}	66.88±4.58*	66.38±3.46*^{A}	86.63±4.29*	86.63±6.24*^{A}
50	113.88±7.31	113.88±8.28^{A}	20.00±0.00	18.75±0.49*^{A}	99.25±0.75	95.63±0.96^{A}	116.13±4.24*	115.00±2.79*^{A}	64.25±2.76*	64.75±2.65*^{A}	86.00±8.12*	86.25±3.11*^{A}
60	113.25±5.98	111.25±9.83^{A}	20.00±0.00	18.50±0.87*^{A}	98.88±0.93	95.25±0.77^{A}	115.88±3.36*	114.63±4.58*^{A}	63.25±3.19*	64.00±3.61*^{A}	85.88±7.32*	86.00±3.23*^{A}
70	118.63±4.79	116.50±8.17^{A}	22.63±1.26	22.88±0.61^{A}	99.25±1.01	96.88±0.98^{A}	126.88±3.11	127.88±4.39^{A}	74.25±3.01	73.88±4.15^{A}	96.25±3.22	93.75±6.51^{A}
80	121.00±6.98	118.25±5.42^{A}	22.88±0.82	23.75±0.98^{A}	98.63±0.97	98.25±0.63^{A}	127.00±5.41	127.50±2.99^{A}	75.50±2.42	73.50±2.77^{A}	96.00±6.13	94.63±4.77^{A}

** datum comparison: denote the differences compares with T_0 were extremely significant, P<0.05. The different upper cases of the superscript mean that the data of the two groups were significantly different at P<0.05. A represent inconspicuous difference P>0.05, B represent significant difference P<0.05*

but the others revealed good anesthetic effects, and this state was maintained until the end of anaesthesia.

The results of cardiopulmonary parameters of IA group and EI group were summarized in *Table 3*. The HR of the two groups increased significantly (P<0.05) between 0-5 min after anesthesia, and then decreased gradually. The alteration was close to the normal values 20 min after anesthesia. From induction to the end of anaesthesia, HR of these groups had no discrepancies. In IA group, values of RR had no significant changes during anaesthesia. In EI group, the RR increased significantly during first five min after administration, then the RR began to decrease at 10th min and continued to decline until 30 min, remained stable from 30 to 60 min. Values of RR returned to normal ranges in a short time at the end of anaesthesia. Discrepancies that were overt came up (P<0.05) between two groups in RR at 5 min and 10 min. SpO_2 had been maintained at 97-100% in IA group. In EI group, SpO_2 was maintained at above 95%. During anaesthesia, mucous membranes of only a few dogs had slight color changes to white. Values of SAP, DAP and MAP were slightly higher after induction of anaesthesia, then decreased in both sets. In terms of these indicators, diversities which were obvious did not take place in both groups.

DISCUSSION

In terms of the quantity of advantages, the method of intravenous administration of volatile anaesthetics has even more advantages than the way of inhalation. Anaesthesia induction will be quick with the anaesthesia circuit rapidly and pulmonary functional residual ability is bypassed. The vaporizer which aims to set the concentration of the anaesthetic would be weed out, hence, the charge that is applied to get, as well as maintain the equipment which is used for volatile anaesthetic could be decreased. When newer inhalation anaesthetics are in use, this can be salutary in particular. Reports related to volatile anesthetics used intravenously point out that whether they occur accidentally in humans or animals, they are currently causing death or morbidity [2,3,6]. Rats as well as dogs are both the objects of halothane injection through the veins in the state of emulsion in intralipid [2,3,7] Anaesthesia for dogs via intravenous injection isoflurane were made a comparison with the way of narcotizing dogs by inhaled isoflurane. The anaesthetic using in an inhaled manner that used most far-ranging, currently in practice of veterinary medicine is isoflurane [8]. We found that 8% of EI in the aspect of induction and recovery, the first mentioned of two was faster, the latter was quieter, and in terms of chemical inhibition, it was also efficacious in dogs.

Traditionally, measurement of the depth or level of anaesthesia chiefly relies on the observation that there is an incision in the skin of humans or the tail or the interphalangeal skin of animals is clamped, a painful irritation [9]. In the present study, the assessment had to be done with the depth or level of anaesthesia depending on the method of scoring, which in group of EI was higher than that of IA groups. Scores of anaesthesia in EI group showed better analgesic aspect than IA groups when clamping interphalangeal skin for 3 secondsusing Kocher's forceps. The value of HR augmented without delay, under the circumstances of putting both of the treatments into effect and returned to near-normal at the end of the anaesthesia. This may be due to the augmentation of the velocity of heart has something to do with isoflurane [1]. Isoflurane will decrease total autonomic nervous system activity during anaesthesia, a momentous system of getting command of nervous with a view to hold the stabilization of cardiovascular is the nervous system which is autonomic [10]. No significant discrepancies were achieved under circumstance of using EI group to

compare IA group. Although the HR decreased with the continuing of anaesthesia; HR in both groups was within physiologic acceptable limits.

Similar to HR, RR increased immediately after the administration in EI group. After five min RR decreased and reached the lowest levels from 30 min to 60 min. This may be due to isoflurane has been related to increased heart rate and would be resulted in a drop off in the dose, which was followed by a decline in the rate which have to do with the respiration of dogs [11]. The decline relies on dosage would occur in the aspect of blood pressure, cardiac output as well as systemic vascular resistance of dogs, sheep, goats and humans on account of the impact to cardiovascular which generated by isoflurane in line with the report [3].

The presence of discrepancy in the matter of statistics is none when come down to SAP, DAP and MAP that pertain to both of the agents on the basis of the outcomes of this study. By reason of being short of irritation which made by operation, led to a decline of SAP, DAP as well as MAP in the state of narcotizing by both isoflurane and EI anaesthetics for a period of 10 to 60 min. In spite of transient descend in MAP within five min, these parameters became nearly normal after anaesthetic drugs. There were no significant differences among these values. Some studies verified that the stability of hemodynamic of lipid emulsion was facilitated by injecting through the way of vein of isoflurane [11,12]. IA group in contrast to EI group is a little higher in the aspect of density of SpO_2, nevertheless there were no statistical differences noted between two groups, the lower of SpO_2 concentration in EI group may be due to the way of elimination of EI. Both groups were within normal reference ranges. While injecting EI by vein, it draw a conclusion that MAC is less, in the meantime, the usage of isoflurane is even less in the case of contrasting with in drawing the steam of isoflurane [13]. In the case of the two agents, dramatic differences did not occur in the wake time of the dogs. The depth of anesthesia can be determined by 8% EI through anesthesia injection, and then the infusion speed is adjusted by the concentration of isoflurane at the end of tidal wave. Finally, the partial pressure of isoflurane in arterial blood is calculated.

As shown in *Table 3*, we found the discrepancies are not evident for HR, RR, SAP, DAP, MAP and SpO_2 between the two anaesthetics, but EI which consisted in this study, developed anaesthesia with sufficient analgesia, muscle relaxation as well as inexistence of complication to dogs. There are many links in the process of using inhalation anesthetics leaking to the external environment, causing pollution and endangering human health. Moreover, some inhalant anesthetics have irritating effects on respiratory tract at high concentrations, or they can be absorbed by ventilator. EI is a type of intravenous anesthetic which may be useful clinically for the induction of anaesthesia. Some studies demonstrated that anesthetic induction and recovery produced by EI were more rapid than that by propofol. EI has been demonstrated to protect many organs including heart, brain, spinal cord, lung, kidney and liver against the injury induced by ischemia or ischemia-reperfusion in animal models [13-16]. The EI that was used in this study provided an adequate anaesthesia effect in dogs, which was characterised by adequate analgesia and muscle relaxation without any complications. Considering that the organ protection and lower cost which belongs to intravenous EI, EI is a real innovation, it is not only a novel administrative protocol for isoflurane, but also with some unquestionable advantages. The results of our study revealed that no conspicuous differences were discovered between intravenous emulsified isoflurane and inhaled isoflurane in dogs. This study showed that there is a good prospect for using EI intravenously in dog anaesthesia.

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Conflicts of interest

The author declares no conflict of interest

Authors Contributions

Lin Li defined the research theme, gave the conception of the research. Jing Dong and Lin Li carried out experimental part of the study. Honggang Fan and Lin Li have made supervised the analysis of the results, and contributed to the writing of the manuscript. Jing Dong and Honggang Fan were involved in drafting the manuscript and revising it critically for important intellectual content and have made a substantial contribution to conception and design, analysis and interpretation of data. All authors discussed the results and contributed to the final manuscript.

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