

Effects of intrathecal administration of ketamine HCl in young calves: a clinical trial

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Abstract

The purpose of the study was to investigate the clinical, biochemical, and cardiovascular effects of intrathecal (IT) administration of ketamine HCl in calves. The study was performed on seven Simmental and three Montofon calves, 1.70 ± 1.16 weeks old, weighing approximately 37 kg, undergoing surgical procedures including femur fracture repair (one case), atresia anus (five cases), prolapsed rectum (one case), suturing on rear limbs (two cases), and urethrostomy (one case). After administering IT ketamine HCl at a dose of 3 mg/kg to all calves, the level and depth of the anaesthesia was checked with a pin-prick test. Each animal was monitored by recording heart rate, arterial blood pressure, respiratory rates, and rectal temperature. Furthermore, certain biochemical parameters, blood gases, oxygen-total haemoglobin, and electrolyte levels were measured. All data were statistically evaluated using Minitab 16 software. Anaesthesia occurred in all calves at an average of 5.00 ± 1.41 min (range: 3-7) and continued for an average of 61.4 ± 40 min (range: 55-70). Sufficient anaesthesia was achieved in all animals for the required operations, and no complications occurred with regard to clinical and haemodynamic measurements. We concluded that in calves, which are not deemed suitable for administration of local anaesthetic *via* IT due to certain side effects, sufficient anaesthesia can be provided with ketamine by the same method for operations performed in the perineal area and hind extremities, and that this could be a good alternative for anaesthesia under field conditions.

Keywords: calves, intrathecal anaesthesia, ketamine.

Introduction

Intrathecal (IT) anaesthesia is a simple and economical method that can be used without any need for devices and equipment which is necessary for inhalation anaesthesia; however, it does require experience (2, 14, 20, 21).

Ketamine causes a dissociative anaesthesia characterised by deep analgesia and amnesia by cutting off communication between the thalamocortical center and the limbic system (1, 7, 9, 10, 12, 16). It has been shown that it provides sensory and motor blockage when administered *via* IT (7, 17). Its action is based on two mechanisms: ketamine is an antagonist of the N methyl-D aspartate (NMDA) receptors located in the dorsal root of the spinal cord (15, 16, 17, 19), and it reduces depolarisation by blocking the sodium channels similarly to local anaesthetics (7, 12, 13, 15, 17, 18). In addition, it is claimed that ketamine is beneficial for the respiratory system due to its bronchodilator effect (10,

12, 16). However, considering the effect of its local anaesthesia, it can be said that ketamine is less advantageous than local anaesthetics with regard to the duration and quality of the anaesthesia (7, 18).

When using local anaesthetic agents *via* IT, the occurrence of bradycardia and hypotension is unavoidable (7, 12, 17, 21). The fact that ketamine HCl does not cause hypotension when administered *via* IT due to its known effects on the heart and respiratory system, gives it a significant advantage over local anaesthetics (13).

Although it has been claimed that spinal myopathy can develop when an overdose of IT ketamine HCl is used (12), no evidence of neurological damage has been identified in numerous human and animal studies (5, 12, 16).

The purpose of this study was to investigate the clinical and biochemical effects and certain haemodynamic effects of IT administration of ketamine HCl in calves, and to determine whether or not the

anaesthesia achieved makes it a good alternative for on-site administration.

Material and Methods

The study was performed on 10 calves, 4 female and 6 male, brought to the Surgery Clinics in the Faculty of Veterinary Medicine at Kafkas University for operations on soft or bone tissues in the perineum, pelvis, and hind extremities. Surgical procedures included femur fracture repair (one case), atresia ani (five cases), prolapsed recti (one case), suturing on rear limbs (two cases), urethrostomy (one case). Body weight, age, sex and breed of each calf were recorded before the operation. The live weight of the animals was 37.50 ± 2.63 kg and the age was 1.70 ± 1.16 weeks. The calves comprised seven Simmentals and three Montofons.

All animals were given atropine (0.04 mg/kg i.m., Atrol-F® 20 mL vial, Sanovel-Turkey). After 20 min they were sedated with 0.2 mg/kg i.m. of Xylazine HCl (Rompun®, 2% 50 cc, Bayer, Germany). The sedated animals remained in the lateral position throughout the procedures. After the lumbosacral region was shaved and disinfected, local infiltration anaesthesia was achieved from the skin to the spinal space using 2 mL of lidocaine (Adokain®, 50 mL vial, Sanovel-Turkey). Subsequently, an 18 G spinal needle was inserted into the spinal space through the lumbosacral space. After this procedure was verified with the flow of cerebrospinal fluid, 3 mg/kg of ketamine HCl (Ketasol 10% inj. 10 mL vial Richter Pharma, Turkey) were injected very slowly (1 mL/min) into the spinal space.

Each animal was monitored (Veteriner Monitör® MMED6000DP S6-V) by recording heart rate, arterial blood pressure, electrocardiogram (ECG), respiratory rate, and rectal temperature initially, at sedation, and during the anaesthesia at 5, 15, 30, 60, and 90 min. During these procedures, three measurements were taken for each calf and calculated as an average. In addition, blood gases, oxygen-haemoglobin, and certain electrolyte readings were measured in venous blood at the same time intervals (IDEXX VetStat® Electrolyte and Blood Gas Analyzer, USA). Furthermore, venous blood was collected before the procedure and at 5, 15, 60 and 120 min after the IT injection to measure serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity, as well as glucose, blood urea nitrogen (BUN), and creatinine concentrations using a colorimetric method.

Extremity leads were used for the ECG measurements. QT measurements were corrected for the heartbeat to calculate corrected QT (QTc) intervals. The formula $QTcF = QT/(RR)^{1/3}$ developed by Fridericia (6) was used for this purpose.

A deep pinprick was performed every 5 min in order to determine the start time and end time of the anaesthesia. After IT injections were completed,

painful stimuli were applied with a 23-gauge needle to assess superficial and deep pain in the tail, perineum, and hind limbs. The deep pinprick was evaluated on a scale from 1 to 4 as reported by De Rossi *et al.* (4): 1 - no analgesia and normal strong reaction to stimulus; 2 - mild analgesia and depressed reaction to stimulus; 3 - moderate analgesia and no response to superficial needle-prick stimulation of the skin in response to stimulus; and 4 - complete analgesia and no response to insertion of the needle deep into the muscle layer. Even if the operation ended early, the pinprick procedure was continued until the end of the anaesthesia.

The operations on the calves were performed with routine surgical procedures, followed by postoperative antibiotics and analgesia as well as daily care.

Statistical evaluation of the data obtained was performed by a normality test (Anderson-Darling) using the Minitab programme, followed by Kruskal-Wallis test for non-parametric data and the ANOVA method (One-way Analysis of Variance-Tukey's pairwise comparisons), with $P < 0.05$ considered as significant.

Results

The findings were evaluated based on clinical, haemodynamic (Table 1), and haematological parameters (Tables 2, 3).

Clinically, all calves were anaesthetised after, on average, 5.00 ± 1.41 min (min. 3, max. 7 min), and the anaesthesia lasted for on an average of 61.4 ± 40 min (min. 55, max. 70 min).

There was a statistically significant difference with regard to pulse measurements from the start time to the sedation and 5 and 15 min after the induction of the anaesthesia ($P < 0.05$), but this difference disappeared 30 min after the induction (Table 1). No statistically significant difference was found with regard to systolic measurements initially, during sedation, and throughout the anaesthesia (Table 1). Although there was a statistically significant difference with regard to diastolic measurements from the start time to the sedation and first 5 min of the anaesthesia ($P < 0.05$), this difference disappeared after 15 min from the induction of the anaesthesia. No statistically significant differences were found in ECG measurements.

There was a statistically significant difference between respiratory measurements from the start time until 30 min after the induction of the anaesthesia ($P < 0.05$), but later this difference disappeared (Table 1). No statistically significant difference was found between body temperature measurements (Table 1).

A statistically significant difference was found in the glucose measurements between the start time and 60 min, start time and 120 min, and between 5 and 120 min ($P < 0.05$) (Table 2). No statistically significant differences were found between ALT and AST

measurements (Table 2). Statistically significant differences were found in the BUN measurements between the start time and 60 min, start time and 120 min, and between 5 and 120 min ($P < 0.05$) (Table 2). For creatinine measurements, a statistically significant difference was found between the start time and 15 min, start time and 30 min, start time and 60 min, start time and 120 min, and between 5 and 120 min ($P < 0.05$) (Table 2).

Furthermore, no statistically significant differences were found between blood gases, oxygen-total haemoglobin and electrolyte measurements (Table 3).

None of the animals died or showed any indication of neurological damage or insufficient anaesthesia for the operation.

Table 1. Haemodynamic parameters and evaluation periods

Value	Time (min)					
	Initial value	Sedation	5	15	30	60
Pulse	101.70 $\pm$ 11.01 ^a	71.50 $\pm$ 19.10 ^b	77.90 $\pm$ 12.64 ^b	82.60 $\pm$ 5.36 ^{bc}	92.40 $\pm$ 7.03 ^{ac}	101.50 $\pm$ 10.75 ^{ac}
Systolic	104.00 $\pm$ 20.68 ^a	78.60 $\pm$ 25.53 ^a	84.80 $\pm$ 23.41 ^a	91.10 $\pm$ 22.24 ^a	98.60 $\pm$ 20.76 ^a	104.30 $\pm$ 20.73 ^a
Diastolic	95.80 $\pm$ 12.00 ^a	68.00 $\pm$ 14.48 ^b	66.50 $\pm$ 13.15 ^b	70.20 $\pm$ 14.38 ^{ab}	79.20 $\pm$ 21.63 ^{ab}	90.80 $\pm$ 16.68 ^{ab}
Respiration	17.00 $\pm$ 2.78 ^a	13.50 $\pm$ 2.27 ^b	11.60 $\pm$ 0.96 ^b	10.90 $\pm$ 1.44 ^b	13.00 $\pm$ 1.49 ^b	14.80 $\pm$ 2.20 ^{ab}
Temperature	37.66 $\pm$ 0.17 ^a	37.48 $\pm$ 0.18 ^a	37.38 $\pm$ 0.22 ^a	37.54 $\pm$ 0.08 ^a	37.69 $\pm$ 0.16 ^a	37.71 $\pm$ 0.12 ^a

Differences between average values are shown by different letters (a-c) on the same line ($P < 0.05$)

Table 2. Biochemical measurements

Value	Time (min)				
	Initial	5	15	60	120
Glucose	58 $\pm$ 5.59 ^b	61.78 $\pm$ 7.01 ^b	67.53 $\pm$ 6.21 ^{ab}	78.80 $\pm$ 6.46 ^a	79.76 $\pm$ 11.92 ^a
ALT	33.61 $\pm$ 5.95 ^a	33.02 $\pm$ 5.88 ^a	30.46 $\pm$ 6.13 ^a	30.88 $\pm$ 3.70 ^a	26.70 $\pm$ 4.35 ^a
AST	27.30 $\pm$ 5.17 ^a	21.58 $\pm$ 5.07 ^a	20.71 $\pm$ 4.61 ^a	22.08 $\pm$ 4.57 ^a	18.13 $\pm$ 4.76 ^a
BUN	14.36 $\pm$ 2.81 ^b	16.54 $\pm$ 1.86 ^{bc}	18.54 $\pm$ 2.23 ^{ab}	20.38 $\pm$ 2.42 ^{ac}	21.44 $\pm$ 2.42 ^a
Creatinine	0.98 $\pm$ 0.18 ^b	1.38 $\pm$ 0.24 ^{bc}	1.58 $\pm$ 0.18 ^{ac}	1.79 $\pm$ 0.32 ^{ac}	2.04 $\pm$ 0.39 ^a

Differences between average values are shown by different letters (a-c) on the same line ($P < 0.05$)

Table 3. Blood gases, oxygen-haemoglobin and electrolyte measurements

Value	Time (min)		
	Initial	30	60
PH	7.43 $\pm$ 0.04 ^a	7.40 $\pm$ 0.04 ^a	70.44 $\pm$ 0.04 ^a
pCO ₂ (mmHg)	45.60 $\pm$ 6.05 ^a	46.80 $\pm$ 5.99 ^a	46.00 $\pm$ 5.94 ^a
HCO ₃ (mmol/L)	27.24 $\pm$ 3.00 ^a	27.91 $\pm$ 3.05 ^a	27.52 $\pm$ 3.03 ^a
AnGap (mmol/L)	11.86 $\pm$ 3.78 ^a	12.33 $\pm$ 4.02 ^a	11.27 $\pm$ 4.38 ^a
tCO ₂ (mmol/L)	28.67 $\pm$ 3.14 ^a	29.26 $\pm$ 2.71 ^a	29.43 $\pm$ 2.79 ^a
PO ₂ (mmHg)	29.50 $\pm$ 3.97 ^a	27.10 $\pm$ 4.43 ^a	29.20 $\pm$ 4.46 ^a
tHb (g/dL)	11.44 $\pm$ 0.51 ^a	12.08 $\pm$ 0.53 ^a	11.60 $\pm$ 0.55 ^a
SO ₂ (%)	65.40 $\pm$ 1.77 ^a	61.70 $\pm$ 0.94 ^a	63.60 $\pm$ 1.50 ^a
Na (mmol/L)	140.40 $\pm$ 2.80 ^a	142.40 $\pm$ 0.97 ^a	141.20 $\pm$ 1.23 ^a
K (mmol/L)	4.71 $\pm$ 1.14 ^a	4.25 $\pm$ 0.23 ^a	4.67 $\pm$ 0.12 ^a
Cl (mmol/L)	106.50 $\pm$ 3.21 ^a	104.30 $\pm$ 0.82 ^a	103.80 $\pm$ 0.92 ^a

Discussion

It has been reported that ketamine HCl administered *via* IT provides sensory and motor blockage both by its antagonist effect on NMDA receptors and by blocking calcium channels (7, 12, 13, 15-17, 19). The purpose of this study was to use these characteristics of IT administration of ketamine and evaluate its efficacy on calves.

Clinically, all calves were anaesthetised after, on average, 5.00 ± 1.41 min (min. 3, max. 7) and the anaesthesia lasted for 61.4 ± 40 min (min. 55, max. 70). It seems that this anaesthetic effect might have occurred by the mechanism mentioned above. On the other hand, the use of a strong analgesic agent is suggested for postoperative pain. Hence, this technique may contribute to a decrease in postoperative analgesic drug use and an increase in postoperative comfort of animals, because IT ketamine HCl causes analgesia besides anaesthetic effect. Lee *et al.* (14) reported that although the use of epidural ketamine in cows provided analgesia in the tail, perineum, and hind legs, ataxia could develop as an undesirable effect (14). In our study, however, analgesia and muscle relaxation was achieved in the tail, perineum and hind legs, but the calves did not have post-operative problems, and there was no indication of ataxia. General or inhalation anaesthesia for this type of operations may also be preferred in calves. However, inhalation anaesthesia, requiring more staff and equipment, is more expensive. Thus, IT anaesthesia may be practical and economic for surgical procedures on such body parts as tail, perineum, and hind legs. It has been reported that in epidural or spinal administration of ketamine HCl, no statistically significant difference occurred in measurements of pulse, arterial blood pressure, respiration, and body temperature (9, 10, 14). In our study, we determined that the statistical differences in the pulse and arterial blood pressures (Table 1) were due to sedation, and they improved within 15 min after administering ketamine. No statistically significant differences were found in ECG measurements. Although there was a statistically significant difference with regard to respiratory measurements from the start time until 30 min after the induction of the anaesthesia ($P < 0.05$), the respiratory rates were within clinical reference ranges. Based on the data, it can be stated that ketamine does not have a negative effect on the heart rate or respiration when administered as an epidural or IT.

Different local anaesthetics, such as bupivacaine, levobupivacaine, or ropivacaine are commonly used in epidural, spinal, or IT anaesthesia for caudal operations in calves. However, one of the most common side effects of local anaesthetic is rapidly developing hypotension. The anaesthetic agent that spread along the spinal cord would depress the respiration (20, 21). To prevent possible respiratory and circulatory problems, either the operation table or the neck and

thorax of an animal should be maintained in an upward position. Thus, anaesthetic safety of this technique can be advantageous compared to other techniques. No statistically significant differences were found between ALT and AST measurements. The statistically significant differences in glucose, BUN, and creatinine measurements (Table 2) were not considered to be clinically significant since all measurements remained within the reference ranges (3).

It has been reported that intravenous administration of ketamine in dogs causes statistically insignificant changes in blood gases (11). In our study, the changes in blood gases, oxygen-haemoglobin, and electrolyte concentrations were not found to be statistically significant and all measurements remained within the reference ranges (3).

It has been stated that an increase in pulse, respiration, and systolic blood pressure by 20% or more in relation to initial values during an operation can be considered a sign of intraoperative pain (1, 18), but no increase in pulse, respiration, or systolic measurements was observed. No evidence of intraoperative pain in this regard, nor any other symptoms indicating pain, were found.

It has been stated that although IT administration of ketamine HCl produces a local anaesthetic effect, neurotoxic and vasotoxic effects can occur (15). However, the results achieved in studies using ketamine HCl (0.3-0.6 mg/kg/IT) in rats, rabbits, and primates (8, 16) have shown that neurotoxicity was at a negligible level. A different study reported that spinal myelopathy developed depending on dosage, but no information has been found regarding nerve damage caused by IT ketamine (17). In our study, no direct clinical findings or behaviour change indicating spinal anaesthesia complications were found in any of the calves. Furthermore, no abnormal symptoms in the overall condition of the animals, such as inactivity, loss of appetite, or moaning after the anaesthesia and in the post-operative period, were observed. Moreover, the animal owners did not offer any subsequent negative feedback.

In conclusion, sufficient anaesthesia can be provided with ketamine *via* IT perineal area and hind extremities operations in calves, which are not deemed suitable for administration of local anaesthetics *via* the same method due to certain side effects. Thus it could be a good alternative for anaesthesia under field conditions.

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