



Epidural Analgesia with Bupivacaine, Ketamine, and the Combination of Bupivacaine and Ketamine in Sheep

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Abstract

Objective- To evaluate the effects of bupivacaine (B), ketamine (K), and a combination of bupivacaine and ketamine (BK) after lumbosacral epidural analgesia in sheep.

Design- Experimental study.

Animals- Nine healthy male and non-pregnant female Iranian Chall sheep with mean body weight of 38.9 ± 15.1 kg.

Procedures- Animals were selected randomly and three treatments administered. The drugs were administered in the lumbosacral epidural space. The onset and duration of analgesia and sedation were determined and heart rate, respiratory rate, and rectal temperature, were recorded at 0, 5, 10, 15, 20, 30, 40, 50, and 60 min after administration. Analgesia was determined by lack of response to pin pricking and pinch test in the skin of caudal areas.

Results- The onset of analgesia was significantly faster in BK than that in B and K alone. Treatments with ketamine, either alone (K) or in combination (BK) lead to mild sedation. The heart rate increased significantly with B treatment at 15 and 20 min, and the respiratory rate showed a significant decrease with K treatment at 10 and 15 min.

Conclusion and Clinical Relevance- Epidural administration of bupivacaine/ketamine combination resulted in fast onset and moderate duration of analgesia of caudal areas. The employed doses in BK treatment probably reduced the side effects observed in B and K treatments. It is concluded that the combination of BK could be used epidurally in sheep to perform operations without any marked side effects.

Key Words- Epidural Space, Analgesia, Bupivacaine, Ketamine, Sheep.

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Introduction

Epidural analgesia is the most frequently used technique for regional analgesia of caudal areas. General anesthesia in ruminants has inherent risks such as regurgitation of ruminal contents, excessive salivation and the possibility of pulmonary aspiration; therefore it is not always recommended and local or regional techniques may be used instead.¹ Sheep and goats are ideally suited to local analgesic techniques under manual restraint with or without sedation.² Historically, local anesthetics have been the most widely used class of drugs for epidural anesthesia/analgesia. More recently, however, opioids, α 2-adrenergic agonists, and experimental classes of drug have been administered epidurally to enhance or produce anesthesia and/or analgesia.³ Many anesthetics/analgesics are commonly used for epidural analgesia, e.g. 2% lidocaine, 0.5% bupivacaine, 0.1 and 1.5% morphine, 0.1% medetomidine, and 2% xylazine. Since each of these agents can potentially cause side effects produced by high doses, one should attempt to employ the most appropriate and lowest possible dose with proper efficacy. To attain this purpose, the technique of mixing two anesthetic/analgesic agents may be employed; hereby we may profit the advantages of both. The agents used in combination should be physicochemically compatible. The choice of an analgesic regimen in a particular setting is thus a complex matter, dependent on factors such as the animal species involved, the type and duration of surgery, the severity of the pain and the efficacy of the analgesics. The effects of bupivacaine and xylazine have been compared to that of their combination in goats.⁴ Epidural administration of bupivacaine produced complete analgesia of tail, perineum, inguinal and thigh regions in healthy and uremic goats.⁵ Ketamine and xylazine have been evaluated in epidural administration with regard to clinicophysiological and hematobiochemical parameters in goats.⁶ Epidural administration of ketamine in horses⁷ or subarachnoid administration of ketamine and lidocaine in goats⁸ can provide sufficient analgesia without any alteration of cardiovascular and respiratory functions. Addition of ketamine enhances the analgesic effect of epidurally administered xylazine while reducing its cardiopulmonary side effects.⁹ Sheep is a good model for spinal and epidural analgesia.¹⁰ It represents the principal economic output in Africa and Asia, contributing a large share of the income of farmers¹¹ and its production is a crucial sector of human activity.¹² To date, the use of bupivacaine and ketamine mixture in sheep has not been reported. In this study, we chose ketamine and bupivacaine for assessment. The aim of this study was to compare the effects of the epidurally administered bupivacaine, ketamine and bupivacaine-ketamine combination in sheep and to evaluate if there are any beneficial properties of using them in combination.

Materials and Methods

Nine healthy male and non-gravid female Iranian Chall sheep with average body weight of 38.9 ± 15.1 kg were used. They were kept for one week in the stable to acclimatize to the new environment. They were then kept under similar conditions and provided with hay and water ad libitum. On the basis of clinical and hematologic evaluations, the sheep were judged to be in good health, just before the commencement of the trials. To make sure that the animals are in similar state of health, however, they were treated with oxytetracycline 5% (Oxyvet® 5%, Razak

Laboratories, Iran) for 3 days at 10 mg kg⁻¹, IM, s.i.d and albendazole (Albendazole 600mg, Iran Veterinary Drugs Production Co., Iran) at 15 mg kg⁻¹, PO, single dose.

Three series of trials were carried out in all sheep with 7 days between trials and randomly allocated to each trial. Group I received epidural administration of 0.5 % bupivacaine hydrochloride (B; Bupivacaine Merk®, Merk génériques, France) alone; group II received similar administration of 5 % ketamine hydrochloride (Ketamine Hydrochloride 50 mg mL⁻¹, Rotex Medica, Germany) alone; while group III received similar administration of 0.5 % bupivacaine hydrochloride plus 5% ketamine hydrochloride (BK) mixture at half their doses when used alone.

A preliminary pilot study was carried out on five sheep to determine the lowest effective doses of B and K. These were found to be 0.5 mg kg⁻¹ and 2.5 mg kg⁻¹ for B and K, respectively; hence in combination, half of their determined effective doses would be 0.25 mg kg⁻¹ and 1.25 mg kg⁻¹ for B and K, respectively. The calculated volumes of K and BK were diluted with injectable saline solution so that they equaled that of B. The calculated volumes were 1, 0.75, and 0.5 mL 10kg⁻¹ for B, BK and K, respectively (Table 1). No color change or precipitation resulted from mixing.

Table 1. Implemented doses of drugs based on pilot study and calculated volumes of each

Drug	Dose (mg kg ⁻¹)	Volume (ml 10kg ⁻¹)
Bupivacaine	0.5	1
Ketamine	2.5	0.5
Bupivacaine + Ketamine	0.25 + 1.25	0.5 + 0.25

For each injection, the sheep was restrained in lateral decubitus with the lumbosacral spine in full flexion. Before positioning, the lumbosacral region was clipped and prepared as for surgery to perform an aseptic epidural injection. The lumbosacral site was identified and the site of introduction of needle was infiltrated with 1-2 mL (depending on body mass) of 2 % lidocaine without epinephrine solution using a 20 gauge needle. A sterile 18 gauge 3.25 cm long hypodermic needle was inserted through the skin at a 90° angle and directed to lumbosacral space. When the needle point was judged to have penetrated the ligamentum flavum, a 10 mL syringe containing 2 mL of air was attached to the needle. Then the needle was advanced cautiously while exerting a concomitant pressure on the plunger until resistance to injection of the air was lost. Verification of correct epidural placement was also assessed by the absence of CSF flow before injection and lack of resistance upon injection of the drug(s). The second syringe containing appropriate anesthetic drug was then attached to needle and administration was made over 10 seconds.

The onset and duration of analgesia were recorded. Analgesia was determined by lack of response to pin pricking and pinch test of the skin of caudal areas (rump, anal region, caudal sacral region, caudal gluteal region, caudal thigh region). Then, these tests were applied until the animal responded to the stimulus; thereby duration of desensitization was determined. Sedation was rated according to the following scale from 1-4: 1= No sedative effect; 2= Mild sedation, reduced alertness with no other signs; 3= Moderate sedation with drowsiness and slight drop of

head; and 4= Severe sedation with marked drowsiness. Heart rate (HR), respiratory rate (RR), and rectal temperature (RT) were determined before injection (Baseline) and 5, 10, 15, 20, 30, 40, 50, and 60 min thereafter. HRs and RRs were recorded with a stethoscope and counting thorax respiratory movements per minute, respectively. RTs were taken by a digital thermometer. All the data (time to onset of analgesia, duration of analgesia, sedation scale, heart rate, respiratory rate, and rectal temperature) were expressed as (means \pm S.D.) of nine sheep in each group. Time to onset of analgesia, duration of analgesia, and sedation were analyzed between the three groups (B versus BK; K versus BK; and B versus K) using two-way ANOVA for repeated measures. Within group comparison of the effects of the treatments (B, K, and BK) on HR, RR, and RT compared to the baseline value was performed using one-way ANOVA. Where significant differences were indicated by ANOVA, least significant difference test was employed as post-test. In each analysis, differences were considered statistically significant if $P < 0.05$ (SPSS for Windows, version 15.0, SPSS Inc.).

Table 2. Cardiopulmonary function and rectal temperature following epidural administration of bupivacaine (B; 0.5 mg kg⁻¹), ketamine (K; 2.5 mg kg⁻¹), and bupivacaine+ketamine combination (BK; 0.25+1.25 mg kg⁻¹) in sheep.

TR. Time (min)	Values								
	B			K			BK		
	HR (min ⁻¹)	RR (min ⁻¹)	RT (°C)	HR (min ⁻¹)	RR (min ⁻¹)	RT (°C)	HR (min ⁻¹)	RR (min ⁻¹)	RT (°C)
Baseline	91.6 \pm 2.8	36.6 \pm 10.5	39.8 \pm 0.1	85.6 \pm 10.5	34.6 \pm 7.5	39.7 \pm 0.3	93 \pm 14.5	32.6 \pm 4.1	39.3 \pm 0.2
5	99 \pm 6.9	36.3 \pm 14	40 \pm 0.2	96.3 \pm 5.5	34 \pm 9.2	39.8 \pm 0.4	97.3 \pm 9.3	32.6 \pm 7.2	39.3 \pm 0.2
10	103.6 \pm 5.1	37 \pm 11.5	40.1 \pm 0.2	98.3 \pm 4.2	25.6 \pm 4*	39.7 \pm 0.2	96.3 \pm 15.3	30.3 \pm 8	39.3 \pm 0.2
15	96.3 \pm 1.5*	38.6 \pm 13	40.1 \pm 0.2	96 \pm 5.5	26.3 \pm 6.4**	39.7 \pm 0.5	98.3 \pm 21.3	34 \pm 6.9	39.4 \pm 0.3
20	106.3 \pm 5*	40 \pm 14	40 \pm 0.1	94 \pm 6	32 \pm 6	39.8 \pm 0.3	98.6 \pm 17.6	30 \pm 3.4	39.4 \pm 0.3
30	104 \pm 8	41.3 \pm 10.5**	40.1 \pm 0.3	89.3 \pm 3.2	34 \pm 3.6	39.7 \pm 0.5	101 \pm 23.8	33.3 \pm 2.5	39.4 \pm 0.2
40	100.6 \pm 8.3	40.6 \pm 10.5	40.1 \pm 0.2	94.3 \pm 8	31 \pm 2.6	39.8 \pm 0.4	98.3 \pm 21.4	36.3 \pm 2	39.6 \pm 0.3
50	96 \pm 7.9	45 \pm 12.3	40 \pm 0.2	87.3 \pm 4	32.6 \pm 5.6	39.9 \pm 0.2	101 \pm 26.1	35 \pm 3.6*	39.5 \pm 0.4
60	90.3 \pm 15.7	43.3 \pm 13.8	39.9 \pm 0.2	78.3 \pm 6.3	34.6 \pm 4	40 \pm 0.3	101.3 \pm 30.1	39.3 \pm 3	39.5 \pm 0.4

Values are presented as mean \pm S.D.; HR: Heart rate, RR: Respiratory rate, RT: Rectal temperature.

* $P < 0.05$; ** $P < 0.01$ compared to baseline.

Results

Complete analgesia was obtained in all treatments in caudal areas, however, no notable desensitization was observed in cranial areas. The onset of analgesia in caudal areas was at 9.5 ± 0.9 min (mean \pm S.D.), 9.4 ± 2.4 min, and 2.2 ± 0.8 min by B, K, and BK treatments, respectively (Fig. 1). BK significantly had faster onset than two other treatments ($P < 0.05$). The duration of analgesia in caudal areas by B, K, and BK was 183.7 ± 7.3 , 51 ± 3 , and 102.3 ± 4.5 min, respectively (Fig. 2). These were significantly different from each other ($P < 0.01$). B produced longer duration compared to K and BK. BK treatment, however, showed moderate duration of analgesia. Treatments with ketamine, either alone (K) or in combination (BK) lead to mild sedation (scale 2). The sedation was diminished before complete return of pain sensation. Recumbency and ataxia were not observed with any of the treatments.

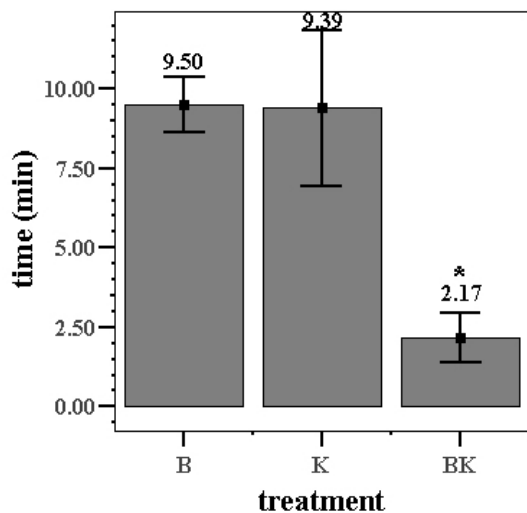
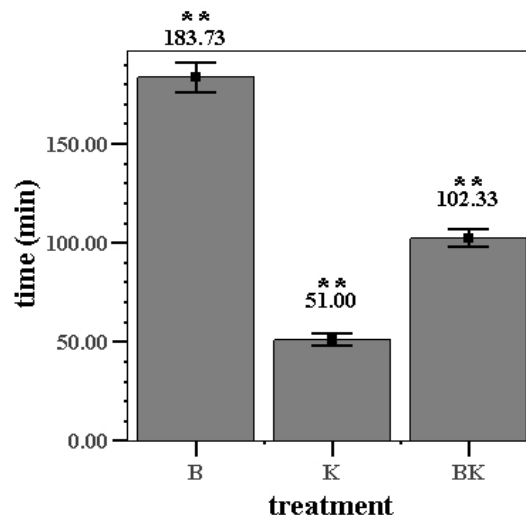


Figure 2. Duration of analgesia in caudal areas after lumbosacral epidural administration of bupivacaine (B; 0.5 mg kg⁻¹), ketamine (K; 2.5 mg kg⁻¹), and bupivacaine plus ketamine combination (BK; 0.25+1.25 mg kg⁻¹) in sheep; Bars show mean time (min); Error bars show mean ± S.D.; ** significantly different from other two groups (*P* < 0.01).

Figure 1. Time to onset of analgesia in caudal areas after lumbosacral epidural administration of bupivacaine (B; 0.5 mg kg⁻¹), ketamine (K; 2.5 mg kg⁻¹), and bupivacaine plus ketamine combination (BK; 0.25+1.25 mg kg⁻¹) in sheep; Bars show mean time (min); Error bars show mean ± S.D.; * significantly different from B (*P* < 0.01) and significantly different from K (*P* < 0.05).



The heart rate increased significantly with B treatment at 15 and 20 min compared to baseline. The respiratory rate showed a significant decrease with K treatment at 10 and 15 min, but increased with B at 30 min (*P* < 0.01) and with BK at 50 min (*P* < 0.05) compared to baseline values of each treatments. No other significant alterations in cardiopulmonary function and rectal temperature of treatments were observed (Table 2).

Discussion

Bupivacaine is dl-1butyl-2',6'-pipecoloxylidine hydrochloride (an amide-type or lidocaine-like local anesthetic) a remarkably stable component, having four times the potency of lidocaine and twice its duration of action.¹³ These make it the most desirable local analgesic drug. But bupivacaine like all commonly used local anesthetic has vasodilator activity. It possess moderate onset of action and 95 % plasma protein binding activity.¹⁴

Ketamine is dl-2-(o-chlorophenyl)-2-(methylamino)-cyclohexanone hydrochloride, a dissociative agent. We now know that it is an N-methyl-D-aspartate (NMDA) receptor noncompetitive antagonist in the central nervous system and interacts with opioid receptors in spinal cord.¹⁵ It is classified as intravenous anesthetic agents, but clinically has local anesthetic effects.^{16,17} More recently, its use for intrathecal and epidural blockade has been described.^{18,19,6,7,8,9}

The beneficial effect of adding ketamine to local anesthetic agents for spinal blockade is controversial. Kathirvel et al.²⁰ noticed that ketamine added to spinal bupivacaine had local anesthetic-sparing effects in humans. It has been reported that caudal epidural ketamine

administration induced analgesia without sedation in cattle.²¹ However, Yanli and Eren²² and Weir and Fee²³ showed that ketamine combined with local anesthetics alone did not produce any improved analgesic effects in humans. In this study, addition of ketamine at the dose of 1.25 mg kg⁻¹ to epidural bupivacaine at the dose of 0.25 mg kg⁻¹ which based on our pilot study seems to be not effective for epidural blockade, produced adequate analgesia of caudal areas in sheep. Reducing the dose of bupivacaine used in spinal anesthesia helps to achieve rapid anesthetic recovery but may result in anesthetic failure.²⁴ Addition of a low dose ketamine to epidural bupivacaine may prevent this failure without any necessity to increase its dose.

The results of present study showed that epidurally administered bupivacaine and ketamine combination (BK) in sheep produced faster onset than each agent alone and duration longer than ketamine alone and shorter than bupivacaine alone. The faster onset may be just an effect of multimodal analgesia. Ketamine added to bupivacaine for spinal analgesia decreased the sensory and motor blockade onset time insignificantly in humans.²⁰ Yanli and Eren²² suggested that addition of ketamine to bupivacaine given epidurally appears to be useful in the reduction of onset time to blockade.

Recumbency and ataxia were not observed with any of the treatments. When a nerve trunk is subjected to an anesthetic, the nerves will be desensitized with the following order which depends on the amount and diameter of myelin sheath; Autonomic nerves, Sensory nerves, Motor nerves.²⁵ The minimum effective doses used for both agents probably were not able to affect motor nerve, since no motor blockade was observed.

The epidural venous plexus provide ideal conditions for vascular absorption of injected solutions.²⁶ Lipid solubility of ketamine results in extensive intravascular absorption from epidural space.²³ Ketamine is absorbed slowly from epidural space.²⁷ In our study epidural ketamine, either alone or in combination with bupivacaine, had mild sedative effects. Epidural ketamine produced sedation in humans,²³ horses⁷ and goats.⁸ However, there was no sedative effect in three doses of 5, 10, and 20 mL of 5% ketamine after caudal epidural administration in cows.²¹ This may arise from anatomical differences,⁷ and different methods of administration.²⁸

None of the sheep of BK treatment in our study showed significant cardiopulmonary function and rectal temperature changes after epidural analgesia. Increased heart rate at 15 and 20 min after injection in sheep receiving bupivacaine alone probably was due to primary normal compensatory mechanism for hypotension caused by sympathetic block. Bupivacaine like all local anesthetics injected epidurally reduces the sympathetic tone.²⁹ In healthy animal, ketamine increases sympathetic tone,³⁰ so this effect can prevent sympathetic blockade and its sequent hypotension caused by epidural bupivacaine. Decreased respiratory rate at 10 and 15 min in K treatments may be due to respiratory depression.

It is concluded that combination of bupivacaine (0.25 mg kg⁻¹) plus ketamine (1.25 mg kg⁻¹) can be used safely for epidural analgesia in sheep. Low dose ketamine added to low dose bupivacaine enhanced the analgesic efficacy and is effective in reduction of onset time to blockade. The employed doses of BK treatment in this study probably reduced the side effects observed in B and K treatments. The combination of BK could be used epidurally in sheep to perform operations without any marked side effects.

Acknowledgment

We thank those who assisted us in performing this study, especially Mr. Gardeshi, Mr. Hasan Pour, Mr. Parsi Pour, Mr. Shadmanesh, and Mr. Pour Masum. We must also appreciate our good friend, Mr. Asgharieh Ahary for his assistance in proofreading the article.

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بیحسی فوق سخت شامه ای با بوپیواکائین، کتامین، و ترکیب بوپیواکائین و کتامین در گوسفند

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هدف- این مطالعه به منظور ارزیابی اثرات بوپیواکائین (B)، کتامین (K) و ترکیب بوپیواکائین و کتامین (BK) بعد از بیحسی فوق سخت شامه ای کمری-عجزی در گوسفند انجام شد.

طرح مطالعه- مطالعه تجربی در روی موجود زنده.

حیوانات- ۹ گوسفند ایرانی شال سالم نر و غیر آبستن ماده با متوسط وزنی $15/1 \pm 38/9$ کیلوگرم.

روش کار- حیوانات به صورت تصادفی انتخاب شدند و ۳ تیمار به انجام رسید. داروها در فضای فوق سخت شامه ای کمری-عجزی تزریق شدند. شروع اثر و طول اثر بیحسی و آرام بخشی ایجاد شده بررسی شد و ضربان قلب، تعداد تنفس و دمای مقعدی در دقایق ۰، ۵، ۱۰، ۱۵، ۲۰، ۳۰، ۴۰، ۵۰ و ۶۰ بعد از تزریق ثبت شدند. بیحسی با فقدان واکنش نسبت به تست های نیش سوزن و نیشگون در پوست نواحی خلفی تعیین شد.

نتایج- شروع اثر بیحسی در گروه BK به طور معنی داری سریع تر از گروه های B و K بود. تیمار های انجام شده با کتامین، چه به تنهایی (K) و چه به صورت ترکیبی (BK) باعث آرام بخشی ملایمی شد. ضربان قلب در تیمار B در دقایق ۱۵ و ۲۰ به طور معنی داری افزایش پیدا کرد، و تعداد تنفس در تیمار K در دقایق ۱۰ و ۱۵ کاهش معنی داری نشان داد.

نتیجه گیری و کاربرد بالینی- تزریق ترکیب بوپیواکائین/کتامین در فضای فوق سخت شامه ای شروع اثر سریع و دوام اثر متوسطی در نواحی خلفی ایجاد می کند. دوزهای به کار گرفته شده در تیمار BK احتمالاً عوارض جانبی مشاهده شده در تیمار های B و K را کاهش داده است. نتیجه گیری می شود که ترکیب BK برای انجام بیحسی فوق سخت شامه ای در گوسفند بدون ایجاد عوارض جانبی مشخص قابل استفاده می باشد.

کلید واژگان- فضای فوق سخت شامه ای، بیحسی، بوپیواکائین، کتامین، گوسفند.

