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Research Article

Comparative Analgesic Effect of Intrathecally Administered Bupivacaine, Dexmedetomidine and Their Combination in Goats (*Capra hircus*)

¹Awad Rizk, ¹Khaled Abouelnasr, ²Eman Nour, ³Rasha Eltaysh and ⁴Abdelnasser Abdalla

¹Department of Surgery, Anesthesiology and Radiology, Faculty of Veterinary Medicine, Mansoura University, 35516 Mansoura, Egypt

²Veterinary Surgery Urology and Nephrology Centre, Faculty of Medicine, Mansoura University, 35516 Mansoura, Egypt

³Department of Pharmacology, Faculty of Veterinary Medicine, Mansoura University, 35516 Mansoura, Egypt

⁴Department of Internal medicine, Infectious and Fish diseases, Mansoura Veterinary Teaching Hospital, Mansoura University, 35516 Mansoura, Egypt

Abstract

Background and Objective: Intrathecal and epidural injection are common techniques for regional analgesia in small ruminants, hence the aim of this study is to evaluate the analgesic effects of intrathecally administered bupivacaine hydrochloride, dexmedetomidine hydrochloride and their combination in goat. **Materials and Methods:** In a prospective crossover study, six clinically healthy goats were injected intrathecally with bupivacaine (1.5 mg kg⁻¹), dexmedetomidine (2 µg kg⁻¹) and their combination (0.75 mg kg⁻¹, 1 µg kg⁻¹, respectively). Heart rate, respiratory rate, rectal temperature and epidural anesthetic indices (time to onset of analgesia, duration of analgesia, duration of recumbency and time to standing) were evaluated before (T0), then at 5, 15, 30, 45, 60, 90 and 120 min post-treatment. **Results:** Dexmedetomidine and bupivacaine/dexmedetomidine treated groups both were associated with significantly decreased heart rate and respiratory rate compared to bupivacaine treated animals. Onset of analgesia after combined bupivacaine/dexmedetomidine was significantly earlier (3.9±1.9 min) than after bupivacaine (9.2±2.7 min) and dexmedetomidine (7.3±2.0 min). The duration of analgesia was significantly longer with dexmedetomidine and bupivacaine/dexmedetomidine mixture when compared with bupivacaine (160.0±27.1, 151.0±62.3 vs. 98.0±22.5 min, respectively). Duration of recumbency was significantly longer with bupivacaine (160.2±60.3 min) than with dexmedetomidine (120.0±17.2 min) or bupivacaine/dexmedetomidine mixture (131.0±63.6 min). Time to standing was shortest with dexmedetomidine (3.2±0.9 min) when compared with bupivacaine (53.2±39.2 min) and bupivacaine/dexmedetomidine mixture (40.4±35.0 min). **Conclusion:** Intrathecal bupivacaine had the shortest duration of analgesia and longest duration of recumbency, therefore, appeared unsuitable for use in small ruminant surgery. Both dexmedetomidine and bupivacaine/dexmedetomidine combination produced similar duration of analgesia and cardiorespiratory depression, however, dexmedetomidine alone was associated with shorter time to standing which could make it a better choice for intrathecal use in goat especially when economic factor is considered.

Key words: Analgesia, bupivacaine, dexmedetomidine, goat, intrathecal

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Corresponding Author: Khaled Abouelnasr, Department of Surgery, Anesthesiology and Radiology, Faculty of Veterinary Medicine, Mansoura University, 35516 Mansoura, Egypt Tel: 02-01018657259

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Regional anesthesia achieved by epidural analgesia is commonly used in ruminant surgery. In addition to being inexpensive and routinely feasible, the specific regional blockade and rapid recovery of the animal are advantages of this technique over others^{1,2}. Ruminants are poor subjects for the general anesthesia as they are prone to regurgitation, ruminal tympany, respiratory embarrassment, hypoxia with uneven ventilation and other associated problems during general anesthesia^{3,4}.

The most frequently used epidural anesthetic/analgesics agents are 2% lidocaine, 0.5% bupivacaine, 0.1 and 1.5% morphine, 0.1% medetomidine and 2% xylazine⁵⁻⁸. Most of these agents provide short duration of analgesia, so re-administration of this agent is important to allow completion of the surgical procedure. Epidural and intrathecal injection of agents with longer duration of action may be more appropriate for procedures requiring long duration of analgesia. These agents include opioids, alpha-2 agonist^{3,9,10}. 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^{10,11}.

Bupivacaine is a long acting local anesthetic agent that is used in small ruminant surgery, with 2-4 times more potent than lignocaine¹². It has been used spinally for pre-emptive and post-traumatic analgesia in buffalo calves¹³ and for epidural anesthesia in normal and uraemic goats¹⁴. It can affect some physiological parameters and may cause bloat, sleepiness and tremors, requiring more accurate monitoring when used in ruminants¹⁵. However, it has not shown to exhibit negative effects on biochemical and hematological parameters and blood gases^{14,16}.

Dexmedetomidine, α_2 -adrenoceptor agonist and S-enantiomer of medetomidine, it has sedative, analgesic and sympatholytic effects more than xylazine with mild cardiopulmonary depressant effect^{17,18}. Epidural injection of dexmedetomidine hydrochloride ($1.13 \mu\text{g kg}^{-1}$) in dogs produces complete intraoperative and postoperative analgesia, which lasts for 24 h¹⁹. Spinal dexmedetomidine in human produces a prolonged motor and sensory fibers block²⁰. Dexmedetomidine can be used in sheep and goats^{8,21}.

Hence the present report is described to be the first one to find out the quality of analgesia and to record the changes in cardio-respiratory and epidural anesthetic indices following

intrathecal administration of bupivacaine, dexmedetomidine and their combination in clinically healthy goats.

MATERIALS AND METHODS

Animals and housing: Six adult apparently healthy goats of both sexes (aged 8-18 months, average body weight 15-25 kg) were used in this study. All animals were housed in Surgery Clinic and kept in individual free stalls on straw bedding and were fed diet based on hay and concentrates. No analgesics were given within 1 week before the experiment. Just before the commencement of the trials, the goats were judged to be in a good health condition based on clinical findings and hematological evaluation. This study was performed in Mansoura Veterinary Teaching Hospital of Mansoura University, Mansoura, Egypt at April, 2017. The protocol was approved by the Mansoura Medical Research Ethics Committee (MMREC).

Study design: Experimental goats were randomly subjected to three series of trials at 1 week intervals (crossover design study). The first series involved lumbosacral subarachnoid administration of bupivacaine (BUP, Bucaine 0.5%, vial Weimar, Germany), the second trial involved similar administration of dexmedetomidine (DEX, Precedex, 200 mcg/2 mL, Hospira, inc., Lakeforest, USA), while the third series involved similar administration of bupivacaine/dexmedetomidine mixture (BUP/DEX) at half their doses when used alone. No surgery was performed on the goats.

Experimental procedure: The doses of drugs were selected based on earlier pilot study. Treatment consisted of 1.5 mg kg^{-1} (3 mL/10 kg) BUP, $2 \mu\text{g kg}^{-1}$ (0.2 mL/10 kg) DEX and a combination of both BUP at 0.75 mg kg^{-1} (1.5 mL/10 kg) and DEX at $1 \mu\text{g kg}^{-1}$ (0.1 mL/10 kg). The calculated volume of each drug was withdrawn into the syringe and further diluted with 1 mL saline to produce a convenient volume to inject into the subarachnoid space.

The lumbosacral area was aseptically prepared then infiltrated with lidocaine 2% (1 mL) at the entry point. The hypodermic needle (20-gauge, 3.5 cm long) was directed to the spinal cord at a 45° angle along the median plane. The lumbosacral space was identified and the presence of the needle in intrathecal space was confirmed by a free flow of cerebrospinal fluid from the needle. The correct placement of the needle in lumbosacral space was verified by hanging drop technique and lack of resistance during injection.

All animals subjected to intrathecal injection of treatments through 30 sec. After administration of the drugs, the animals were left undisturbed until the onset of the drug effect. The treated goats were placed on straw bedding, when recumbent and observed for any drug-induced side effects. The person who assigned to evaluate the analgesic agents was completely blinded about the treatments.

Measurements: Following intrathecal administration of analgesic agents different cardio-respiratory and epidural anesthetic indices were evaluated at 0, 5, 15, 30, 45, 60, 90 and 120 min post-treatment.

Heart rate (HR, beats min^{-1}), respiratory rate (RR, breaths min^{-1}) and rectal temperature (RT, $^{\circ}\text{C}$) was recorded at the same regular pre-set time points. Untoward reactions of the drugs were also observed such as salivation, apnea, bloat, grunting and urination. Sedation was assessed by observing drowsiness and lowering of the head and ataxia that was noticed in the post-recumbent period.

The onset of analgesia was recorded based on the goat's response to needle pricks using a hypodermic needle (24 gauges) at the base of the tail, perineum, over the spinous processes of the thoracic vertebrae as well as on the flanks, ventral abdomen and both hind limbs.

The epidural anesthetic indices were recorded and calculated for each goat which included:

- **Time to onset of analgesia:** Time interval (in min) from intrathecal injection of drug to loss of response to pin pricks
- **Duration of analgesia:** Time interval (in min) from the onset of loss of response to needle pricks to return of the pain response
- **Duration of recumbency:** Time interval (in min) from the goat's assumption of recumbency to its ability to bear weight on its hind limbs
- **Time to standing:** Time interval (in min) from the goat's assumption of sternal recumbency to its ability to stand and walk

Statistical analysis: The data for objective parameters such as HR, RR and RT were analyzed using one-way ANOVA for repeated measures. Where significant differences were indicated by ANOVA, least significant difference test was employed as post-test. The epidural anesthetic indices were compared using (students) "t" test for paired data. Data were presented as the Mean $\pm$ SE. A p-value of 0.05 was considered significant in all comparisons.

RESULTS

Following-up the animals did not prove any signs of infection at the site of the needle puncture or neurologic injury. Intrathecal administration of DEX or BUP/DEX mixture was associated with some untoward reactions such as salivation, apnoea, ruminal tympany, grunting and urination (Table 1) Intrathecal administration of DEX-induced sedation which made additional physical restraint of the treated goat unnecessary. Treatment with DEX and BUP/DEX mixture induced moderate sedation (Table 1), but no difference in the onset of sedation was detected between the two treatments. Similarly administered BUP was only associated with post-recumbent ataxia which was mild in DEX or BUP/ DEX mixture treated animals.

The effect of intrathecal DEX or BUP/DEX mixture was associated with significantly ($p < 0.05$) decreased HR and RR in both groups from 5 min onwards after intrathecal injection compared to BUP treated animals (Table 2). There was no significant difference between all treated groups at all-time points in RT (Table 2).

The effect of intrathecal injection of BUP, DEX and BUP/DEX combination on epidural anesthetic indices is presented in Table 3. Onset of analgesia was observed (9.2 ± 2.7 min) following intrathecal administration of BUP and 7.3 ± 2.0 min following DEX, whereas, it was significantly earlier in (3.9 ± 1.9 min) BUP/DEX treated animals. Analgesia firstly appeared in the perineum, tail and later spread cranially toward hind limb and flank then ventral abdomen. The duration of analgesia was significantly longer for DEX or BUP/DEX mixture when compared with BUP (160.0 ± 27.1 , 151.0 ± 62.3 vs. 98.0 ± 22.5 min, respectively). Duration of recumbency was significantly longer with BUP than with DEX or BUP/DEX mixture. Time to standing was shortest with DEX when compared with BUP and BUP/DEX mixture.

Table 1: Number of goats showed side effects after intrathecal administration of bupivacaine (1.5 mg kg^{-1} , $n = 6$), dexmedetomidine ($2 \mu\text{g kg}^{-1}$, $n = 6$) and bupivacaine/dexmedetomidine mixture ($0.75 \text{ mg kg}^{-1} + 1 \mu\text{g kg}^{-1}$, $n = 6$)

Variables	BUP group (N = 6)	DEX group (N = 6)	BUP/DEX group (N = 6)
Sedation	0	+5	+4
Salivation	0	+4	+3
Apnoea	0	+3	+2
Bloat	0	+4	+3
Grunting	0	+1	+1
Urination	0	+4	+3
Ataxia ^a	+4	0	+2

0: Not observed, +: Observed, a: In the post-recumbent period

Table 2: Means±SE of heart rate (beat min⁻¹), respiratory rate (breath min⁻¹) and rectal temperature (°C) after intrathecal administration of bupivacaine, dexmedetomidine and bupivacaine/dexmedetomidine mixture in goats

Variables	Groups	Time (min)							
		0	5	15	30	45	60	90	120
HR beat min ⁻¹	BUP	128.6±10.6	122.0±4.8	124.1±4.1	114.1±8.3	127.0±2.1	133.5±7.6	121.9±5.2	125.7±7.2
	DEX	118.0±8.0	69.0±2.4*	67.8±3.8*	69.6±5.0*	68.2±5.7*	64.8±6.5*	68.4±7.2*	69.4±7.1*
	BUP/DEX	121.6±10.0	80.2±8.5*	77.4±7.9*	81.2±8.5*	76.8±8.5*	80.0±8.8*	79.6±8.8*	77.6±7.8*
RR breath min ⁻¹	BUP	44.6±5.6	40.2±5.0	37.6±4.9	30.2±2.6	29.0±4.7	39.8±8.3	48.8±17.0	46.8±14.0
	DEX	40.6±5.9	15.4±3.7*	18.6±1.9*	10.4±8.1*	15.9±2.5*	16.4±2.0*	19.0±2.3*	16.9±2.1*
	BUP/DEX	38.9±4.5	16.0±2.5*	15.6±1.4*	25.0±4.1*	23.4±5.3*	19.1±5.3*	21.0±6.2*	21.0±7.2*
RT (°C)	BUP	38.9±0.4	39.5±0.3	39.4±0.3	39.9±0.4	39.5±0.3	38.9±0.4	39.1±0.3	39.8±0.4
	DEX	38.5±0.6	38.8±0.4	38.7±0.3	38.3±0.6	38.0±0.4	38.1±0.3	37.8±0.6	38.1±0.4
	BUP/DEX	38.3±0.1	38.3±0.4	39.0±0.6	38.7±0.6	38.5±0.4	38.3±0.6	38.1±0.5	38.9±0.3

*p<0.05 vs. bupivacaine group, min: Minute, HR: Heart rate, RR: Respiratory rate, RT: Rectal Temperature

Table 3: Means±SE of epidural anesthetic indices after intrathecal administration of bupivacaine, dexmedetomidine and bupivacaine/dexmedetomidine mixture in goats

Variables	Time (min)		
	BUP group	DEX group	BUP/DEX group
^a Onset of analgesia	9.2±2.7	7.3±2.0	3.9±1.9*
^b Duration of analgesia	98.0±22.5	160.0±27.1*	151.0±62.3
^c Duration of recumbency	160.2±60.3	120.0±17.2	131.0±63.6
^d Time to standing	53.2±39.2	3.2±0.9*	40.4±35.0

^aInterval between epidural drug injection and loss of pain response, ^bInterval between loss and return of pain response, ^cInterval between onset of recumbency and standing, ^dInterval between sternal and standing postures, *p<0.05 vs. bupivacaine

DISCUSSION

Lumbosacral epidural analgesia is highly recommended in small ruminants to avoid the need for general anesthesia as well as to provide long duration of analgesia and to reduce surgical stress. Therefore, this study was performed to evaluate the efficacy and safety of BUP, DEX and BUP/ DEX combination following intrathecal administration in clinically healthy goats.

The distribution of the anesthetic agent within the lumbosacral subarachnoid space is influenced by a variety of factors, including age, obesity, pregnancy and body posture¹¹, therefore, aged, obese and pregnant goats were not included in this study. In addition, the goats were restrained in sternal recumbency for a while after epidural injection thereby keeping the spine horizontal to obtain a bilateral block^{12,22,23}.

The selection of anesthetic and analgesic agents which used in ruminants is closely related to both recovery from anesthesia and side effects of these agents^{3,16}. In this study, researchers chose bupivacaine as it is one of the most commonly used local anesthetics in both human and veterinary medicine and combined it with dexmedetomidine because the combination of

bupivacaine and alpha2- agonists has produced a good and satisfactory results in pain control in ruminants^{1,19,22}.

Interestingly, solutions of bupivacaine (an amide type local anesthetic) and dexmedetomidine (an alpha2-adrenergic agonist) appeared completely miscible in the syringe that was compatible with previous studies^{22,23}. This suggests that the pH values of both agents do not differ widely. Nonetheless, it is reasonable to expect other drugs from both pharmacological classes to be similarly miscible.

The results of the present study indicated that intrathecally administrated DEX/BUP mixture in goats had a faster onset of analgesia than either component, a similar duration of analgesia to DEX treated animals, a shorter duration of recumbency than with BUP treated animals, but a longer time to standing when compared with DEX alone.

In the current study, BUP/DEX combination has a rapid onset of analgesia (3.9±1.9 min) when compared with BUP (9.2±2.7 min) or DEX (7.3±2.0 min) treated animals. These findings correlate with Adetunji *et al.*¹¹, they noted that intrathecal administration of xylazine/bupivacaine mixture in goats induced rapid onset of action and longer period of analgesia when compared with xylazine or bupivacaine alone, also this effect was a somewhat shorter than that seen after intrathecal administration of medetomidine (10 µg kg⁻¹) in goats⁹.

Alpha-2 agonists such as xylazine and medetomidine have been reported to induce bradycardia in horses, cattle and goats after epidural or subarachnoid injections^{9,24-26}. In the present study, a significant reduction in HR and RR was noticed after intrathecal injection of DEX and BUP/DEX mixture when compared to BUP treated animals until the end of the recorded time points. Bradycardia could be attributed to decreased sympathetic outflow from the CNS and increased vagal tone²⁶. Respiratory effects of intrathecally administered alpha-2 agonists could be related to alpha-2 adrenoceptor activity and depression of the respiratory centre^{24,26}.

Intrathecaly administered BUP/DEX combination and DEX alone in this study associated with some side effects. It is supposed that most of these side effects were produced by DEX as component of the mixture since they were not observed with intrathecal BUP alone. Furthermore, similar side effects have been associated with systemically administered xylazine in ruminants^{3,27}, intrathecal injection of romifidine in goats¹⁰. Among those side effects; the induced sedation was beneficial and made additional manual restraint of the treated goats unnecessary. Salivation, bloat and urination have profound clinical implications while grunting is clinically non-significant, therefore, intrathecal administration of DEX and BUP/ DEX mixture would appear to be good only in selected patients.

In the present study, the duration of analgesia with intrathecal administration BUP (98.0 ± 22.5 min) is inconsistent with the results reported by Trim⁵, who used 0.75% solution at a dose rate of 1.9 mg kg^{-1} and Dos Santos Silva *et al.*¹⁶, where a 0.5% solution at a dose of 1.5 mg kg^{-1} was used. This inconsistency may relate to differences in the concentrations and dosages of the drug which used in this and previous similar studies.

Furthermore, 0.5% bupivacaine might have produced partial motor blockade as in humans²⁸ which could explain the withdrawal of pelvic limbs in treated goats when stimulated. This phenomenon might have been confused with the return of pain responses, thereby leading to gross underestimation of the duration of analgesia.

Duration of analgesia of 160.0 ± 27.1 min produced by intrathecaly administered DEX in this study compares well with 148.0 ± 23.1 min reported by Adetunji *et al.*¹¹ in a similar study using 0.5 mg kg^{-1} xylazine in WAD goats. Duration of analgesia produced by intrathecaly administered DEX/BUP mixture is 151.0 ± 62.3 min clearly represent a synergistic effect of both agents.

In this study, time to standing of 53.2 ± 39.2 and 40.4 ± 35.0 min after BUP and DEX/BUP, respectively compares well with 58 ± 148 min reported by Lucky *et al.*¹⁵ in a similar study using 0.5% bupivacaine in WAD goats. Such prolonged recovery is certainly undesirable. The time period during which a ruminant is recumbent should ideally be minimal, to enable the animal to become ambulatory before the practitioner leaves the premises. This requirement would appear to be best met by subarachnoid DEX with a time to standing of 3.2 ± 0.9 min.

CONCLUSION

A shortest duration of analgesia but the longest duration of recumbency was associated with BUP intrathecal injection

at the dose rate of 1.5 mg kg^{-1} , therefore, its use for small ruminant surgery seems unsuitable. These results reported that, intrathecal administration of DEX and BUP/DEX mixture produced similar duration of analgesia and cardiorespiratory depression. Indeed, the short time to standing associated with intrathecal DEX would appear to make it a better choice for intrathecal administration in goat. The used doses of BUP/DEX mixture probably reduced the side effects observed with BUP and DEX treatment groups. Therefore, the combination of DEX/BUP could be also safely used intrathecaly in goat to perform different surgical interventions without any marked untoward effects.

SIGNIFICANCE STATEMENT

This study highlights the different analgesic effects of bupivacaine, dexmedetomidine and their combination after intrathecal injection in goats. From clinical point of view, both dexmedetomidine alone and its combination with bupivacaine shares the same advantage of long duration of action, however, short time to standing after dexmedetomidine make it the most preferred choice for veterinarians under field conditions. In contrary, bupivacaine alone deemed unsuitable for intrathecal analgesia in goats as it was associated with shortest duration of analgesia and longest duration of recumbency which is undesirable for both owners and anesthetist.

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