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Original Research Article

Comparison of tramadol, lidocaine and tramadol-lidocaine combination for epidural analgesia in goats

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ABSTRACT

The aim of this study was to compare the analgesic effect of tramadol, lidocaine and tramadol-lidocaine combination injected in the epidural space in goats. Nine goats were used to compare the epidural analgesic effect of tramadol (3 mg / kg), 2% lidocaine (2.86 mg/kg) and tramadol-lidocaine combination (1 mg /kg and 2.46 mg kg, resp.). Onset time, duration, and degree of analgesia and ataxia were recorded as well as Heart rate (HR), respiratory rate (RR), rectal temperature (RT), and biochemical parameters were recorded. Time to onset and duration of analgesia, were tramadol 10 min and 225 min; lidocaine 4 min and 85 min and tramadol-lidocaine 4 min and 130 min respectively. Onset time and duration were significantly longer with tramadol and tramadol-lidocaine combination than the other treatment. Ataxia was not observed in tramadol and mildly observed in tramadol-lidocaine combination and was severing in lidocaine. Tramadol and tramadol-lidocaine combination might be clinically useful to provide analgesia in goats for long-duration surgical procedures than lidocaine alone.

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1. Introduction

Ruminants are generally not considered to be good subjects for general anesthesia, mainly because of hazards of regurgitation and inhalation of ruminal contents or saliva into the lungs if the airway is left unprotected. Thus, regional analgesia produced by the perineural or epidural injection of analgesic agents is most frequently employed in these species (Azari, 2014).

Caudal epidural analgesia is frequently used in large animals for surgical procedures in the perineal region (Elmore, 1980). Lidocaine is the most commonly local analgesic drug used in epidural analgesia but has a relatively short duration (Ghazy et al., 2015).

Assessment of the analgesic effects of tramadol administered epidurally has been reported in horses (Natalini and Robinson, 2000), cattle (Bigham et al., 2010), dogs (Natalini et al., 2007), cats (Castro et al., 2009) and goats (Dehkordi et al., 2012). Tramadol appeared to give prolonged anti-nociception without serious side effects.

The objective of the present study was to evaluate the clinical, biochemical parameters and the analgesic effect of tramadol (TR), lidocaine (LD) and a combination of tramadol-lidocaine (TRLD) when administered in the epidural space of the goats.

2. Materials and methods

The present study was done at the Department of Surgery, Anesthesiology and Radiology, Faculty of Veterinary Medicine, Beni-Suef University.

Nine goats (6 bucks and 3 non pregnant does) weighed 20-25 kg body weight and aged 1.5-2 years were randomly selected for the study. All goats were deemed healthy by physical examination. Animals were kept under observation for two weeks before the experiment and were injected by ivermectin (Iveen Plus® Egyptian company for chemicals and pharmaceuticals, ADWIA) subcutaneously in a dose of 1ml/50kg body weight and the dose repeated after two weeks.

Animals were fasted for 24 hours and water was withheld for 6 hours prior to the experiment. Area of lumbosacral space was aseptically prepared. The prepared goats were randomly divided into 3 equal groups, each of 3 animals. Animals were used to evaluate the following drugs for epidural analgesia:

Group E1: Tramadol hydrochloride (100 mg / 2ml) (koralodol®, AMRIY Pharmaceuticals) was injected alone at a dose of 3 mg / kg body weight (Ajadi et al., 2012).

Group E2: Lidocaine Hcl 2% (Debocaine® AL-Debeiky pharmaceutical industries Co.) was injected alone at a dose of 2.86 mg/kg (Dehkordi et al., 2012)

Group E3: A mixture of tramadol and lidocaine (1 mg/kg tramadol hydrochloride (100 mg / 2ml + 2.46 mg/kg lidocaine 2%) was injected at a dose 1 ml per 7 kg of this mixture to one goat.

For the epidural analgesia, goats were in the right lateral recumbence with hind limbs extended forward. A 16-gauge 8 cm long needle was inserted into the epidural space at the lumbosacral space (Sadegh et al., 2009).

Drugs in all groups were injected slowly over a period of about 30 seconds (Ghazy et al., 2015). The onset of analgesia was defined as the time interval (in minute) from the epidural injection of the drug to loss of response to pin-prick in the perineal region.

The duration time of analgesia was defined as a time interval (in minute) from loss and reappearance of pain response to pin-prick in the perineal region. The stimulus was applied first to the perineal area and then moved cranially toward the thoracic region until a response (movement associated with pin prick test or haemostat pressure) was observed (Dehkordi et al., 2012).

Skin pinching, anal and tail reflex were recorded before (baseline, 0) then at 5, 10,15,30,60,120 minute and 4-hour intervals after epidural injection. The ataxia was graded on a 0 to 3 scale according to (Grubb et al., 2002) using the following scoring system:

0 = normal (walking without staggering).

1 = mild (slight stumbling, easily able to continue walking)

2 = moderate (marked stumbling, walking but very ataxic).

3 = severe (animal unable to stand and falling)

Heart rate, respiratory rate, and rectal temperature were recorded before (baseline, 0), 10.20,40,80 and 120 minutes.

Blood samples were collected from the jugular vein for biochemical parameters determination before (0 minute), at 15, 30, 60, 120 minutes, and 4-hour intervals according to Ghazy et al. (2015). Biochemical parameters including blood urea nitrogen (BUN), creatinine, aspartate amino transferase (AST), alanine aminotransferase (ALT),

blood glucose, cortisol and cholesterol level were estimated.

The blood serum urea was estimated according to the method described by Kaplan (1984). Creatinine level was performed according to the method of Kroll et al. (1987). Estimation of serum aspartate aminotransferase activity and serum aspartate aminotransferase activity (AST) were estimated after the method described by Reitman and Frankel (1957). Moreover, estimation of serum alanine aminotransferase activity was estimated after the method described by Reitman and Frankel (1957). Furthermore, estimation of serum glucose level was estimated according to the method described by Trinder (1969). Estimation of cortisol concentration in plasma was determined after the method described by Kannan et al. (2001). Estimation of serum total cholesterol level was estimated according to the method described by Meiattini et al. (1978) and its level was expressed in mg/dl.

Statistical Analysis

All data were presented as mean ± SD. Data of the time of onset and duration of analgesia, HR, RR, rectal temperature, and biochemical parameters were analyzed by ANOVA (analysis of variance) and Duncan's test as a post hoc. Statistical analysis was undertaken using Graph pad Prism version 5 software program. $P<0.05$ was considered significant.

3. Results

Caudal epidural analgesia was produced in all treated goats. The mean time of onset was 10, 4 and 4 in groups I, II, and III respectively while, the mean time for duration of analgesia was 225, 85 and 130 in groups I, II, and III respectively (Table 1).

The onset of analgesia was at the tail, perineal area, and the order of blockade progressed from caudal to cranial. No observed ataxia (score = 0) in tramadol epidural injection, while sever ataxia (score = 3) was observed with epidural injection of lidocaine but mild ataxia (score = 1) was noted in goats with epidural injection of lidocaine-tramadol combination (Table 2).

Results of heart rate, respiration rate and temperature, there are no significantly differentiation between the values (Table 3).

Results of biochemical parameters increase in blood glucose, cortisol, ALT, AST and creatinine at 60min and 120 min but return to normal range at 240 min. while BUN and cholesterol remain at normal range (Table 4).

Table 1. the time of onset and duration after caudal epidural administration of tramadol (TR), lidocaine (LD) and tramadol-lidocaine (TRLD) in goats (mean ±SD).

Onset of anesthesia	Duration of anesthesia
10±2 min	225±5min
4±1 min	85±5 min
4±2 min	130±10min

Table 2. Ataxia score after caudal epidural administration of tramadol (TR), lidocaine (LD) and tramadol-lidocaine (TRLD) in goats.

Group	Ataxia score	
Tramadol	3* normal score	(0)
Lidocaine	3* severe score	(3)
Tramadol +	2* mild score	(1)
Lidocaine	1* moderate score	(2)

* Number of animals that show respective signs in each goat group.

Table 3. Heart rate, respiratory rate and body temperature after caudal epidural administration of tramadol (TR), lidocaine (LD) and tramadol-lidocaine combination (TRLD) in goats (mean ± SD).

time		Heart rate	Respiration rate	Temperature C
0	**Group I**	79.67±5.03	26.33±1.53	39.00±0.10
	Group II	85.33±0.58	26.33±0.58	38.93±0.12
	Group III	85.67±0.58	27.00±1.73	39.13±0.23
5 minutes	**Group I**	80.33±6.11	26.67±1.53	39.00±0.10
	Group II	87.00±0.00	28.00±0.00	38.90±0.00
	Group III	87.00±0.00	28.00±0.00	39.03±0.23
10 minutes	**Group I**	81.67±2.89	24.33±2.31	38.97±0.06
	Group II	85.00 ±0.00	26.00±0.00	38.50±0.00
	Group III	85.33 ±0.58	26.00±0.00	38.77±0.46
20 minutes	**Group I**	82.33±3.21	24.00±1.73	38.83±0.12
	Group II	86.00± 0.00	27.00±0.00	38.70±0.00
	Group III	86.00±0.00	27.00±0.00	38.93±0.40
40 minutes	**Group I**	81.33 ±4.16	23.33±0.58	38.93±0.12
	Group II	84.00 ±0.00	25.00±0.00	38.93±0.06
	Group III	84.00 ±0.00	25.00±0.00	38.93± 0.06
80 minutes	**Group I**	83.00±2.65	26.00±0.00	39.00±0.00
	Group II	86.00±0.00	26.00±0.00	38.97±0.06
	Group III	86.00±0.00	26.00±0.00	39.07±0.12
120 minutes	**Group I**	80.00±0.00	26.67±1.15	39.00±0.00
	Group II	86.00±0.00	26.00±0.00	38.80±0.00
	Group III	86.00±0.00	26.67±1.15	38.97±0.29

Table 4. Biochemical parameters after caudal epidural administration of tramadol (TR), lidocaine (LD) and tramadol-lidocaine combination (TRLD) in goats (mean ± SD).

Parameter	Group	0 min	15 min	30 min	60 min	120 min	240 min
BUN (mg/dL)	Group I	16.03± 2.00	16.13±2.00	16.17± 2.05	16.23±0.06	16.33± 0.06	16.0333± 1.950
	Group II	17.17±1.04	17.27± 1.04	17.40±0.06	17.43± 0.06	17.27± 0.06	17.1667± 1.040
	Group III	13.83± 0.29	13.97±0.23	14.07±0.06	14.20± 0.06	14.17± 0.06	13.9667± 0.152
Creatinine	Group I	0.80±0.10	0.97± 0.06	1.23± 0.21	1.67*± 0.15	1.73*± 0.12	1.03± 0.06
mg/dl	Group II	0.87±0.06	1.09± 0.02	1.30 ± 0.10	1.57*± 0.21	1.43± 0.15	1.03± 0.06
	Group III	0.80± 0.10	0.93± 0.12	1.13± 0.06	1.30± 0.10	1.30± 0.10	0.93± 0.06
AST	Group I	117.33± 16.17	128.33± 7.64	151.00± 10.58	172.67± 2.52	177.33*± 2.52	116.67± 12.58
(Unit/mL)	Group II	114.33± 4.04	118.67± 3.21	122.33± 2.52	134.67± 1.53	125.67± 3.51	117.00± 2.00
	Group III	126.67± 5.77	132.33± 2.52	139.33± 1.15	149.00± 5.29	150.67± 7.64	131.33± 2.08
ALT (Unit/mL)	Group I	27.00± 2.00	30.33± 2.52	41.33± 3.21	46.00*± 1.00	47*.33± 1.15	29.33± 0.58
	Group II	27.67± 2.08	29.33±1.53	32.33± 2.52	33.67± 4.04	29.33±2.31	27.67± 2.08
	Group III	29.00± 2.65	31.00± 3.46	36.00± 1.73	40.00± 1.00	44.00*± 3.46	31.67± 3.51
Blood glucose	Group I	55.67± 4.5	59.67±5.03	70.67±4.041	86.67*± 2.081	91.33*±5.03	57.33±5.03
(mg/dL)	Group II	58.00± 2	61.67±2.08	67.33± 2.081	72.00±2	67.00±1.52	59.67±1.52
	Group III	61.33±7.76	66.33±8.082	74.00±9.081	77.67±5.859	79.33±6.350	65.00±8.88
Cortisol	Group I	1.40 ± 0.10	1.90± 0.10	2.90± 0.00	3.20± 0.10	3.30± 0.20	1.53± 0.06
(nmol/L)	Group II	1.97± 0.06	3.07± 0.12	3.53± 0.06	4.60*± 0.10	3.40± 0.10	2.23± 0.06
	Group III	1.80± 0.26	2.43± 0.49	2.87± 0.25	3.27± 0.31	3.33± 0.23	2.20± 0.44
Cholesterol	Group I	90.33 ± 2.52	83.00± 2.65	74.00± 4.58	71.00± 3.46	69.00± 1.00	89.00 ± 1.00
(mg/dl)	Group II	82.33± 6.66	81.33± 6.81	78.00± 3.00	71.67± 7.37	76.33± 7.77	80.67± 6.43
	Group III	85.33± 3.51	81.33± 2.31	76.67± 6.81	75.33± 5.51	75.67± 4.93	83.67± 4.04

4. Discussion

Lidocaine is one of the most common drugs used for epidural caudal analgesia in animals. Analgesia provided by lidocaine is relatively short duration and may require re-administration of the agent, which can cause unwanted effects including recumbency (DeRossi et al., 2010).

Epidural opioid (tramadol) administration is one of the most common techniques for postoperative pain control. Epidural administration of low-dose opioids provides strong and long-lasting segmental analgesia via opioid receptors (Rawal, 1999).

Tramadol is a weak agonist at all types of opioid receptors with some selectivity for μ-receptors. Also, tramadol inhibits the reuptake of norepinephrine and serotonin, thus increasing the concentrations of these two neurotransmitters in the central nervous system.

The pharmacological profile of tramadol such as inhibition of the monoaminergic system, activation of opioid receptors, and local analgesic effects makes it an absorbing drug for epidural administration (Collart, 1993; Raffa, 1993; Altunkaya, 2003).

Time to onset of analgesia was significantly prolonged following tramadol (10 min) in comparison with lidocaine (4 min) and lidocaine-tramadol (4min). Tramadol produced significantly longer duration of analgesia (225 min) than that produced by lidocaine (85 min) and lidocaine-tramadol (130 min). The onset of analgesia was at the tail, perineal area, and the order of blockade progressed from caudal to cranial. The obtained results were agreed with those obtained by (Delilkan and Vijayan, 1993; Natalini and Robinson, 2000; Guedes et al., 2005; Bigham et al., 2010; Azari, 2014). No ataxia observed in tramadol epidural injection, while sever ataxia was observed with epidural injection of lidocaine but mild ataxia was noted in goats with epidural injection of lidocaine-tramadol combination. Drug mass (drug volume and concentration related ataxia and recumbence) are expected following the epidural injection of lidocaine because local analgesic block both sensory and motor fibers (Day and Skarda, 1991).

Prolonged duration of analgesia (225 min) following the injection of tramadol has been reported in dogs and horses (Natalini and Robinson, 2000; Guedes et al., 2005). These results support the prolonged duration of analgesia observed in our study after epidural injection of tramadol and tramadol-lidocaine group in comparison with lidocaine group. Murthy (2000) found a lower volume of distribution for epidural tramadol that it may be related to prolonged duration of pain recognition. The tramadol-lidocaine combination produced a shorter duration of effect than tramadol alone. The vasodilatation due to sympathetic blockage produced by epidurally injected local analgesic agents such as lidocaine decreased the duration of analgesia (Gomez de Segura, 2000).

Body temperatures, HRs, and RRs were not significantly different in comparison with baseline values throughout the study in the all treatments. The obtained results were agreed with those obtained by (Day and Skarda, 1991; Natalini and Robinson 2000; Bigham et al., 2010; Dehkordi et al., 2012; Azari, 2014).

BUN and serum creatinine are markers for assessing renal damage (Meyer et al., 1992; Dehkordi et al., 2010). In the present study, BUN and serum creatinine increased at 60 and 120 min while these level returns to normal range at 240 min. an increase of BUN and serum creatinine level might be attributed to the temporary inhibitory effect of these drugs on the renal blood flow, which in turn might have caused the changes in the values of measured parameter (Kinjavadeker et al., 1999).

A significant increase in both AST and ALT suggests that the increase in AST might be hepatic in origin (Lees et al., 1994). A significant increase in AST and ALT levels after all treatments might be related to some alternations in cell membrane permeability, which may permit these enzymes to leak from the cell with intact membranes (Koichev et al., 1988). Similar observations were recorded after detomidine injection in cattle (Singh et al., 2005).

Blood glucose and serum cortisol levels are used as indicators of pain (Gellasch et al., 2002; Eze and Nweke, 2004; Landa, 2012; Udegbunam et al., 2012). Pain lead to increased production of cortisol and catecholamines which facilitates glucose production as a result of increased hepatic glycogenolysis and gluconeonesis (Breznock, 1980; Desborough, 2000). Therefore, the significant increase in cortisol level of the lidocaine treated groups may suggest that animals in this group felt more pain than other treated groups.

Increase in blood glucose levels might be due to an increase in adrenocortical hormone during anesthesia and mobilization of liver glycogen under

the influence of increased adrenaline level (Tiwari et al., 1994)

Epidural tramadol or tramadol-lidocaine combination induced more potent anti-nociceptive effect than lidocaine. In clinical practice, utilizing a tramadol or tramadol-lidocaine combination, long duration anti-nociceptive effect could commence relatively soon after single-dose epidural administration and no to mild ataxia to enable surgical and obstetrical procedures to be completed as mentioned by Marzok and El-Khodery (2015).

5. Conclusion

Tramadol and tramadol-lidocaine combination might be clinically useful to provide analgesia in goats for long-duration surgical procedures rather than lidocaine alone.

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