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Comparison of the application of lidocaine, lidocaine-dexamethasone and lidocaine-epinephrine for caudal epidural anesthesia in cows

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Summary

The aim of the present study was to determine whether the addition of dexamethasone or epinephrine to lidocaine altered the characteristics of anesthesia and cardiorespiratory variables following caudal epidural application in cows. Twenty adult dairy cows were randomly assigned to receive one of the treatments of lidocaine (LID, 0.2 mg/kg), dexamethasone (DEX, 8 mg), lidocaine-dexamethasone (LIDEX; 0.2 mg/kg and 8 mg, respectively) and lidocaine-epinephrine (LIDEP; 0.2 mg/kg and 5 µg/ml, respectively) by epidural injection with the final volume of 0.018 ml/kg and 10 ml of solution as the upper limit. The time to the onset and duration of anesthesia as well as heart rate (HR), respiratory rate (f_R) and rectal temperature (RT) were recorded. No local anesthetic effects were observed in DEX. The onset of anesthesia did not show significant differences among LID, LIDEX and LIDEP. The duration of anesthesia was significantly longer in LIDEX (152.4 ± 25.8 min) as compared to LID (116.0 ± 11.5 min). Although the duration of anesthesia in LIDEP (137.7 ± 10.0 min) was longer in comparison to LID, the difference was not statistically significant. There was no significant difference regarding the onset and duration of anesthesia between LIDEX and LIDEP. HR, f_R and RT did not show significant changes over time. Mild transient ataxia was observed in groups that received lidocaine-containing solutions. In conclusion, addition of dexamethasone to lidocaine, without altering the time to onset, produced more prolonged anesthesia than that of lidocaine alone following caudal epidural application in cows.

Key words: Cow, Dexamethasone, Epidural, Epinephrine, Lidocaine

Introduction

Caudal epidural anesthesia is employed to perform a variety of diagnostic, obstetrical and surgical procedures in cows. One of the main advantages of caudal epidural anesthesia in cattle is the animals' ability to stand during the intervention due to the fact that with the use of lower volume of anesthetics, this technique provides sensory blockade with minimal effects on sparing motor fibers (i.e. sciatic and femoral nerves) (Valverde and Sinclair, 2015). Various pharmacological agents including local anesthetics (Grubb *et al*., 2002; Dehghani and Bigham, 2009; Bigham *et al*., 2010; Vesal *et al*., 2013), α2-agonists (Caron and LeBlanc, 1989; Ko *et al*., 1989; Gomez de Segura *et al*., 1993; Lin *et al*., 1998; Grubb *et al*., 2002), opioids (Fierheller *et al*., 2004; Baniadam *et al*., 2010) and ketamine (Marsico *et al*., 1999; Lee *et al*., 2003; DeRossi *et al*., 2010) (alone or in combination with other agents) have been evaluated for producing caudal epidural anesthesia in cows.

Lidocaine is the most commonly used local anesthetic for caudal epidural anesthesia because of its rapid onset, intermediate duration of action and moderate toxicity (Garcia, 2015). However, the duration of action of epidural lidocaine may not be enough for some procedures as well as postoperative analgesia and re-administration may be required (Vesal *et al*., 2013).

Moreover, because of the indiscriminate blocking characteristic of lidocaine, sensory, motor and sympathetic nerves can be affected, causing a number of undesirable effects such as ataxia, recumbency and vasodilation at the surgical site (Dehghani and Bigham, 2009). To provide more prolonged anti-nociception and postoperative analgesia in single-shot blocks and to lessen some of the adverse effects associated with the administration of high doses of lidocaine, different combinations of lidocaine with other drugs and pharmacological agents have been evaluated (Grubb *et al*., 2002; Lee and Yamada, 2005; Dehghani and Bigham, 2009; Bigham *et al*., 2010; DeRossi *et al*., 2010; Vesal *et al*., 2013; Noss *et al*., 2014). Among these different agents, epinephrine has mostly been used as an adjunct to local anesthetics due to its vasoconstrictive and direct analgesic traits; nevertheless, some concerns about local effects and systemic absorption of epinephrine have been raised (Garcia, 2015).

Dexamethasone, a highly potent long-acting glucocorticoid, is routinely used to control and treat acute and radicular pain by systemic or epidural administration in humans (Naghipour *et al*., 2013; Knezevic *et al*., 2014). This drug is one of the latest agents of interest for use as an adjunct to lidocaine in various nerve blocks. The addition of dexamethasone to lidocaine has provided long-lasting anti-nociception and

analgesia and has reduced pain scores and opioid consumption in human patients (Knezevic *et al.*, 2014; Noss *et al.*, 2014).

To the authors' knowledge, no study has evaluated the effects of lidocaine in combination with dexamethasone on epidural local anesthesia characteristics in veterinary medicine. In addition, limited information is available on the addition of epinephrine to lidocaine for caudal epidural anesthesia in cows. Therefore, the objective of the present study was to investigate and compare the anesthetic efficacy and characteristics as well as the cardiorespiratory changes of lidocaine, dexamethasone, lidocaine-dexamethasone and lidocaine-epinephrine following caudal epidural administration in standing cows.

Materials and Methods

Animals

Twenty 3-5 years old Holstein cows with body weights of 565 ± 118 kg (mean±SD) and body condition scores of 2.75 ± 0.4 (on a scale of 0-5) were used. The cows were considered healthy based on their history and a thorough physical examination. Food and water were not withdrawn prior to each experiment. All procedures were performed at 9:00 am to 3:00 pm. This experimental investigation was approved by the Institutional Animal Care and Research Committee.

Experimental design

After determining their health status and weight, cows were moved into a restraining chute. After 30 min, heart rate (HR), respiratory rate (f_R) and rectal temperature (RT) were recorded and the presence or absence of ruminal motility as well as the normal responses to superficial and deep pin prick tests were evaluated. The first intercocygeal space (Co1-Co2) was then explored and identified. After aseptic preparation of the skin overlying the predetermined space, a 20 G, 3.5 cm hypodermic needle was inserted into the epidural space. Correct needle placement was confirmed by hanging drop test and/or lack of resistance against drug injections. With the bevel of the needle directed cranially, all the drugs were administered slowly over about 1 min.

Cows were assigned randomly to one of four groups and received one of the four treatments of lidocaine (LID, 0.2 mg/kg, Lignodice 2%, Caspian Tamin, Rasht, Iran), dexamethasone (DEX, 8 mg, Dexamethasone, Darou Pakhsh, Tehran, Iran), lidocaine-dexamethasone (LIDEX, 0.2 mg/kg and 8 mg, respectively) and lidocaine-epinephrine (LIDEP, 0.2 mg/kg and 5 µg/ml, respectively, Epinephrine, Darou Pakhsh, Tehran, Iran) by epidural injection. The final volume of the administered drugs was adjusted to 0.018 ml/kg using normal saline. To avoid administration of excessive volumes to the cows, 10 ml of the solution was considered as the final limit of volume. The pH of each solution was determined using a digital pH meter (Suntex, Taiwan).

Assessment and data collection

The time to the onset and the duration of tail paralysis and anti-nociception in the anus, perinea, vulva and medial regions of the animals' thighs were determined. Tail paralysis after epidural administration was identified when the tail was flaccid and the cow was not able to move it. Superficial skin and deep muscular (<1 cm deep) pin prick tests (2 or 3 for each site) using a 25 G needle, were employed to evaluate anti-nociception. Paralysis and anti-nociception assessments were performed every 30 s after completing the epidural administration until desirable effects were observed to determine the onset. To determine the duration of tail paralysis and anti-nociception in the anus, perinea, vulva and medial thigh regions, evaluations were carried out every 10 min until defined reactions (tail shaking for tail paralysis and restlessness, moving or kicking for anti-nociception) were seen.

HR, f_R, RT, and presence or absence of ruminal motility were determined and recorded at base and at 5, 10, 20, 30, 45, 60, 90 and 120 min after epidural administration. HR was monitored through thoracic auscultation and f_R was counted via chest movement in a 1-min period. RT was measured per rectum using a digital thermometer (AEG, Germany). Ruminal motility was assessed by auscultation of the left paralumbar fossa during a 2-min period. All epidural injections were performed by one investigator and all evaluations were done by another who was unaware of the treatments.

Statistical analysis

Statistical analysis was undertaken by IBM SPSS Statistics for Windows Version 22 (IBM Corporation, NY, USA). The normal distribution of data was evaluated using Kolmogrov-Smirnov test. All normal data were expressed as mean±SD. A one-way ANOVA followed by Bonferroni's test was employed to compare weight, onset and duration of tail paralysis and anti-nociception in anus, perinea, vulva and medial thigh regions as well as differences in HR, f_R and RT between treatments. HR, f_R and RT were also compared with base values using analysis of variance (ANOVA) with repeated measures. A value of P<0.05 was considered significant.
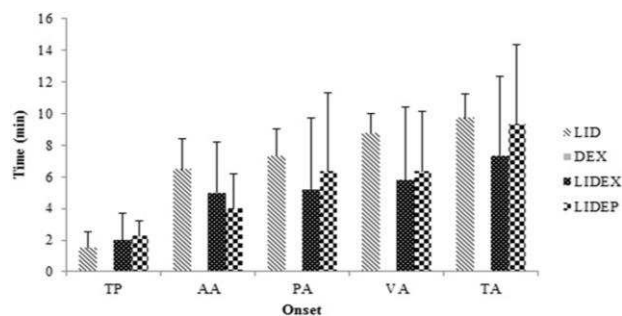
Results

There were no significant differences among groups with respect to body weights: LID: 530 ± 136 kg, DEX: 515 ± 121 kg, LIDEX: 500 ± 58 kg, and LIDEP: 533 ± 63 kg (P>0.05). No difficulty was experienced in locating the correct site of the epidural puncture. All the cows tolerated the procedure well without any complications afterward. The pH of the administered solutions were 6.34 ± 0.09, 7.45 ± 0.14, 6.81 ± 0.09 and 6.36 ± 0.13 in LID, DEX, LIDEX, and LIDEP, respectively. No visible incompatibility including precipitation was observed macroscopically when lidocaine and dexamethasone or lidocaine and epinephrine mixtures were prepared.

Table 1: Mean±SD of HR, f_R and RT after epidural administration of LID, DEX, LIDEX and LIDEP in cows (n=5)

Variable	Group	Base	5	10	20	30	45	60	90	120
HR (beats/min)	LID	66±9	65±8	60±11	65±9	63±6	62±8	64±10	64±7	65±8
	DEX	73±18	73±16	73±18	74±13	77±3	77±4	79±4	75±6	77±11
	LIDEX	68±8	67±16	65±14	66±14	67±13	64±10	66±13	68±13	66±13
	LIDEP	75±3	72±3	74±4	74±3	73±3	74±4	76±1	73±3	71±3
f_R (breaths/min)	LID	36±4	37±4	37±4	36±4	35±3	34±5	37±5	39±4	37±5
	DEX	37±1	40±6	38±6	39±5	38±8	40±8	40±7	35±7	40±6
	LIDEX	40±5	41±6	38±2	36±3	36±3	37±1	37±1	41±4	40±3
	LIDEP	40±6	37±3	38±2	38±2	38±2	38±3	38±2	37±3	38±3
RT (°C)	LID	38.8±0.4	38.8±0.6	38.8±0.6	38.9±0.3	39.1±0.3	39.0±0.4	39.1±0.4	39.2±0.5	39.1±0.5
	DEX	39.1±0.4	39.0±0.6	39.0±0.7	39.0±0.5	39.0±0.5	38.9±0.4	38.9±0.5	38.7±0.3	38.8±0.1
	LIDEX	38.8±0.3	38.9±0.2	38.9±0.3	38.9±0.3	38.8±0.4	38.8±0.3	38.7±0.3	38.7±0.3	38.8±0.1
	LIDEP	38.7±0.1	38.7±0.4	38.8±0.3	38.8±0.4	38.8±0.2	38.7±0.2	38.8±0.2	38.7±0.2	38.7±0.3

No local anesthetic effects were observed in cows that received dexamethasone alone. The onset of anesthesia was not significantly different among the other three groups (P>0.05; Fig. 1). The duration of tail paralysis and anti-nociception in anus, perinea, vulva and medial thigh regions were significantly longer in LIDEX (mean = 152.4 ± 25.76 min) compared with those of LID (mean = 116 ± 11.52 min) (P=0.002; Fig. 2). Although the duration of tail paralysis and anti-nociception in anus, perinea, vulva and medial region of thigh were higher in LIDEP (mean = 137.7 ± 9.98 min) compared to LID,

these differences were not statistically significant (P=0.077). No significant differences were found between the onset and duration of anesthesia for the LIDEX and LIDEP groups (P>0.05).

HR, f_R, RT and base values were not significantly different between groups (P>0.05; Table 1). The evaluation of ruminal motility revealed that at least one motion was hearable at the time of evaluation in all the groups. Mild transient ataxia was occasionally observed in the groups that received lidocaine alone or in combination with dexamethasone or epinephrine.

Fig. 1: Onset (mean and SD) of tail paralysis and anti-nociception in anus, perinea, vulva and medial thigh regions after epidural administration of LID, DEX, LIDEX, and LIDEP in cows (n=5). TP: Tail paralysis, AA: Anus anti-nociception, PA: Perinea anti-nociception, VA: Vulva anti-nociception, and TA: Medial region of thigh anti-nociception
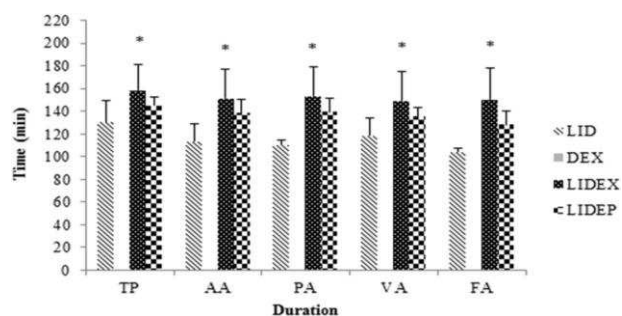
Fig. 2: Duration (mean and SD) of tail paralysis and anti-nociception in anus, perinea, vulva and medial thigh region after epidural administration of LID, DEX, LIDEX, and LIDEP in cows (n=5). TP: Tail paralysis, AA: Anus anti-nociception, PA: Perinea anti-nociception, VA: Vulva anti-nociception, and TA: Medial thigh region anti-nociception. * Significant differences from LID group

Discussion

The present study was designed to evaluate the efficacy of adding dexamethasone to lidocaine and to compare it with lidocaine alone and a lidocaine-epinephrine mixture on caudal epidural anesthesia in cows. Several studies in humans have investigated the effectiveness of the addition of dexamethasone to local anesthetics in different regional nerve blocks including spinal and epidural anesthesia (Bani-hashem et al., 2011; Lauretti et al., 2013; Naghipour et al., 2013), brachial plexus block (Movafegh et al., 2006; Parrington et al., 2010; Vieira et al., 2010; Cummings et al., 2011; Tandoc et al., 2011; Kim et al., 2012; Persec et al., 2014), sciatic and femoral (Fredrickson et al., 2013) and fascial and dental nerve blocks (Aggarwal et al., 2011; Jürgens et al., 2012). To the authors' knowledge, this is the first study evaluating dexamethasone as an adjuvant to local anesthetics in veterinary literature. Epinephrine was also chosen to be compared with dexamethasone and used as another additive in the current study, because it has widely been used in local and regional anesthesia to provide more prolonged nerve blocks. There is limited information about the effects of epinephrine on caudal epidural anesthesia in cows.

In the current study, the dosage and concentration of lidocaine (0.2 mg/kg and 2%; respectively) was selected based on the recommended dose for caudal epidural anesthesia in cattle (Vesal et al., 2013; Valverde and Sinclair, 2015). Dexamethasone was administered at the dose rate of 8 mg regardless of body weight. Dexamethasone has been used with higher (8-10 mg) and lower (4-5 mg) dosages in regional nerve blocks in

humans (Knezevic *et al*., 2014). While both higher and lower doses resulted in more prolonged analgesia, the higher (i.e. 8 mg) was chosen for the present study to increase the likelihood of successful prolonged blocks. Using just one dose rate of dexamethasone is a limitation of the present study. The recommended concentration of epinephrine to add to a local anesthetic solution is 2.5 to 5 µg/ml (Garcia, 2015). The latter has been used in previous studies in sheep (Rostami and Vesal, 2011, 2012; Ghadirian and Vesal, 2013) and was selected for the current investigation. The final volume of solution administered for caudal epidural anesthesia in cows has been recommended to be less than 10 ml, because larger volumes may involve femoral and sciatic nerves and result in recumbency (Valverde and Sinclair, 2015). In the current study, 10 ml was set as the final limit of the administered volume.

In the present work, dexamethasone alone did not exert any anesthetic effects after caudal epidural anesthesia in cows. No significant differences with respect to the onset of anesthesia were detected when dexamethasone was added to lidocaine (LIDEX) in comparison to lidocaine alone (LID) and lidocaine-epinephrine mixture (LIDEP). Dexamethasone has been reported to cause delays in the onset of sensory blockades when combined with local anesthetics for brachial plexus blocks in humans (Knezevic *et al*., 2014). In contrast to human studies, in the present investigation the onset of anti-nociception in LIDEX tended to be shorter than that of LID and LIDEP; however, the difference was not significant.

Epinephrine is expected to delay the onset of anesthesia by decreasing the pH of the anesthetic solution and subsequently decreasing the amount of non-ionized local anesthetic (Garcia, 2015). It can also delay the onset with its vasoconstriction effects which limits the subsequent spreading of local anesthetics (Rostami and Vesal, 2011, 2012; Ghadirian and Vesal, 2013). In the present study, the addition of epinephrine to lidocaine did not delay the onset of anesthesia after caudal epidural application. The absence of delays in the time to onset can be attributed to the lack of lowering pH in freshly prepared epinephrine-containing lidocaine. Epinephrine (5 µg/ml) did not drop the mean pH of lidocaine, and the pH was much more than that of commercially-prepared lidocaine-epinephrine solutions (i.e. 4.24) (Rostami and Vesal, 2011, 2012; Ghadirian and Vesal, 2013).

The duration of anesthesia was significantly longer in LIDEX compared to LID. The ability of dexamethasone to produce block prolongations has been documented by several studies in humans (Knezevic *et al*., 2014; Noss *et al*., 2014). Although the exact mechanism(s) of dexamethasone regarding the enhancement of the duration of the blocks is yet to be explained, some authors have attributed it to the vasoconstrictive properties of corticosteroids (Bani-Hashem *et al*., 2011). Vasoconstrictor effects of corticosteroids are mainly mediated by the occupancy of classical glucocorticoid receptors rather than nonspecific pharmacological pathways (Seidenari *et al*., 1997). It should also be

mentioned that one of the main reasons for using dexamethasone in human studies is the benefits of providing postoperative analgesia. Analgesic characteristics appearing after the perineural application of dexamethasone have been attributed to systemic absorption rather than local effects (Knezevic *et al*., 2014; Noss *et al*., 2014). Even though potential analgesic effects were not evaluated in the current study, dexamethasone alone did not show any local anesthetic properties after epidural administration.

Due to the vasoconstrictor effects of epinephrine in LIDEP, the prolongation of anesthesia has been anticipated after epidural administration. Furthermore, there is some evidence of direct analgesic effects of epinephrine caused by the stimulation of α2-agonist receptors (Collins *et al*., 1984; Sonohata *et al*., 2004). However, epinephrine did not increase the duration of anesthesia compared to lidocaine alone. Paralysis and anti-nociception tended to be higher in LIDEX than those of LID; nevertheless, the differences were not significant. These findings might have been due to small sample sizes and low concentrations of epinephrine. The maximum recommended concentration of epinephrine to add to local anesthetics solutions (i.e. 5 µg/ml; Garcia, 2015) was used in the current study. This concentration could be reduced by adjusting the final volume with normal saline.

HR, f_R and RT did not change over time and among treatments. Consistent with the results of the present study, HR have not shown any changes in paediatric cases that have received dexamethasone as an adjuvant to local anesthetics for caudal analgesia (El-Feky and El Aziz, 2015). Due to its systemic absorption, epinephrine can cause some cardiovascular effects such as increase in HR and even arrhythmia with higher doses (Garcia, 2015). A transient increase in HR without changes in f_R and RT has been reported following lumbosacral epidural and brachial plexus administration of lidocaine-epinephrine in sheep (Rostami and Vesal, 2011; Ghadirian and Vesal, 2013). The lack of visible changes in HR in the present study could be attributed to species' differences and the attenuation of epinephrine after the addition of normal saline in which plasma concentration of epinephrine is not high enough to induce alteration in HR in cows.

Some degrees of ataxia were seen in the cows receiving one of the solutions containing lidocaine. Since local anesthetics block both sensory and motor fibres, drug mass (volume and concentration) - related ataxia is expected after epidural application (Day and Skarda, 1991). The ataxia observed in the present study has likely occurred due to the relatively large volume of administered solutions; however, it was not severe and long-lasting.

One of the major concerns regarding perineural administration of drugs and additives is neurotoxicity. There is controversy regarding the neurotoxic properties of dexamethasone. While some studies have reported the neurotoxicity of dexamethasone (Shishido *et al*., 2002; Williams *et al*., 2014), others have documented

dexamethasone as a non-neurotoxic and even neuroprotective (Kroin *et al*., 2000; Ma *et al*., 2010; Williams *et al*., 2011). The available studies indicate a dose of 8 mg perineural dexamethasone as safe (Knezevic *et al*., 2014). Neuraxial epinephrine may also be associated with a decrease in peripheral nerve or spinal cord blood flow, subsequently resulting in nerve or spinal cord ischemia. Nevertheless, the neurotoxicity of an appropriate dose of epinephrine has not been supported by clinical experiences and experimental studies in animals (Garcia, 2015). In the present study, no complications related to neural damage or cytotoxicity were observed for dexamethasone or epinephrine; however, further studies are required to rule out the potential neurotoxicity of these two agents.

Dexamethasone (8 mg) added to lidocaine (0.2 mg/kg), without altering the time to onset, produced more prolonged anesthesia than that of lidocaine alone (0.2 mg/kg) following the caudal epidural application in cows. Further studies are needed to establish the optimum dose, potential postoperative analgesia and safety of dexamethasone and epinephrine for caudal epidural anesthesia in cows.

Acknowledgements

Conflict of interest

The authors do not have any potential conflicts of interest to declare.

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