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Clinical and Behavioral Changes Associated with using Xylazine only or Xylazine-epinephrine Combination for Caudal Epidural Analgesia in Cattle

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Abstract

In recent years, various anaesthetic agents and mixtures had been evaluated for caudal epidural analgesia in cattle with a variety of results. Caudal epidural analgesia is a routine and established technique for a variety of surgical and obstetrical procedures in cattle and might depend on the volume of local analgesic. The objective of the present work to compare between the analgesic efficacy of xylazine alone and that of Xylazine-epinephrine combination in caudal epidural analgesia through studying the clinical and behavioral changes as well as estimating degrees of ataxia, sedation and analgesia in cows throughout monitoring their efficacies pre-epidural (Minute 0) injection or post-epidural injection (Minutes 10, 30, 60, 90, 120, 150 and 180). The study was conducted on clinically healthy non-pregnant cross cows (n=20). They were classified into two equal groups. The first one received epidural injection of 0.05 mg/kg xylazine and thus was referred as Xyla^{gr}. The second group was epidurally treated through injection of combination of 0.05 mg/kg xylazine and Epinephrine and thus was referred as Xyla-Epin^{gr}. All animals were subjected for through clinical examination as well as monitoring of different degrees of ataxia, sedation and analgesia parameters. There was no statistically significant difference in the onset of analgesia between xylazine epidural injection (11.85±1.25 minutes) and xylazine with epinephrine (12.01±1.05 minutes). Epidural administration of xylazine with epinephrine produced a significantly longer duration of analgesia (161.0±7.62 minutes) than that produced by epidural injection xylazine alone (136.20±7.13 minutes). Administration of xylazine alone resulted in mild to moderate sedation with mild ataxia, as well as cutaneous analgesia for the perineal region while xylazine with epinephrine produced mild sedation without ataxia, as well as cutaneous analgesia for the perineal region. The study concluded the higher efficacy of xylazine-epinephrine combinations as a caudal epidural analgesic drug compared with that of xylazine alone. Xylazine-epinephrine combination has more rapid onset of recovery from signs of ataxia and sedation than xylazine alone, which make it more suitable than xylazine in cattle as an intraoperative and postoperative analgesia.

KEYWORDS
Clinical changes, Cattle, Caudal epidural analgesia, Xylazine, Xylazine-epinephrine combination.

INTRODUCTION

Farm animals were not good subjects for general anaesthesia under field condition due to the economic cost and the lack of surgical facilities. The danger of regurgitation and inhalation of ingesta was much greater in these animals compared with other common domestic animals. Therefore, physical restraint with various techniques of local and/or regional analgesia was most employed to allow many surgical procedures to be performed with the animal in a standing position (Fierheller *et al*., 2004; Lee and Yamada, 2005).

Various techniques for providing local anaesthesia in bovine animals undergoing flank and udder surgery in the standing position had been described (Skarda, 1996). Each of these techniques had various advantages and disadvantages; the ideal technique would be one that provides complete analgesia following injection of a small volume of the anaesthetic, without leading to any adverse events (Lee and Yamada, 2005).

Caudal epidural analgesia is a routine and established technique for a variety of surgical and obstetrical procedures in cattle and may be described as 'high' or 'low' depending on the volume of the local analgesic (Clarke *et al*., 2014). Local anaesthetics were the most used drugs for producing epidural anaesthesia; however, epidural anti-nociception was also obtained with opioids (Valverde *et al*., 1990) and alpha-2 adrenergic agonists (Caron and LeBlanc, 1989; Gomez De Segura *et al*., 1993), which produced selective sensory blockade, without the unfavorable depression of motor or autonomic neurons. Therefore, they offered several advantages over local anaesthetics, including a lower degree of hindlimbs weakness and prolonged duration of action (Ishii *et al*., 2008).

Moreover, Epidural anesthesia was historically produced using local anesthetic agents., which indiscriminately blocked motor, sensory, and sympathetic fibers, increasing the risk of hind limb weakness, ataxia, and in extreme cases, recumbency (Ismail, 2016).

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As an alternative to local anaesthetics, the a2-agonist xylazine was used for epidural anaesthesia in cattle (Zaugg and Nussbaum, 1990; Abid, 2002; Lee and Yamada, 2005). The advantage of xylazine was the longer duration of analgesia compared with local anaesthetics but the onset of analgesia was generally prolonged (Grubb *et al*., 2002). Furthermore, xylazine selectively blocked sensory fibers, thereby providing significant analgesia with decreased likelihood of rear limb dysfunction but the depressive effect of xylazine on the cardio-respiratory function was its disadvantage (Picavet *et al*., 2004).

The combination of epinephrine in the local anesthetic solution was reported to result in a substantially prolonged duration of analgesia. Epinephrine was thought to prolong analgesia by vasoconstriction and delayed absorption of the local anesthetic. A second possibility was that the epinephrine might act via alpha2-adrenergic receptors in a manner like that proposed for xylazine (Collins *et al*., 1984; Sonohata *et al*., 2004).

According to the authors' knowledge, this study is the first that evaluated epinephrine as an adjuvant to xylazine as caudal epidural analgesia. Therefore, the objective of the present study was to evaluate the efficacy of adding epinephrine to xylazine through comparing between the analgesic efficacy of xylazine alone and that of xylazine-epinephrine combination in caudal epidural analgesia through studying the clinical and behavioral changes as well as estimating degrees of ataxia, sedation and analgesia in cows throughout monitoring their efficacies pre-epidural (Minute 0) injection or post-epidural injection (Minutes 10, 30, 60, 90, 120, 150 and 180).

MATERIALS AND METHODS

Ethical approval

All procedures conducted in this study were carried out according to the Institutional Animal Care and Use Committee, Faculty of Veterinary Medicine, Assiut University, Egypt, which are in accordance with the international reference standards for the guide to the use of animals in various research experiments and their care without prejudice to ethics and laws and which controlled the conduct of different scientific research experiments.

Animals

The study was conducted on clinically healthy non-pregnant cross breed Holstein-Friesian dairy cattle (n=20). Their body weight was ranged between 350-400 kg. Their age was ranged between 4-6 years. They had been fed on total mixed ration (TMR). The cows were allowed ad libitum access to food and water until the start of the study. The study was carried out indoors and in a comfortable environment with daylight. The investigated cows were classified into two equal groups. The first one (n=10) received epidural injection of 0.05 mg/kg xylazine (Xylaject 2%, ADWIA Co., Cairo, Egypt) and thus was referred as Xyla^{gr}. The second group of cattle (n=10) was epidurally treated through injection of combination of 0.05 mg/kg xylazine (Xylaject 2%, ADWIA Co., Cairo, Egypt) and Epinephrine (Epinephrine® 0.25mg/1ml Misr Co. for Pharmaceutical Industries) and thus was referred as Xyla-Epin^{gr}. The total volume administered for the two treatments was fixed at 5.0 mL by adding normal saline. Each cow received both treatments with a two weeks' washout period.

Drugs safety

To alleviate concerns about the safety of drug compounding, Epinephrine (Epinephrine® 0.25mg/1ml Misr Co. for Pharmaceutical Industries) was added to 1mL of 2 % xylazine (Xylaject 2%, ADWIA Co., Cairo, Egypt) and the mixture was centrifuged and microscopically examined for precipitate. The pH of xylazine, epinephrine and xylazine with epinephrine was measured using a digital pH meter (model 68 ESD 19713, USA).

Epidural analgesia technique

The epidural injection technique used in this study was previously described by Mulroy *et al*. (1997); Marzok and El-khodery (2016) and Ismail *et al*. (2018). Briefly, each cow was restrained in a stanchion and the sacrococcygeal region was meticulously aseptically prepared. In a standing position, the epidural injection was performed through the sacrococcygeal space by using a sterile 18-gauge 3.7 cm long needle with the bevel pointed forward. Proper needle placement was determined by the loss of resistance against drugs injection.

Clinical examination

All animals underwent a thorough clinical examination as described by Cockcroft (2015). The animals were examined before epidural injection (T0) of drugs (Pre-epidural injection) and post-epidural injection at T10, T30, T60, T90, T120, T150 and T180 minutes after drug administration. The rectal temperature (RT), heart rates (HR) and respiratory rates (RR) were monitored either pre- or post-epidural injection (Cockcroft, 2015; Elmeligy *et al*., 2021; Khalphallah *et al*., 2021).

Anesthetic parameters and degrees of analgesia, sedation and ataxia

According to Mulroy *et al*. (1997); Grubb *et al*. (2002); Marzok and El-khodery (2016) and Ismail *et al*. (2018), degrees of analgesia, sedation and ataxia were monitored before epidural injection of drugs [Pre-epidural injection] at minute 0 (T0) and post-epidural injection at minutes 10 (T10), 30 (T30), 60 (T60), 90 (T90), 120 (T120), 150 (T150) and 180 (T180) minutes after drug administration. as follow;

Observations were performed at 1-minute intervals until onset occurred and then at 5-minute intervals for the remainder of the study period. The onset of analgesia (Antinociceptive effect), its duration and its anatomic distribution. Antinociception and its anatomical extent was assessed by applying a standard stimulus (needle pin pricks) in different areas including the tail, anus, perineum, vulva and inguinal area but extended up to the chest areas and the coronary bands of hindlimbs and chest areas.

Analgesia was defined as the absence of movement in response to pin prick or hemostat pressure that was delivered close to the first ratchet first in the perineal area, then moved cranially toward the thoracic region. The onset of analgesia, duration and anatomic distribution in each cow were recorded. Time of the onset of analgesia defined as the period of time from injection to loss of sensation. Time of the analgesia duration was defined as the time between the loss and restoration of the pain response. Responses were measured every minute until no reaction occurred, and then every 5-minutes until a response occurred

Sedation was graded in the following way: (grade 0) absent, (grade 1) mild (slight lowering of the head or/and protrusion of the lower lip), (grade 2) moderate (signs of mild sedation, as well as ptyalism and prolapsed third eyelid) or (grade 3) severe (signs of moderate sedation, as well as the animal need to lean on stanchions for support).

Ataxia was graded in the following way: (grade 0) absent, (grade 1) mild (slight stumbling but the animal able to walk), (grade 2) moderate (marked stumbling and ataxia) or (grade 3) severe (recumbency).

Statistical analysis

The data were analyzed using the SPSS statistical software program for Windows (ver. 16.0; SPSS, USA). Data were expressed as mean ± standard deviation (M±SD) values. The data obtained were analyzed by general linear model repeated measures ANOVA and significance level of results was set at $p<0.05$ either in Xyla^{gr} or in Xyla-Epin^{gr}. The significance of differences was evaluated between the means at selected sampling times (0, 10, 30, 60, 90, 120, 150 and 180 minutes). The data obtained were also analyzed by independent-sample t-test. The significance of differences between the means in Xyla^{gr} and Xyla-Epin^{gr} at selected sampling times was estimated by Dunnett's test at $p<0.05$.

RESULTS

Clinical findings

The clinical findings were significantly changed after caudal epidural administration either in Xyla^{gr} or in Xyla-Epin^{gr} whereas RT, HR and RR were significantly ($p<0.05$) decreased after treatment at minutes 10, 30, 60 and 90 comparing to their pre-administration values, thereafter at 120-180 minutes, they started to increase gradually and significantly ($p<0.05$). The onset of improvement of clinical findings (RT, HR and RR) following caudal epidural analgesia either in Xyla^{gr} or in Xyla-Epin^{gr}, was 2 h following epidural analgesia. No significant changes were reported for RT, HR and RR between Xyla^{gr} and Xyla-Epin^{gr} except at minute 120 for HR and at minute 180 for RR whereas HR was significantly ($p<0.05$) increased, and RR was significantly ($p<0.05$) dropped at Xyla^{gr} comparing with those at Xyla-Epin^{gr} (Table 1). They were within their reference ranges.

Anesthetic parameters (degrees of ataxia, sedation and analgesia)

Regarding drug safety, the pH values were 5.36, 5.18 and 5.25 for xylazine, epinephrine and xylazine-epinephrine mixture respectively. There was no microscopically detectable precipitation for the mixture of xylazine-epinephrine.

Ataxia was observed in both of Xyla^{gr} and Xyla-Epin^{gr} at 30 minutes' post administration. The highest significant ($p<0.05$) degree of ataxia (Highest ataxia score) was observed at 30-60 minutes for Xyla^{gr} and at 90 minutes for Xyla-Epin^{gr} following caudal epidural injection then it was significantly ($p<0.05$) reduced particularly at 90, 120 and 150 minutes until complete disappearance of signs of ataxia at 150 minutes for Xyla-Epin^{gr} (zero ataxia score) and at 180 minutes for Xyla^{gr} (zero ataxia score). The degree of ataxia lasted at least for 120 minutes' post administration at Xyla-Epin^{gr} and for 150 minutes' post administration at Xyla^{gr}. Following epidural injection, the number of cows with clear signs of ataxia (ataxia score) was significantly ($p<0.05$) increased at 30-90 minutes either at Xyla^{gr} or Xyla-Epin^{gr} when they compared with those at 0-10 minutes. Furthermore, the number of cows with clear signs of ataxia (ataxia score) was significantly ($p<0.05$) increased at Xyla^{gr} when they compared with those at Xyla-Epin^{gr} at minutes 30-150 following epidural injection. Although, all cattle maintained in a standing position after caudal epidural analgesia (0-10 minutes), only Xyla^{gr} which had all animals with signs of ataxia within 30-60 minutes after

Table 1. Mean values (M±SD) of temperature, pulse and respiration in each of Xyla^{gr} (n=10) and Xyla-Epin^{gr} (n=10) with caudal epidural analgesia.

	Time following with caudal epidural injection (minutes)															
	$T0^{\#}_{min}$		$T10_{min}$		$T30_{min}$		$T60_{min}$		$T90_{min}$		$T120_{min}$		$T150_{min}$		$T180_{min}$	
	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}
RT (°C)	38.75±0.24^{a}	38.45±0.68^{abc}	38.41±0.62^{b}	38.56±0.427^{abc}	37.97±0.33^{c}	38.14±0.43^{ce}	37.64±0.36^{cd}	37.62±0.31^{d}	37.48±0.40^{d}	37.58±0.27^{d}	37.93±0.21^{c}	37.83±0.27^{de}	38.28±0.33^{b}	38.35±0.27^{b}	38.48±0.24^{ab}	38.57±0.30^{a}
HR (Beats/min)	66.40±3.20^{a}	67.80±3.29^{a}	65.30±2.16^{a}	66.20±3.26^{ab}	53.50±3.92^{d}	55.50±3.31^{c}	51.40±2.88^{d}	52.30±2.54^{d}	53.10±2.56^{d}	51.30±3.65^{d}	57.50±4.55^{c}	53.30±3.80^{cd*}	59.60±4.48^{bc}	62.80±5.26^{b}	62.80±3.49^{b}	62.60±3.57^{b}
RR (Breaths/min)	33.90±1.91^{a}	34.30±1.75^{a}	33.40±1.71^{a}	34.40±2.01^{a}	25.50±3.53^{b}	26.40±2.37^{b}	24.20±2.89^{bd}	22.00±2.49^{cd}	20.00±6.88^{d}	23.50±1.58^{c}	22.60±2.01^{d}	22.60±1.89^{c}	23.60±2.63^{bd}	24.70±2.63^{cd}	24.30±2.31^{bd}	28.60±2.14^{bd*}

$^{\#}$Treatment day. Xyla^{gr}: Xylazine treated group. Xyla-Epin^{gr}: Xylazine-Epinephrine treated group. RT: Rectal temperature. HR: Heart rate. RP: Respiratory rate. $^{a-e}$Means within the same row with different superscript letters in different sampling times were significantly different ($P<0.05$) either in. Xyla^{gr} or in Xyla-Epin^{gr}. *Significant when the values in Xyla-Epin^{gr} compared with those in Xyla^{gr} either at minute 0, 10, 30, 60, 90, 120, 150 or 180 ($p<0.05$). Reference values according to Jackson and Cockcroft (2002)1.

administrations. In contrast, very small numbers of cows that had ataxia within 30-60 minutes after administrations in Xyla-Epin^{gr}. After 180 minutes follow up period following treatment in Xyla^{gr}, all treated cows could stand without assistance, however, in Xyla-Epin^{gr}, they needed 150 minutes for recovery (Tables 2 and 3).

Apparent sedative effects were induced within 30 minutes following epidural treatment whereas these sedative effects reached their highest significant ($p<0.05$) values rapidly in Xyla^{gr} (Minute 60) compared with those in Xyla-Epin^{gr} (Minute 90). Afterwards, the degree of sedation (Sedation score) was significantly ($p<0.05$) reduced particularly at minutes 90, 120 and 150 until complete disappearance of signs of sedation at minute 180 for Xyla^{gr} and Xyla-Epin^{gr} (zero sedation score). Post-epidural injection, number of cows with clear signs of sedation (Sedation score) was significantly ($p<0.05$) increased in minutes 30-90 either in Xyla^{gr} or Xyla-Epin^{gr} when they compared with those at minutes 0-10. This score was significantly reduced either in Xyla^{gr} or Xyla-Epin^{gr} in minutes 120-180. Furthermore, the number of cows with high sedation score was significantly ($p<0.05$) increased at Xyla^{gr} when they compared with those at Xyla-Epin^{gr} either at minutes 30-60 following epidural injection. At minutes 90-150, however, this higher sedation score at Xyla^{gr} compared with that at Xyla-Epin^{gr} but it was not significant. After caudal epidural analgesia (0-10 minutes) in both Xyla^{gr} and Xyla-Epin^{gr}, all cows were normal, conscious, and maintained in a standing position. Soon later, signs of sedation (Maximal sedative effect) were clearly observed in most cows in Xyla^{gr} (Minutes 30-150) while they were reported in few cows in Xyla-Epin^{gr} (Minutes 30-60). This maximal sedative effect in which the treated cattle appeared calm and was not aware of their surroundings. Drooping (ptosis) of the eyelids, lowering the head carriage, deviation of the neck, protrusion of the tongue from the mouth and ptyalism were recorded. Afterwards, some of the treated cows were mildly sedated with drooping of lower eyelids, a decreased response to external stimuli and lack of appetite (Mild sedation effect). By180 minutes after epidural administration in both Xyla^{gr} and Xyla-Epin^{gr}, all treated cows were no longer sedated, ate well and could stand without assistance (Tables 2 and 3).

Onset of analgesia in Xyla^{gr} was 11.85±1.25 minutes' post-epidural administration of Xylazine, while it was 12.01±1.05 minutes' post-epidural administration of xylazine and Epinephrine. No significance in the onset of analgesia was reported between the two treated group. Duration of analgesia in Xyla^{gr} was 136.20±7.13 minutes' post-epidural administration of Xylazine, while it was 161±7.62 minutes' post-epidural administration of xylazine and Epinephrine. Significance was reported between the two treated group where the duration of analgesia was significantly ($p<0.05$) higher in Xyla-Epin^{gr} when they compared with that in Xyla^{gr}.

Caudal Epidural administration in both Xyla^{gr} and Xyla-Epin^{gr} produced an apparent antinociceptive effect (Analgesic effect) within 30 minutes following epidural injection. This analgesic effect was reflected by absence of pain response by applying a standard stimulus (needle pin pricks) in different areas including the tail, anus, perineum, vulva, and inguinal area but extended up to the coronary band of the hindlimbs and chest areas. The analgesia score was significantly ($p<0.05$) higher either in Xyla^{gr} or in Xyla-Epin^{gr} following administration at minutes 30-120 compared with their values at minutes 0-10. Later, this analgesia score reached their highest significant ($p<0.05$) values in Xyla^{gr} and in Xyla-Epin^{gr} at 60 minutes following administration. This analgesia score (antinociceptive effect) reduced gradually till its complete disappearance at minutes 150 for Xyla^{gr} and at minutes 180 for Xyla-Epin^{gr}. There were significant changes between

Table 2. Mean values (M±SD) ataxia score, sedation score and analgesia score in each of Xyla^{gr} (n=10) and Xyla-Epin^{gr} (n=10) with caudal epidural analgesia.

	Time following caudal epidural injection (minutes)																	
	$T0^{\#}_{min}$		$T10_{min}$		$T30_{min}$		$T60_{min}$		$T90_{min}$		$T120_{min}$		$T150_{min}$		$T180_{min}$	
	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}
Ataxia score	0^{d}	0^{b}	0^{d}	0^{b}	1^{a}	$0.20\pm0.42^{a*}$	1^{a}	$0.40\pm0.52^{a*}$	0.80 ± 0.42^{b}	$0.30\pm0.48^{a*}$	0.40 ± 0.52^{bc}	$0.10\pm0.32^{a*}$	0.20 ± 0.42^{c}	0^{b*}	0^{d}	0^{b}
Sedation score	0^{e}	0^{e}	0^{e}	0^{e}	1.30 ± 0.48^{bc}	$0.40\pm0.52^{cd*}$	1.80 ± 0.42^{a}	$0.80\pm0.42^{b*}$	1.60 ± 0.52^{ab}	1.20 ± 0.42^{a}	1.00 ± 0.67^{cd}	0.60 ± 0.52^{bd}	0.70 ± 0.48^{d}	0.40 ± 0.52^{bc}	0^{e}	0^{e}
Analgesia score (Antinociception)	0^{d}	0^{e}	0^{d}	0^{e}	1.25 ± 0.41^{bc}	1.30 ± 0.48^{c}	1.67 ± 0.32^{a}	1.82 ± 0.38^{a}	1.51 ± 0.51^{ab}	1.54 ± 0.38^{b}	1.12 ± 0.62^{c}	1.27 ± 0.47^{d}	0^{d}	$1.12\pm0.48^{d*}$	0^{d}	0^{e}

$^{\#}$Treatment day. Xyla^{gr}: Xylazine treated group. Xyla-Epin^{gr}: Xylazine-Epinephrine treated group. $^{a-e}$Means within the same row with different superscript letters in different sampling times were significantly different ($P<0.05$) either in Xyla^{gr} or in Xyla-Epin^{gr}. *Significant when the values in Xyla-Epin^{gr} compared with those in Xyla^{gr} either at minute 0, 10, 30, 60, 90, 120, 150 or 180 ($p<0.05$).

Table 3. Degree (median and range) of ataxia, sedation and analgesia score in each of Xyla^{gr} (n=10) and Xyla-Epin^{gr} (n=10 with caudal epidural analgesia.

	Time following caudal epidural injection (minutes)															
	$T0^{\#}_{min}$		$T10_{min}$		$T30_{min}$		$T60_{min}$		$T90_{min}$		$T120_{min}$		$T150_{min}$		$T180_{min}$	
	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}	Xyla^{gr}	Xyla-Epin^{gr}
Ataxia score	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1 (1-1)	(-0.1-0.5)	1 (1-1)	(0.03-0.7)	1 (0.5-1.1)	(-0.04-0.6)	1 (0.03-0.7)	(-0.1-0.3)	0 (-0.1-0.5)	0 (0-0)	0 (0-0)	0 (0-0)
Sedation score	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1 (0.9-1.6)	0 (0.03-0.7)	2 (1.4-2.1)	1 (0.4-1.1.)	2 (1.2-1.9)	1 (0.8-1.5)	1 (0.5-1.4)	1 (0.2-0.9)	1 (0.3-1.04)	0 (0.03-0.7)	0 (0-0)	0 (0-0)
Analgesia score (Antinociception)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1 (0.8-1.7)	0 (0.04-0.6)	2 (1.7-2.3)	1 (0.3-1.2)	2 (1.1-2.2)	1 (0.9-1.4)	1 (0.5-1.5)	1 (0.3-0.9)	1 (0.5-1.06)	0 (0.05-0.8)	0 (0-0)	0 (0-0)

#Treatment day. Xyla^{gr}: Xylazine treated group. Xyla-Epin^{gr}: Xylazine-Epinephrine treated group.

the treated groups for the analgesic score whereas it was significantly lower in Xyla^{gr} compared with Xyla-Epin^{gr} at 150 minutes post-injection whereas all cows in Xyla^{gr} gave pain response by applying a standard stimulus (needle pin pricks) in different areas of the investigated cattle. From 60-120 minutes following drugs injection, the analgesia score in Xyla^{gr} was still lower than that in Xyla-Epin^{gr} but it was not significant (Tables 2 and 3).

DISCUSSION

Administration of epidural and spinal drugs was used to provide surgical anaesthesia and/or postoperative analgesia in veterinary medicine. alpha-2 adrenoceptor agonists are becoming increasingly popular for providing intraoperative and postoperative analgesia in domestic species (LeBlanc *et al*., 1988; St Jean *et al*., 1990; Zaugg and Nussbaum, 1990; Caulkett *et al*., 1993a, 1993b; Clarke *et al*., 2014). Moreover, caudal epidural analgesia had received plenty of research over the last years. Many anaesthetic drugs and combinations thereof had been experimented on in ruminants with variable success rates (Ismail, 2016). The current study reported significant changes in the estimated clinical parameters, following caudal epidural administration in both treated groups where they were significantly decreased after treatment at minutes 10-90 compared to their pre-administration values at minute 0, followed by significant elevations thereafter at minutes 120-180. The onset of improvement of clinical findings, following caudal epidural analgesia either in Xyla^{gr} or in Xyla-Epin^{gr}, was 2 h following epidural analgesia. RT, HR and RR were still within the reference ranges mentioned by Jackson and Cockcroft (2002). Previous research studies supported these findings (Livingston *et al*., 1984) which reported that xylazine induced hypothermia in cattle. In contrast, others (St. jean *et al*., 1990; Chevalier *et al*., 2004) indicated that xylazine caused hyperthermia after epidural xylazine injection. This variation might be due to that xylazine depressed thermoregulatory mechanism, thus perhaps either hypothermia or hyperthermia might be occurred depending on the ambient temperature (Chevalier *et al*., 2004). There was significantly decreased respiratory rate compared with the baseline in both groups and this agreed with studies that described significant reduction in RR following epidural administration of xylazine in calves (Meyer *et al*., 2010) and in adult cows (St. Jean *et al*., 1990; Rehage *et al*.,1994; Skarda *et al*., 1990a; Junhold and Schneider, 2002; Eesa, 2007). Other authors had described a much greater reduction in respiratory rate after systemic injection (IV or IM) (Campbell *et al*., 1979; Trachsel and Schatzmann, 1984; Picavet *et al*., 2004; Yadav *et al*., 2008). It was suggested that this oligopnoea was due to a specific depressive action of xylazine on central respiratory areas in the brain (Meyer *et al*., 2010). Moreover, the treated cows in the present work showed no significant changes for the clinical parameters between Xyla^{gr} and Xyla-Epin^{gr} except at minute 120 for HR and at minute 180 for RR, whereas HR was significantly increased, and RR was significantly dropped at Xyla^{gr} comparing with those at Xyla-Epin^{gr}. Several studies reported bradycardia in calves (Campbell *et al*., 1979; Meyer *et al*., 2010), cattle (St. Jean *et al*., 1990; Rehage *et al*., 1994) and in pregnant cattle (Eesa, 2007) after epidural administration of xylazine and this effect is less than that produced by intravenous or intramuscular injection of xylazine (Junhold and Schneider, 2002; Picavet *et al*., 2004; Ede *et al*., 2019). This bradycardia effect of xylazine could be attribute to a central decrease in sympathetic tone leading to a relative increase in vagal tone (Meyer *et al*., 2010). In contrast, the base values of RT, HR and RR were not significantly different in cattle between the groups that received caudal epidural lidocaine alone or in combination with epinephrine (Rastabi *et al*., 2018). The lack of visible changes in cardiopulmonary system could be attributed to species' differences and the attenuation of epinephrine after the addition of normal saline in which plasma concentration of epinephrine was not high enough to induce alteration in cardiopulmonary system (Rastabi *et al*., 2018). On the other side, due to its systemic absorption, epinephrine could

cause some cardiovascular effects such as an increase in HR and even arrhythmia with higher doses (Garcia, 2015). A transient increase in HR without changes in RR and RT had been reported following lumbosacral epidural and brachial plexus administration of lidocaine-epinephrine in sheep (Rostami and Vesal, 2011; Ghadirian and Vesal, 2013) suggesting rapid systemic absorption of epinephrine from the injection site following drug administration and this might be attributed to the vasodilator effect of lidocaine that might accelerate the systemic absorption of epinephrine (Ghadirian and Vesal, 2013).

The present study was designed to evaluate the efficacy of adding epinephrine to xylazine and to compare it with xylazine alone on caudal epidural anesthesia in cattle. Epinephrine was chosen because it had been shown, not only to decrease local anesthetic systemic absorption rate, but also to prolong duration and improve quality of the epidural block (Ghadirian and Vesal., 2013; Han *et al*., 2020). One of the major concerns regarding perineural administration of drugs and additives was neurotoxicity (Rastabi *et al*., 2018). Neuraxial epinephrine might 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 had not been supported by clinical experiences and experimental studies in animals (Garcia, 2015). In the present study, no clinical complications related to neural damage or cytotoxicity were observed for addition of epinephrine to xylazine; however, further studies are required to rule out the potential neurotoxicity of these agents.

In the current study, the dosage and concentration of epinephrine added to xylazine was 5 µg/mL-1 (1: 200,000). The recommended concentration of epinephrine to add to a local anesthetic solution was 2.5 to 5 µg/ mL-1 (Garcia, 2015). The latter had been used in previous studies in sheep (Rostami and Vesal, 2011, 2012; Ghadirian and Vesal, 2013) and in cattle (Rastabi *et al*., 2018) and was selected for the current investigation and this agree with several studies evaluated the anesthetic success of different concentrations of epinephrine in 2% lidocaine and reported no significant differences in the success rates between them, however, hemodynamic stability was greater with the low-dose epinephrine group than with the high-dose epinephrine group (Dogru *et al*., 2003; Aggarwal *et al*., 2022).

Ataxia and apparent sedative effects were observed in both of Xyla^{gr} and Xyla-Epin^{gr} 30 minutes' post administration. All cattle maintained in a standing position, were not sedated, were eating well and could stand without assistance after caudal epidural analgesia (0-10 minutes). Although α-2 adrenoceptor agonists selectively inhibited sensory nerve fibers without affecting motor fibers (Yaksh, 1985), in the present study ataxia had been observed in cattle following the epidural injection of xylazine and this agreed with previous studies of epidural injection of xylazine in cattle (Caron and LeBlanc, 1989; St. Jean *et al*., 1990; Abid., 2002) and more ataxia had been observed in cattle following intramuscular and intravenous injection of xylazine in cattle (Lemke, 2007), and this agreed with Kamiloglu *et al*. (2005) who reported that ataxia and recumbency might occur following epidural administration of alpha 2 agonists, especially at higher doses due to systemic absorption of the drug. However, at appropriate doses, xylazine had been reported to be a suitable agent for providing analgesia without excessive ataxia and recumbency. In the current study, only Xyla^{gr} in which all cows had signs of ataxia as well as sedation like appeared calm, was not aware of their surroundings, drooping (ptosis) of the eyelids, lowering the head carriage at etc., were recorded within 30 minutes after administrations. In contrast, very small numbers of cows that had signs of ataxia and sedation within 30 minutes after administrations in Xyla-Epin^{gr}. These findings might be attributed due to vasoconstrictive properties of epinephrine, limiting the systemic absorption of local anesthetics and therefore the systemic effect (Swain *et al*., 2017), and this agreed with Caulkett *et al*. (1993a, 1993b); Pagliosa *et al*. (2015) who proposed that the ataxia exhibited in the cattle was most likely due to xylazine- mediated central effects (sedation) rather than to xylazine-mediated local effects on motor nerves. The degree of ataxia in the present study lasted for 120 and 150 minutes' post administration in Xyla-Epin^{gr} and Xyla^{gr}, respectively. Furthermore, the signs of sedations were reported in most of treated cows in Xyla^{gr} from 60-150 minutes following epidural treatment, however, they were reported in few treated cows in Xyla-Epin^{gr}. The study also reported significantly higher scores of ataxia and sedation in Xyla^{gr} comparing with those in Xyla-Epin^{gr} at 30-150 minutes for ataxia scores and at 30-60 minutes for sedation scores. Therefore, the time required for most cows until complete recovery from signs of ataxia and sedation was shorter in Xyla-Epin^{gr} than that in Xyla^{gr}. The other articles revealed that sedation after epidural administration of xylazine was common in cattle and was considered as a systemic effect of absorption through the longitudinal epidural veins and that were most obvious in the ruminants because of their increased sensitivity to this group of drugs (Robinson and Natalini, 2002; Lemke, 2007) and this had been confirmed by a previous study in which sedation and sedation-induced ataxia caused by epidurally administered xylazine in cattle could be attenuated by IV tolazoline, an alpha-1/alpha-2 adrenoceptor antagonist (Skarda *et al*., 1990b; Lee *et al*., 2001).

Onset of analgesia in Xyla^{gr} was 11.85±1.25 minutes' post-epidural administration of Xylazine, while it was 12.01±1.05 minutes' post-epidural administration of xylazine and Epinephrine. Moreover, no significance in the onset of analgesia was reported between the two treated group in the present work. These findings were supported with the previous reports which was in consistent with the onset of analgesia following the epidural administration of xylazine in goats (DeRossi *et al*., 2003), buffalo calves (Singh *et al*., 2009), sheep (Aminkov *et al*., 2002) and cows (St. Jean *et al*., 1990). But the addition of epinephrine to local anaesthetic was anticipated to delay the onset of action both by decreasing the pH of anaesthetic solution, thus reducing the amount of non-ionized local anaesthetic (Skarda and Tranquilli, 2007), and by producing vasoconstriction, reducing spread to the site of action. The absence of delays in the time to onset in the present study could be attributed to that the addition of epinephrine (5 µg/ mL-1) to xylazine only changed the pH from 5.36 to 5.25, and there was no significant difference. This agreed with (Rostami and Vesal, 2012) who reported that there was no significant difference, with respect to the mean onset of sensory blockade in the perineum, flank and hindlimbs, between plain lidocaine and lidocaine containing epinephrine after lumbosacral epidural analgesia in fat-tailed sheep and after the addition of epinephrine to lidocaine for caudal epidural anaesthesia in cows (Rastabi *et al*., 2018). The mean duration till onset of Antinociception following epidural administration of xylazine in cattle was 17.5 minutes (St Jean *et al*., 1990).

The current study reported that caudal epidural administration in both Xyla^{gr} and Xyla-Epin^{gr} produced an apparent antinociceptive effect (Analgesic effect) within 30 minutes following epidural injection. This analgesic effect was reflected by absence of pain response by applying a standard stimulus in different areas including the tail, anus, perineum, vulva, and inguinal area but extended up to the chest areas and coronary bands of the hindlimbs. The previous reports mentioned that α-2 agonists like xylazine induced their analgesic effects by inducing the α-2 adrenergic receptors in the dorsal horn of the spinal cord (Ismail, 2016). In the present study, epidurally administered xylazine and xylazine with epinephrine induced analgesia for the perineal region and this agreed with Skarda *et al*. (1990a); Abid (2002) who use the same dose and volume of 2% solution of xylazine HCl (0.05 mg/kg of body weight, diluted to a 5-ml volume with sterile water) for caudal epidural in cattle. Another study by Caulkett *et al*. (1993a) found that a dose of xylazine 2% at 0.07 mg/kg, diluted to a final volume of 7.5ml provided sufficient analgesia to permit flank surgery, and this could be explained by the fact that, by raising the injection total volume of drug, it was possible to extend the anaesthetized area (Marzok and El-khodery, 2017).

The analgesia score in the current study was significantly

higher in all treated groups post-administration (Minutes 30-120) comparing their values at minutes 0-10. This score reached its highest values in Xyla^{gr} and Xyla-Epin^{gr} at 60 minutes following administration. Afterwards, the analgesia score reduced gradually till its complete disappearance of analgesia at minutes 150 and 180 for Xyla^{gr} and Xyla-Epin^{gr}, respectively. There were significant changes were reported between the treated groups for the analgesic score whereas it was significantly lower in Xyla^{gr} comparing with Xyla-Epin^{gr} particularly at minutes 150 post-injection. Moreover, significant changes in duration of analgesia were demonstrated between the two treated group whereas the duration of analgesia was significantly longer in Xyla-Epin^{gr} (161±7.62 minutes) than that in Xyla^{gr} (136.20±7.13 minutes). The synergistic effect of epinephrine when injected with epidural local anesthetics had been reported previously in many studies as with lidocaine in cattle (Rastabi *et al*., 2018), sheep (Rostami and Vesal, 2012), Goats (Kayod, 2017) and dogs (Vnuk *et al*., 2011). The extended duration of epidural analgesia of lidocaine with epinephrine had been found to be due to the vasoconstrictor effects of epinephrine at the injection site, which, in turn, reduces the rate of systemic absorption and prolongs the duration of the local anaesthetic effect (Ghadirian and Vesal, 2013). Furthermore, prolonged duration and improved quality of the epidural block could be at least in one part explained by epinephrine's ability to induce analgesia through the interaction with alpha-2-adrenergic receptors located in the brain and spinal cord (Marija *et al*., 2014).

CONCLUSION

The study concluded that xylazine-epinephrine combination has higher efficacy as caudal epidural analgesic drug compared with that of xylazine alone. Xylazine-epinephrine combination has more rapid onset of recovery from signs of ataxia and sedation than xylazine alone that make it more suitable than xylazine in cattle as an intraoperative and postoperative analgesia. xylazine needs longer duration to achieve relative reasonable response of analgesia and requires more time to relieve from signs of ataxia and sedation compared with xylazine-epinephrine combinations. Clinical findings, and ataxia, sedation and analgesia scores change significantly between Xyla^{gr} and Xyla-Epin^{gr} most commonly at minutes 30-90 following epidural administration. However, further future studies are warranted to determine the utility of different doses of xylazine-epinephrine combinations for surgical procedures before final recommendations can be made.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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