COMPARISONS OF THE EFFECTS OF MEDETOMIDINE, LIDOCAINE AND THEIR COMBINATIONS AFTER LUMBOSACRAL EPIDURAL INJECTION IN GOATS

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SUMMARY

The present study was carried out in order to compare the behavioral, analgesic and cardio-pulmonary effects of epidurally administered medetomidine, lidocaine and their combinations in adult Small East African goats. Fourteen adult, healthy, Small East African goats of both sexes were used in this study. Medetomidine was administered at a dose of 20 μg/kg while lidocaine was given at a dose of 4.4 mg/kg body weight. Similarly, half of the above doses were combined, administered and evaluated for the same parameters. The drugs were administered in a randomized single blinded study, with a one-week interval between subsequent injections. Lumbosacral epidural injection of medetomidine and medetomidine-lidocaine combinations induced behavioral changes characterized by ataxia, swaying movements, tail flaccidity, low head carriage, sternal and lateral recumbency posture coupled with salivation. Both medetomidine and medetomidine/lidocaine combination induced a significant ($P<0.05$) decrease of the heart rate (HR) and respiration rate (RR) values within 5 and 10 minutes respectively that persisted for the entire 180 minutes of observation period. In contrast, epidural lidocaine induced a significant ($P<0.05$) increase of HR within 5 minutes and thereafter the HR values fluctuated within the normal ranges, no significant changes were observed on RR values. Medetomidine induced moderate raise of Rectal temperature (RT) values within 5 minutes, and followed by a significant fall ($P<0.05$) one-hour post injection, which persisted for the rest of observation period. No significant difference was noted between medetomidine-lidocaine combinations on RT values. However, lumbosacral epidural injection of 4.4 mg/kg lidocaine induced a sustained increase of RT values throughout ($P>0.05$). Lumbosacral

epidural injection of medetomidine and medetomidine-lidocaine combination induced a generalized analgesia, while lidocaine alone-induced bilateral flank and perineal analgesia with variable cranial extension. The duration of adequate analgesia was longer with medetomidine alone than either lidocaine or medetomidine-lidocaine combination. It was therefore concluded that, lumbosacral epidural injection of 20 μg/kg medetomidine induces adequate analgesia of longer duration than either 4.4 mg/kg lidocaine or a combination of half the dose of medetomidine and lidocaine mixed together and given epidurally.

INTRODUCTION

Medetomidine is a more selective and full agonist for central α_2-adrenergic receptor than xylazine or detomidine. It has analgesic, sedative and muscle relaxation properties similar to that of xylazine and detomidine. The α_2/α_1 receptor binding selectivity of medetomidine is 1620 whereas that of xylazine is 160 and detomidine 260 (Virtanen *et al.,* 1988, Virtanen, 1989). Medetomidine is also reported to be more lipophilic than either xylazine or detomidine (Savola *et al.,* 1986). Clinically, medetomidine is indicated for use mainly in dog and cats (Short, 1992) although, report by Abass (1997) described a successfully use of medetomidine in goats after intra muscular and intravenous injection. Its use for lumbosacral epidural analgesia in cattle (Lin *et al.,* 1996) and goats (Mpanduji, 1998, Mpanduji *et al.,* 2000) has been evaluated and found to induce longer duration of analgesia, and less side effects than when given either by intramuscular or intravenous routes.

Epidural use of α_2-adrenergic receptor agonist drug such as xylazine had been reported to offer a long duration of perineal analgesia in equids after caudal epidural injection as compared to lidocaine (Fikes *et al.,* 1989, Makady *et al.,* 1991). Furthermore, the combination of α_2-adrenergic receptor agonist drug such as xylazine and local analgesic drug such as lidocaine have shown to prolong the duration of analgesia in horses than either of the two drugs given alone. (Grubb *et al.,* 1992). Surgical procedures have been performed in cattle using similar mixture and found to have the advantage of high spread of analgesia to anatomical areas (Nowrouzian and Ghamsari, 1991). However, the effects of combining an α_2-adrenergic receptor agonist drug and local analgesia in epidural analgesia of goats had not been reported. This study was therefore conducted to compare the effects of medetomidine (a potent α_2-adrenergic receptor agonist drug), lidocaine (a conventional drug for epidural analgesia) and their

combinations after lumbosacral epidural injections in goats.

MATERIAL AND METHODS

Experimental animals, study design and allocation procedures

Fourteen, clinically healthy adult Small East African goats of both sexes and weighing between 10 and 25kg body weights were used in this study. Of these, 8 goats were used for behavioral study while the rest were used for analgesia and cardio-pulmonary studies. The design was a single-blinded study, where an anaesthetist not involved in the study prepared the test solutions. Four coded test solutions of 2% plain lidocaine hydrochloride (Dose 4.4 mg/kg), 0.1% medetomidine hydrochloride (Dose 20 µg/kg), (Domitor^R, Farmos Group-Finland), 5 ml sterile physiological normal saline and a combination of half dose of lidocaine and medetomidine were evaluated. With the exception of physiological normal saline, the calculated volume of lidocaine, medetomidine, and medetomidine-lidocaine combination was adjusted to total volume of 5 ml by additional of sterile water. All test solutions were administered epidurally through the lumbosacral interspace as described by Gray and MacDonell (1986) with the injection taking over 20 seconds. The order of administration was random, with a one-week interval between injections. Twelve hours prior to the experiment, feed were withheld but the animals were provided water adlibitum. Pre-injection (base line) cardiopulmonary, rectal temperature and analgesia values were determined and recorded at least, 30 minutes before the start of the experiment. The various behavioral, analgesia and cardio pulmonary parameters were noted and recorded as described by Mpanduji *et al* (2000).

Behavioral changes, Heart and Respiration rates, Rectal temperature and analgesia

Sedation was evaluated basing on observation such as decreased alertness, lowered head, drooping of the lower lip, and ears, partial to complete closure of the eyelids, ataxia, and recumbency. The onset of these signs were noted and recorded. Heart and respiration rates were measured by thoracic auscultation using stethoscope at 5 minutes intervals up to 30 minutes and thereafter, at 30 minutes intervals up to 180 minutes. Rectal temperature was monitored continuously and recorded at similar intervals as heart and respiration rates, using digital thermometer (Exacon^R, Exacon Scientific, Rosklide Denmark) with a rectal thermocouple probe placed deep into rectum. Animals designated for behavioural study were left free and observed for the entire 180 minutes observational period, while the cardio-pulmonary parameters and analgesic

measurements were determined in the animal placed on its right side.

Analgesia of the flank, perineum, and the hind limb extremities was determined after cardio-pulmonary measurements and was evaluated at 0, 10, 20, 40, 60, 120 and 180 minutes. The levels of analgesia for the flank, perineum and hind limb extremities was determined using a scoring system of 0 to 3 as described by Skarda and Muir (1996a,b), and Mpanduji *et al* (2000). During each test period, superficial skin prick and deep muscular pricks were performed using a 2.54 cm, 23-gauge needle. The skin pricking was performed for 3-5 seconds. A score of 0 (no analgesia) was given if there was an avoidance response to pricking the surface of the skin. A score 1 (mild analgesia) was given if there was no avoidance response to superficial skin pricks by the needle. A score of 2 (moderate analgesia) was given if there was no avoidance response to the insertion of half the needle length and a score of 3 (adequate analgesia) was given if there was no avoidance response to inserting the needle through the skin and the underlying tissues (deep muscle pricks). The spread of analgesia to the thorax, head and forelimbs were also determined and noted.

Data analysis

The cardiopulmonary, rectal temperature values and analgesia scores were subjected to the general linear model (GLM) procedure. Pair wise comparisons of the various cardiopulmonary, rectal temperature and analgesia scores were performed using the least square means (LSM). The computer statistical package SAS (1998) was used to analyze the data. No statistics was performed on behavioral effects. Differences of the data were significant when P was less than 0.05. All data are expressed as mean ± SE.

RESULTS

Ataxia, swaying movements, tail flaccidity, low head carriage, sternal and lateral recumbency characterized both medetomidine and medetomidine-lidocaine combinations. These effects started as early as 8 minutes and continued for about 70 minutes. Thereafter, animals showed several unsuccessful attempts to stand. Recoveries from sternal to standing postures were observed between 80 to 90 minutes post injection. However, signs of sedation were still evident as the animals showed extended forelegs, low head carriage, salivation and ataxia.

Table 1. Comparison of the mean heart rate (HR) values after epidural injection of 4.4 mg/kg lidocaine, 20 μg/kg medetomidine, combination of 2.2 mg/kg lidocaine and 10 μg/kg medetomidine, and 5 ml of physiological normal saline in six goats

Time	Drugs			
	Lidocaine	Medetomidine	Normal saline	Lidocaine/Medetomidine combination
0	73±3.9[a]	76±3.9[a]	70±3.9[a]	75±3.9[a]
5	88±3.9[a]*	55±3.9[b*]	80±3.9[a]	63±3.9[b*]
10	71±3.9 [a]	45±3.9 [b*]	72±3.9[a]	59±3.9[c*]
15	68±3.9 [a]	45±3.9 [b*]	71±3.9[a]	53±3.9[b]
20	70±3.9 [a]	47±3.9 [b]	71±3.9[a]	51±3.9[b*]
25	72±3.9 [a]	45±3.9 [b]	71±3.9[a]	52±3.9[b*]
30	73±3.9 [a*]	50±3.9 [b*]	69±3.9[a]	50±3.9[b*]
45	73±3.9 [a]	49±3.9 [b]	72±3.9[a]	47±3.9[b*]
60	73±3.9 [a]	52±3.9 [b*]	70±3.9[a]	50±3.9[b*]
75	76±3.9 [a]	48±3.9 [b*]	70±3.9[a]	51±3.9[b*]
90	80±3.9 [a]	49±3.9 [b*]	74±3.9[a]	51±3.9[b]
105	82±3.9 [a]	46±3.9 [b*]	71±3.9[c]	51±3.9[b]
120	79±3.9 [a]	49±3.9[b]	72±3.9[a]	50±3.9[b*]
135	77±3.9 [a]	48±3.9 [b]	72±3.9[a]	51±3.9[b]
150	80±3.9 [a]	49±3.9 [b*]	68±3.9[c]	53±3.9[b*]
165	77±3.9 [a]	48±3.9 [b*]	73±3.9[a]	53±3.9[b*]
180	71±3.9 [a]	49±3.9 [b*]	73±3.9[a]	55±3.9[b]

NOTE: * values significantly (P<0.05) difference from values recorded at base line (t = 0). Mean in the same row having same superscripts are not significantly different (P< 0.05). All values are expressed as mean ± SE

Lumbosacral epidural injection of 2%lidocaine hydrochloride was characterized by fetlock knuckling, which was followed by drugging movement 5-6 minutes post injection. About 6-11 minutes later, most of the goats underwent flaccid tail paralysis, which was followed by a dog sitting posture 24 to 25 minutes later. At about 88 to 92 minutes post injection, animals recovered from the effects of lidocaine. All eight goats injected with physiologic normal saline did not show any significant changes in behavior throughout the 180 minutes of observation period.

Table 2. Comparison of the mean respiration rate (RR) values after epidural injection of 4.4 mg/kg lidocaine, 20 μg/kg medetomidine, combination of 2.2 mg/kg lidocaine and 10 μg/kg medetomidine, and 5 ml of physiological normal saline in six goats

Time	Drugs			
	Lidocaine	Medetomidine	Normal saline	Lidocaine/Medetomidine combination
0	20±2.3^{a}	21±2.3^{a}	21±2.3^{a}	20±2.3^{a}
5	20±2.3^{a}	18±2.3^{a}	22±2.3^{a}	21±2.3^{a}
10	37±2.3^{a}	16±2.3^{b}	21±2.3^{b}	14±2.3^{c}
15	19±2.3^{a}	12±2.3^{b}	22±2.3^{a}	13±2.3^{ab*}
20	19±2.3^{a}	8±2.3^{b*}	21±2.3^{a}	13±2^{b*}
25	18±2.3^{ab}	14±2.3^{a*}	21±2^{ab}	13±2^{ab*}
30	18±2.3^{a}	13±2.3^{a}	21±2^{ab}	13±2^{a*}
45	19±2.3^{ab}	14±2.3^{a*}	21±2^{ab}	13±2.3^{a*}
60	19±2.3^{a}	12±2.3^{b*}	21±2.3^{a}	11±2.3^{b*}
75	19±2.3^{a}	12±2.3^{b*}	20±2.3^{a}	10±2.3^{b*}
90	19±2.3^{a}	11±2.3^{b*}	21±2.3^{a}	10±2.3^{b*}
105	18±2.3^{a}	12±2.3^{b*}	20±2.3^{a}	10±2.3^{b*}
120	19±2.3^{a}	10±2.3^{b*}	20±2.3^{a}	9±2.3^{b*}
135	20±2.3^{a}	10±2.3^{b*}	20±2.3^{a}	11±2.3^{b*}
150	19±2.3^{a}	9±2.3^{b*}	20±2.3^{a}	11±2.3^{b*}
165	19±2.3^{a}	8±2.3^{b*}	20±2.3^{a}	11±2.3^{b*}
180	19±2.3^{a}	8±2.3b*	19±2.3^{a}	13±2.3^{b*}

NOTE: * values significantly ($P<0.05$) difference from values recorded at base line (t = 0). Mean in the same row having same superscripts are not significantly different ($P< 0.05$). All values are expressed as mean ± SE

Lumbosacral epidural injection of medetomidine and medetomidine-lidocaine combinations induced a significant fall on both HR and RR values within 5 and 10 minutes respectively, which persisted for the entire 180 minutes of observation period (Table 1, 2). Slight fluctuations on HR and RR characterized epidural lidocaine. Comparatively, significant variations were observed between lidocaine and medetomidine treatments where the HR and RR values attributed to epidural lidocaine were higher ($P<0.05$). Same trend was observed between lidocaine and medetomidine-lidocaine combinations. Pair wise comparison of medetomidine, lignocaine, and their combinations showed significant ($P<0.05$) differences on the HR and RR value, but no differences was noted between medetomidine and medetomidine-lignocaine combinations throughout the 180 minutes of observation period (Table 1, 2).

Table 3. Comparison of the mean rectal temperature (RT) values after epidural injection of 4.4 mg/kg lidocaine, 20 μg/kg medetomidine, combination of 2.2 mg/kg lidocaine and 10 μg/kg medetomidine, and 5 ml of physiological normal saline in six goats

Time	Drugs			
	Lidocaine	Medetomidine	Normal saline	Lidocaine/Medetomidine combination
0	38.2±0.4	38.3±0.4	38±0.4	39±0.4
5	38.4±0.4	38.5±0.4	35.6±0.4	39±0.4
10	38.5±0.4	38.4±0.4	39±0.4	39±0.4
15	39±0.4	38±0.4	39±0.4	39±0.4
20	39±0.4 [a]	38±0.4 [b]	39±0.4 [b]	38±0.4 [b]
25	39±0.4 [a]	38±0.4 [b]	39±0.4 [a]	38±0.4 [b]
30	39±0.4[a]	38±0.4 [b]	39±0.4 [a]	38± 0.4 [a]
45	40±0.4 [a *]	38±0.4 [b]	39±0.4 [a]	38±0.4 [b]
60	39±0.4 [a]	37±0.4 [b*]	39±0.4 [a]	40±0.4 [a]
75	39±0.4[a]	37±0.4 [b*]	39±0.4 [a]	38±0.4 [b]
90	39±0.4 [a]	37±0.4[b*]	39±0.4 [a]	38±0.4 [b]
105	39±0.4 [a]	37±0.4[b*]	39±0.4 [a]	38±0.4 [b]
120	39±0.4 [a]	36±0.4[b*]	39±0.4 [a]	38±0.4 [b]
135	38±0.4 [a]	36±0.4[b*]	39±0.4 [c]	38±0.4 [a]
150	39±0.4 [a]	36±0.4[b*]	39±0.4 [a *]	38±0.4 [c]
165	39±0.4 [a]	36±0.4 [b*]	39±0.4 [a *]	38±0.4 [c]
180	39±0.4 [a]	36±0.4 [b*]	39±0.4 [a]	38±0.4 [c]

NOTE: * values significantly ($P<0.05$) difference from values recorded at base line (t = 0). Mean in the same row having same superscripts are not significantly different ($P< 0.05$). All values are expressed as mean ± SE

Lumbosacral epidural injection of lidocaine was characterized by a rise of RT values. The RT values rose significantly from the normal pre-injection value of 38.2ºC to 40ºC at the 45th minutes post injection, and there-after the RT values fluctuated at 39ºC throughout the 180 minutes of observation period (Table 3). Epidurally injected medetomidine showed a gradual fall of the RT values, which was very marked one-hour post injection. This effect persisted for the rest of observational period. The RT values attributed to epidural administration of lidocaine were sustainably higher compared to medetomidine, medetomidine-lidocaine combination, and normal saline (Table 3).

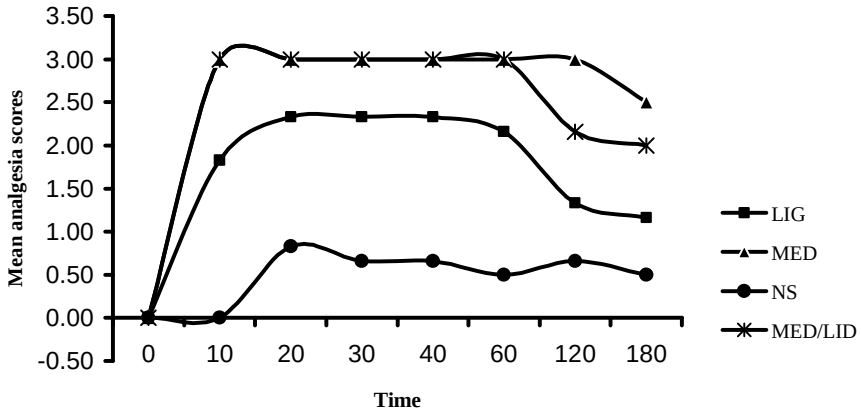

Figure 1: Comparison of the mean analgesia score in response to needle pricks at the flank region after epidural injection of lignocaine, medetomidine, physiological normal saline and A combination of medetomidine/lidocaine in six goats

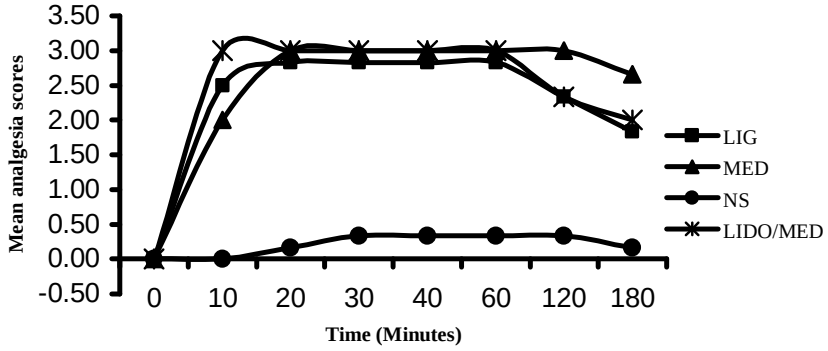

Figure 2: Comparison of the mean analgesia score in response to needle pricks on the perineal region after epidural injection of lignocaine, medetomidine, physiological normal saline and a combination of medetomidine/lidocaine in six goats

Lumbosacral epidural injection of 20 μg/kg medetomidine induced adequate analgesia of the flank and perineum (Figure 1, 2). Analgesia induced by medetomidine extended to the thorax, hind limbs, fore limbs, neck, and head, which persisted for the entire 180 minutes of observation. However, lumbosacral epidural injection of lidocaine at a dose of 4.4 mg/kg induced and maintained a moderate analgesia for one hour after which, it declined progressively for the flank, perineum and hind limb extremities (Figure 1, 2, 3). Pair wise comparisons on the levels of analgesia at different time points showed no significant difference between medetomidine, lidocaine and medetomidine-lidocaine combinations for the flank, perineum and hind limb extremities. All tested parameters differed significantly with normal saline (Table 1, 2, 3; Figure 1, 2, 3)

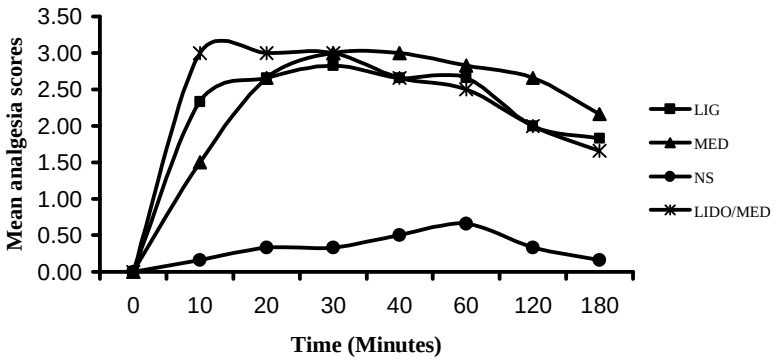

Figure 3: Comparison of the mean analgesia score in response to needle pricks on the perineal region after epidural injection of lignocaine, medetomidine, physiological normal saline and a combination of medetomidine/lignocaine in six goats

DISCUSSION

In this study, lumbosacral epidural injection of medetomidine and medetomidine-lidocaine combination induced sedation that was characterized by low head carriage, sternal and lateral recumbency, salivation, droopy ear and ataxia similar to what was observed by Mpanduji *et al.,* (1999a, 1999b) and Mpanduji *et al.,* (2000) after caudal epidural injection of xylazine and medetomidine respectively. The behavioural changes attributed by lumbosacral epidural injection of medetomidine and medetomidine-lidocaine combinations like low head carriage, salivation, partial or complete closure of the eye, and intermittent sternal to lateral recumbency reflects the central effects of α_2-adrenergic receptor activation. These effects are known to be caused by local (Aziz and Martin, 1978, Chamber, 1993, Le Blanc *et al.,* 1988) and central effects of α_2-adrenergic receptor activation (Short, 1992). The local effects are likely to be caused by inhibition of spinal release of the neuro-transmitter substance P at the spinal cord, which is known to inhibit pain perception and transmission to the brain, and probably by the descending inputs from the locus coerelus to the dorsal horn of the spinal cord (Sternberg, 1986). The locus coerelus has descending projections to the spinal cord as well as extensive ascending projection in the cortical, limbic, and the cerebellum (Moore and Bloom, 1979**)**. The inhibition of neuronal firing at the locus coerelus in the brain contributes to analgesia and sedation (Cedarbaum and Aghajanian, 1977; Desarro *et al.,* 1987). Reversal of analgesia and sedation effects induced by intrathecally-administered clonidine in sheep (Eisenach *et al.,* 1987) was counteracted by administration of idazoxan (an α_2 adrenergic receptor antagonist) but not prozasin (an α_1 antagonist). Similary, analgesia and sedation induced by epidurally administered medetomidine in goats were completely blocked by atipamezole (an α_2 adrenergic receptor antagonist) and partially by tolazoline, a competitive α_1/α_2 antagonist (Mpanduji *et al.,* 2001). Thus analgesia and sedation induced after epidural and intrathecal injection of specific α_2 adrenergic receptor agonists such as medetomidine and clonidine is likely to be mediated through α_2 adrenergic receptor mediation.

Lumbosacral epidural injection of lidocaine was characterized by postural changes, which included fetlock knuckling, drugging movement, and dog sitting posture. The drugging movement was a reflection of the paralysis of the hindquarter. The paralytic effects seen after epidural lidocaine is attributed to the action of the drug on the motor neurone in the spinal cord (Booth and

McDonald, 1988). However, the goats remained full alert throughout the 180 minutes of observation period. Sedation which accompanies epidural use of α_2-adrenergic receptor agonist alone (Mpanduji *et al.,* 1999b), or in combination with local anaesthetic agent as seen in the goats of the present study is of advantage as it decreases movements and needs for physical restraints, as the case could be with local analgesic alone.

Lumbosacral epidural injection of medetomidine induced a significant decrease of HR values. The decrease in HR did not return to the normal pre-injection values throughout the 180 minutes of observation period. These observations are in agreement with the previous report by Mpanduji, (1998) and Ko *et al.,* (1992), after lumbosacral epidural injection of xylazine, detomidine and medetomidine in goats and pigs respectively. Similar effects have been reported in goats (Clark *et al.,* (1983) and dogs (Davis, 1980; Greene and Thurmon, 1988) after systemic injection of detomidine and xylazine respectively. Bradycardia is reported to be common in animals after systemic injection of alpha$_2$-adrenergic receptor agonists (Hall and Clark, 1991). A decreased sympathetic outflow from the CNS and vagal reflex from baroreceptor in response to hypertesion are belived to be the most likely causes (Davis, 1980, Alitalo *et al.,* 1986). Medetomidine-lidocaine combination produced a gradual decrease in HR, which did not return to normal pre-injection values throughout the 180 minutes of observation period. The initial increase of HR values attributed to epidural lignocaine may probably be due to excitements. The depressant effects of medetomidine in the cocktail probably contributed the HR depressions seen after lumbosacral epidural injection of medetomidine, and medetomidine-lidocaine combination.

Lumbosacral epidural injection of medetomidine, and medetomidine-lidocaine combinations exhibited an inhibitory effect on RR values, while lidocaine has no effects. The decrease in RR caused by medetomidine are believed to be attributed by the central effects of alpha$_2$-adrenegic receptor agonist (Short, 1992), while those due to lidocaine are believed to be due to blockade of the thoracic motor nerves supplying the abdominal, intercostals and anterior parts of abdominal muscles (Swaroop *et al.,* 1988). In the present study, lidocaine did not cause such effects.

Lumbosacral epidural injection of lidocaine and medetomidine-lignocaine combinations was shown to induce mild changes in RT, which fluctuated slightly above the normal pre-injection values. However, medetomidine alone induced a significant fall on RT

values one hours post injection and persisted for the entire observation period. Alpha$_2$-adrenergic receptor agonists have been reported to induce either hyper or hypothermia depending on either α_1 or α_2 adrenergic receptor stimulation. (Short, 1992). In contrast, the slight increase on RT values associated with epidural injection of lignocaine is known to be due to sympathetic blockade, which induce vasodilatation and subsequent increase of blood supply to the peripheral vessels. The increase of blood flow to the peripheral contributes to the rise of the rectal temperature.

In this study, lumbosacral epidural injection of medetomidine induced adequate and a more generalized analgesia within 10 minutes. It was however, different from lidocaine hydrochloride to which moderate analgesia was attained in the flank, perineum and extremities. The combination of medetomidine and lidocaine hydrochloride induced a more generalized analgesia of short duration as compared to medetomidine alone. The short lived analgesia induced by the combination of medetomidine and analgesia seem to be caused by several factors including (i) loss of analgesics from the epidural to Para vertebral space by the way of intra vertebral foramen (Cruz, 1992), (ii) vascular uptake of anaesthetics caused by vascular dilatation attributed by sympathetic blockade (iii) low dose of lidocaine (2.2 mg/kg) and medetomidine (10 µg/kg) as compared to the normal recommended dose of 4.4 mg/kg and 20 µg/kg of lidocaine and medetomidine respectively. (iv) The synergistic effects attributed to the mixture of α_2 –adrenergic receptor agonist and lidocaine seen in horses (Grubb *et al.,* 1992) and cattle (Nourouzian and Ghamsari, 1991) does not apply in goats, probably due to specie variation. The combination of these factors may probably be the reasons for the differences in the duration of analgesia between medetomidine and by the combination of medetomidine and lidocaine in the goats of the present study. Therefore, epidural use of medetomidine at the dose of 20 µg/kg body weight alone brought to a total volume of 5 ml by addition of sterile water for injection is superior in terms of analgesia than either lidocaine or half dose of medetomidine and lidocaine combined together.

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