



Effects of Lignocaine-Diazepam Combination in Lumbo-Sacral Epidural Anaesthetized Dogs Undergoing Caudectomy

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Authors' contributions

This work was carried out in collaboration among all authors. Author ASY designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors IBU, HK and AAA performed the statistical analysis and managed the analyses of the study. Authors AB, EIO, NA and HAB managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

General anaesthesia is known to be associated with the risk of cardiopulmonary depression, therefore the use of a safer means of anaesthesia as an alternative has to be explored. Epidural anaesthesia technique is known for its simplicity, safety and effectiveness and is one of the most frequently used regional anesthetic techniques described for surgical procedures caudal to the umbilicus in small animal practice. The main aim of this study was to evaluate the effects of lumbo-sacral epidural injection of a mixture of 7.5 mg/kg of 2% lignocaine solution and 0.2 mg/kg 0.5% diazepam solution in 10 apparently healthy Nigerian local dogs undergoing caudectomy. Onset of neural blocked recorded was 6.5 ± 1.35 min (mean \pm SD), duration of analgesia was 54.4 ± 5.38 min (mean \pm SD) and duration of recumbency was 115.1 ± 36.1 min (mean \pm SD). Changes observed in the Pulse rate (PR), Mean arterial blood pressure (MAP), Respiratory rate (RR) and Rectal temperature (RT) were recorded at 10 min intervals throughout the duration of the procedure.

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There were no significant differences ($p>0.05$) in the mean physiological parameters observed as compared to the baseline values. Blood samples were also taken at 15 min interval throughout the duration of the procedure to determine the effects of the epidurally administered lignocaine-diazepam combination on haematological and serum biochemical indices. No significant differences ($p>0.05$) were observed in the mean haematological (PCV, RBC, WBC, Hb and CBC) and serum biochemical indices (ALT, ALP, Creatinine and BUN). It was concluded that epidurally administered lignocaine-diazepam mixture at 7.5 mg/kg and 0.2 mg/kg respectively had a fast onset of neural blockade, adequate and long duration of analgesia without profound effects on haemodynamic and cardiopulmonary system.

Keywords: Lignocaine; diazepam; epidural; dogs.

1. INTRODUCTION

The popularity of local anesthetic-induced neural blockade in dogs has increased over the past several years. A major driving force behind this increased usage is acceptance of the concept of blocking multimodal pathways to control animals' pain and suffering. Unlike most general anesthetics, which block the perception of pain by inducing anesthesia in an unconscious patient, local anesthesia and regional anesthesia completely block transmission of noxious impulses in a targeted region of the body of a conscious patient. General anesthesia may be advantageous in dogs that are considered difficult to sedate and restrain for surgery and where complete immobilization and relaxation of the patient are required. Local and regional anesthesia also decreases the quantity of opioid and inhalation anesthetic required to obtain the desired intra-operative plane of anesthesia [1].

Topical anesthesia, infiltration anesthesia, field blocks, selected nerve blocks, intravenous regional anesthesia, multiple inter-costal nerve blocks, lumbo-sacral epidural anesthesia and continuous epidural anesthesia are all logical techniques for providing surgical analgesia and Anesthesia in dogs that are considered at risk for inhalant or intravenous anesthesia. Continuous inter pleural analgesia and epidural opioid analgesia can be used to relieve postoperative pain following general anesthesia, [1]. Despite that, the risk factors associated with the general anesthesia, the cost, availability of the general anesthetic agents, sophisticated equipment involved particularly in inhalation anesthesia and the technical know-how are the most common challenges that discourage the choice of the general anesthesia as the sole anesthetic protocol in some surgical procedures in small animal practice [2]. Various combination of drugs have been documented for epidural administration to achieved anesthesia or

analgesia in small animal practice few of these examples are opioids (eg.. morphine or oxymorphone) with local anesthetics (e.g., lidocaine, bupivacaine, or ropivacaine) or 2 adrenoceptor agonists (e.g., xylazine, medetomidine, or dex-medetomidine) have been administered to dogs before surgery to reduce general anesthetic requirements and provide intra-operative and postoperative pain control [1].

This study was designed to overcome some challenges associated with general anesthesia in small animal surgery. Majority of the general anesthetic agents have profound cardiopulmonary depression leading to various challenges of anesthetic emergencies. This technique is noted for its simplicity safety and effectiveness, and is one of the most frequently used regional anesthetic techniques described for surgical procedures caudal to the umbilicus in dogs [3]. Epidural anesthesia is frequently recommended for cesarean section because, unlike other anesthetic techniques, it does not depress the puppies. Because of the excellent postoperative analgesia produced, it is useful in very painful procedures such as rectal, perineal or orthopedic surgery [4]. It also has minimal effect on the body as a whole, giving it some advantages over general anesthesia in the aged, toxic or debilitated patient. Some pre-existing problems that might warrant epidural analgesia include hepatic renal and pulmonary disease [4]. Additionally, epidural analgesia provides excellent muscle relaxation, is minimally expensive and is technically easy to perform.

The main aim of this study was to determine the hematology and serum biochemical effects of Diazepam-Lignocaine combination following lumbo-sacral epidural injection in dogs. We Hypothesized that Lumbo-Sacral epidural anesthesia using lignocaine-diazepam combination will provide sufficient anesthesia/ analgesia stability in heamatological indices to

perform caudectomy in dogs. Lignocaine is one of the most frequently used local anesthetics and is considered to be the prototype of the aminoamide family of drugs. Lidocaine provides quick onset and an intermediate duration of action. It is commonly used for local anesthesia of peripheral nerves, neuraxial anesthesia local infiltration, intravenous regional anesthesia (VRA), and even for topical desensitization of mucosa or skin. For surgical anesthesia, concentrations of 1-2% are commonly used. In addition, lignocaine is used systemically as an intravenous agent for its analgesic, anti-inflammatory, and anti-arrhythmic effects [5].

Diazepam is commonly used to treat anxiety, panic attacks, insomnia, seizures (including *status epilepticus*), muscle spasms, restless legs syndrome, alcohol withdrawal, benzodiazepine withdrawal, opiate withdrawal syndrome and Meniere's disease. It may also be used before certain medical procedures as endoscopies, to reduce tension and anxiety, and to induce amnesia [6]. It possesses anxiolytic, anticonvulsant, hypnotic, sedative, skeletal muscle relaxant, and amnesic properties [7]. The pharmacological action of diazepam enhances the effect of the neurotransmitter GABA by binding to the benzodiazepine site on the GABAA receptor (via the constituent chlorine atom) leading to central nervous system depression [8].

2. MATERIALS AND METHODS

2.1 Experimental Animals

A total of ten (10) apparently healthy adult dogs were used for the experiment: they were housed in the Usmanu Danfodiyo University Veterinary Teaching Hospital kennels, where they were dewormed and prophylactic treated. The animal were fed on table remnant twice a day for a week after which they were examined to ascertain that they are free of any clinical signs of illness. After proper physical restraint and muzzling of the dog, a liberal area around the lumbosacral region up to the cranial aspect and the caudal base of the tail were shaved and aseptically prepared using the routine appropriate scrubbing solutions.

2.2 Epidural Drugs Administration

A 2% Lignocaine at 7 mg/kg in combination with diazepam at 0.2 mg/kg was administered epidurally and 1.5 inch. 21 gauge needle was

inserted into the lumbo-sacral space according to the technique described by several authors [9,10] the correct positioning of the needle was confirmed by the absence of cerebrospinal fluid or blood at the hub and by absence of resistance. A combination of lignocaine and diazepam was then administered. The dogs were maintained on sternal recumbency to facilitate the uniform distribution of the drugs before starting the surgical procedure. Sensory blockade was observed by absence of groaning, biting attempt, looking at the limb and head shaking by painful stimulus using an Allis tissue forceps on interdigital space of hind foot after administration of epidural anesthetics every 5 minutes of the Procedures.

2.3 Hemato-biochemical Parameters

The hematological parameters considered for the analysis included hemoglobin (Hb g/dl), packed cell volume (%), total erythrocyte count (TEC in $10^6/\mu\text{l}$), total leukocyte count (TLC $10^3/\mu\text{l}$), mean corpuscular volume (MCV fl), mean corpuscular Hb (MCH pg), and MCH concentration (g/dL) and differential leucocyte count (neutrophil, lymphocyte, eosinophil, monocyte, basophil, bands cells). The serum biochemistry Alkaline phosphatase (ALP IU/L), Alanine aminotransferase (ALT IU/L), Blood urea nitrogen (mg/dl), creatinine (mg/dl).

2.4 Cardiopulmonary Evaluation

A pediatric blood pressure monitor was wrapped around the forelimb close to cephalic vein for recording systolic and diastolic blood pressure and pulse rate. The respiratory rate was evaluated visually. A digital thermometer was inserted into the rectum for one minute to record the temperature. These parameters were recorded before epidural administration to form the baseline values (time-0), then subsequently at 30 minutes intervals for the period of 120 minutes.

2.5 Evaluation of Quality of Analgesia

The quality of epidural analgesia was evaluated using Allis tissue forceps. This was achieved by observing absence of pedal reflex at interdigital space of hind legs as described by Dzikiti, et al. [11]. The reflex was observed before epidural administration and subsequently at 5 minutes intervals throughout the duration of analgesia.

3. RESULTS

3.1 Effects on Haematological Indices

The results of the mean haematological values of all the dogs used for the experiment following lumbosacral epidural administration of lignocaine-diazepam is as presented in Table 1. From the table it was observed that there were no significant increase or decrease obtained within the hours post lignocaine-diazepam administration. However a statistically significant increase was observed in the MCHC values at 30 min post lignocaine-diazepam administration as compared to the baseline value.

3.2 Effects on Biochemical Indices

The mean biochemical values of all the dogs used for the experiment following lumbosacral epidural administration of lignocaine-diazepam is as presented in Table 2.

From the table it was observed that there were no significant increases or decrease obtained within the hours post lignocaine-diazepam administration. However a statistically significant decrease was observed in the creatinine values at 60 min post lignocaine-diazepam administration as compared to the baseline values.

3.3 Effects on Cardiopulmonary Parameters

The effects of lumbo-sacral epidural administration of lignocaine-diazepam combination on cardiopulmonary parameters were evaluated, the mean of the following parameters, rectal temperature, respiratory rate, pulse rate and mean arterial pressure (MAP) were determined before and during the anaesthesia for a period of 120 minutes as presented in the Table 3.

There was intermittent decrease and increase in the mean rectal temperature (RT) observed at 30 minutes post epidural administration throughout the duration of anaesthesia as compared to the baseline values, however, the changes observed (P value is 0.6547) were not statistically significant.

There was statistically significant intermittent decrease and increase (P value is < 0.0001) in the mean respiratory rate (RR) at 30 minutes

post epidural administration throughout the duration of anaesthesia as compared to baseline values (Table 3). Intermittent non statistically significant (P value is 0.6495) decrease and increase in the mean pulse rate (PR) at 30 minutes post epidural administration throughout the duration of anaesthesia as compared to baseline values were observed (Table 3).

The result obtained for the mean arterial blood pressure (MAP) showed statistically significant intermittent decrease (P value is 0.0063) at 30 minutes post epidural administration throughout the duration of anaesthesia as compared to baseline values (Table 3). The increase or decrease observed in the cardiopulmonary parameters in the present study falls within the normal physiological limits.

3.4 Evaluation of the Quality of Analgesia

The quality of analgesia was evaluated following lumbo-sacral epidural administration of lignocaine-diazepam combination. This was evaluated throughout the duration of analgesia as presented in the Table 4.

The arithmetic mean for the onset of analgesia, duration of analgesia and recovery time of all the 10 dogs were observed to be 6.5 ± 0.4 SEM, 54.4 ± 1.7 SEM, and 115.1 ± 11.4 SEM minutes respectively (Table 4).

4. DISCUSSION

The intermittent transient non statistically significant decrease and increase observed in red blood cells (RCB), packed cell volume (PCV), and haemoglobin concentration (Table 4) could be as a result of rapid systemic absorption of the agents being administered and this lead to the acute shifting of fluid from extra-vascular compartment to intravascular compartment in order to maintain normal cardiac output as reported by Mion and Villeveille, [12] when ketamine is administered epidurally. Also pooling of circulating blood cells in the spleen and other reservoirs secondary to decrease sympathetic activity is suggestive to be possible reason for the decrease in PCV, Hb concentration and RBC during sedation and anaesthetic state .Kilic [13]. Decrease in red blood cell count and haemoglobin concentration but increased in packed volume in xylazine, ketamine diazepam anaesthesia in goat and sheep has also been reported Ismail et al.[14]. Umar & Wakil [15] also reported significant decrease in RBC, PCV and

Table 1. Mean value \pm (SE) of haematological parameters after epidural administration of lignocaine-diazepam in dogs

Timing interval (MINS)	Parameters												
	PCV (%)	Hb (g/dl)	RBC($\times 10^6$)	WBC($\times 10^3$)	MCV (fl)	MCH (pg)	MCHC (g/dl)	N (%)	L (%)	M (%)	E (%)	B (%)	Bd cell (%)
0	38.6 \pm 2.63	12.7 \pm 0.87	5.94 \pm 0.29	12.21 \pm 1.25	64.92 \pm 1.58	21.25 \pm 0.55	32.88 \pm 0.21	69.50 \pm 3.82	23.40 \pm 3.69	3.50 \pm 1.00	0.30 \pm 0.30	0.10 \pm 0.10	3.30 \pm 0.50
30	33 \pm 1.85	11.2 \pm 0.57	5.36 \pm 0.23	11.68 \pm 2.31	61.31 \pm 1.22	20.85 \pm 0.36	34.03 \pm 0.23*	70.40 \pm 1.93	23.00 \pm 1.81	3.50 \pm 0.42	0.20 \pm 0.13	0.10 \pm 0.10	2.80 \pm 0.61
60	35.8 \pm 1.85	11.9 \pm 1.11	5.64 \pm 0.36	11.38 \pm 3.28	62.71 \pm 1.80	20.82 \pm 0.65	33.18 \pm 0.22	70.00 \pm 4.12	23.30 \pm 3.57	2.50 \pm 0.54	0.20 \pm 0.20	0.30 \pm 0.21	1.70 \pm 0.54
90	38.1 \pm 2.93	12.8 \pm 1.01	6.05 \pm 0.32	10.24 \pm 1.81	62.47 \pm 1.74	20.97 \pm 0.61	33.56 \pm 0.28	70.70 \pm 2.50	22.00 \pm 2.72	3.60 \pm 0.70	0.40 \pm 0.27	0.00 \pm 0.00	3.30 \pm 0.68
120	37.4 \pm 2.68	12.5 \pm 0.89	5.86 \pm 0.30	8.84 \pm 0.93	63.24 \pm 1.70	21.15 \pm 0.57	33.43 \pm 0.14	71.50 \pm 2.72	21.40 \pm 3.31	2.30 \pm 0.50	0.20 \pm 0.20	0.40 \pm 0.40	4.20 \pm 1.19

Data are presented in mean \pm SE of ten (10) dogs

Table 2. Mean value \pm (SE) of biochemical parameters after epidural administration of lignocaine-diazepam in dogs

Timing intervals (MINS)	Parameters			
	BUN (mg/dl)	CR (mg/dl)	ALT (IU/l)	ALP (IU/l)
0	7.12 \pm 0.99	1.78 \pm 0.32	37.50 \pm 8.37	116.51 \pm 4.80
30	8.56 \pm 2.02	1.23 \pm 0.08	37.70 \pm 9.81	112.62 \pm 6.68
60	4.85 \pm 0.53	1.11 \pm 0.06*	18.60 \pm 6.45	111.64 \pm 5.55
90	6.69 \pm 0.64	1.34 \pm 0.07	18.30 \pm 5.75	112.68 \pm 7.01
120	6.69 \pm 0.64	1.34 \pm 0.07	18.30 \pm 5.75	112.68 \pm 7.01

Data are presented in mean \pm SE of ten (10) dogs

Table 3. Effects on cardiopulmonary parameters

Timing intervals (minutes)	Parameters			
	RT($^{\circ}$ C)	RR (cycles/min)	PR (beats/min)	MAP
0	38.510 \pm 0.125	45.600 \pm 4.588	118.40 \pm 7.552	91.700 \pm 8.372
30	38.480 \pm 0.08667	20.000 \pm 1.155	115.60 \pm 8.875	81.220 \pm 6.047
60	38.450 \pm 0.0847	22.400 \pm 1.904	106.50 \pm 7.988	86.850 \pm 3.859
90	38.450 \pm 0.1232	22.800 \pm 1.638	114.80 \pm 7.455	90.790 \pm 6.952
120	38.300 \pm 0.08300	26.200 \pm 2.356	104.7 \pm 6.088	113.25 \pm 3.194

Data are expressed as mean \pm SD of 10 dogs

Table 4. Evaluation of the quality of analgesia

Onset of analgesia (minutes)	Duration of analgesia (minutes)	Recovery time (minutes)
6.5 \pm 0.4	54.4 \pm 1.7	115.1 \pm 11.4

Data are expressed as mean \pm SEM of n=10

Hb concentration in ketamine, medetomidine anaesthesia in goat.

The differential leucocyte count (neutrophil, lymphocyte, eosinophil, monocyte, basophil, bands cells) showed no significance difference from the baseline data (Table 1). The transient changes (decrease/increase) in haematological parameters may be due to increase plasma volume during anaesthesia, on account of vasodilatation resulting in vascular pooling [16] or it may be due to sequestration of blood cells in spleen and lungs during anaesthesia [17].

Serum alkaline phosphatase (ALP) and alanine aminotransaminase (ALT) values were ranged between 116.51 \pm 4.80 to 113.18 \pm 7.44 unit/ml and 37.50 \pm 8.37 to 26.30 \pm 7.21 unit/ml respectively. Analysis of variance showed no significant differences for ALP and ALT. The above findings for ALP and ALT are in accordance with the earlier findings recorded by Pandey and Rao [18] which might be due to alteration in the cell membrane permeability which may permit these enzymes to leak from the cells with intact membrane, when there is stress or any damage to the liver cells, the enzyme escapes into the blood and so the ALP, ALT enzymatic activity increases. Vikers et al., [19] Blood urea nitrogen

(mg/dl) increased significantly from the base line value of 7.12 \pm 0.99 to 8.56 \pm 2.02 mg/dl at 30 min. interval after epidural anaesthesia. Thereafter it decreased to 7.09 \pm 1.11 mg/dl at 120 min. The present finding is in agreement with earlier findings of Dwivedi and Sharma [20], who reported increase in level of BUN following epidural administration of xylazine in buffaloes. In the present study the elevation of BUN is attributed to the temporary inhibitory effects of drugs on renal blood flow which in turn might have caused a rise in BUN. Serum creatinine level (mg/dl) showed significance difference at baseline data between 1.78 \pm 0.32 to 1.11 \pm 0.06 mg/dl at 60 min and analysis of variance showed significant difference for serum creatinine level at 60 min.

The result of this study showed that there was statistically insignificant (P value is $>$ 0.05) intermittent decrease and increase observed 30 minutes post epidural administration in the mean rectal temperature for the period of 120 minutes as compared to the baseline values; which were within normal physiological limit [21].

The transient intermittent significant decrease and increase observed in the present study can be attributed to the effect of diazepam that

causes mild depression of the cardiovascular system (Ferreira et al., 2015). However, this intermittent decrease and increase observed were within the normal physiological [21]. The baseline values obtained were however higher than the normal physiologic range, this can be attributed to the excitement or frightening during handling and restrain. Similar result was obtained by Adetunji et al., [22] who worked on the effects of lumbo-sacral epidural ketamine and lidocaine in xylzine-sedated cats and reported that epidurally administered ketamine, lidocaine and ketamine/lidocaine did not induce alteration in respiratory rate.

There was intermittent decrease and increase in the mean pulse rate observed in the present study, however, this is contrary to the report by (Ferreira et al., 2015) who reported that diazepam increases heart rate, but similar to the report by Nolte et al., [23] who reported that epidural administration of local anaesthetics causes hypotension. There was transient intermittent decrease and increase in the mean of MAP observed in this study which is in line with the work conducted by (Ferreira et al., 2015) who reported that the pre-anaesthetic doses of diazepam decreases blood pressure.

The result of this study showed that the onset of anaesthesia was longer than the findings (2.2 minutes) reported by Abdul, et al., [2] and shorter than findings (9.6 minutes) reported by Lawal, et al., [24].

However, the duration of anaesthesia was longer than the findings (50 minutes) reported by Abdul, et al., [2] and shorter than the findings (68.6 minutes) reported by Lawal, et al., [24]. This can be attributed to the sedative and centrally induced muscle relaxation effects of diazepam [25]. Also the extent of sensory, motor and autonomic blockade produced by a lumbo-sacral epidural administration will depend on the cranial distribution of local anaesthetics according to the volume, concentration, velocity of administration, amount of the epidural fat, epidural space size, posture and gravity [26].

5. CONCLUSION

From the result of this study, it can be concluded that epidural administration of lignocaine in combination with diazepam at 7mg/kg and 0.2mg/kg respectively, in a clinically healthy matured dogs can produced onset of analgesia within 6.5 ± 0.4 minutes (Mean \pm SEM) and $54.4 \pm$

14.23 minutes duration of analgesia. With the combination, caudectomy can also be performed. The effect of the combination has minimal effects on cardiopulmonary and haemodynamics of dogs.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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