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Haemato-biochemical effects of intraperitoneal ropivacaine and ropivacaine - dexmedetomidine for pain management in pigs undergoing herniorrhaphy

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Abstract
Different types of laparotomy procedures are common in pigs as they are used as experimental animal model for the biomedical research. In field level, surgeries like caesarean sections, spaying and hernia correction are also usually performed. But the uses of high standard perioperative as well as post-operative analgesic drugs are limited in those animals. This study was conducted for the evaluation of haematobiochemical changes with intraperitoneal ropivacaine and dexmedetomidine in 18 Clinical cases of pigs which were operated for the correction of either umbilical or ventral hernia. The animals were randomly divided into three groups. All the animals were premedicated with meloxicam and anaesthesia was induced and maintained with diazepam-ketamine combination. Intraperitoneal administration of ropivacaine or ropivacaine with dexmedetomidine or normal saline was given in the treatment groups. The blood samples were collected from superficial ear vein before administration of pre medication (zero minute), after induction of anaesthesia (30 minutes), after intraperitoneal infusion (1 hour) and postoperatively after 24 hours for the haemato-biochemical evaluation.
All the haematological as well as serological parameters except serum creatine kinase and cortisol were fluctuated within the physiological limit and animal did not show any sign of anaesthesia related complications after intraperitoneal administration of the drugs.

Keywords: Dexmedetomidine, Haematobiochemical, Herniorrhaphy, Intraperitoneal, pigs, Ropivacaine

Introduction
Pigs are one of the commonly used animals for translational research, so these animals are undergoing verities of surgeries worldwide. In field level laparotomy procedure involving caesarean sections, spaying and hernia correction are common in swine. But these animals are not receiving good standard perioperative as well as post-operative analgesia. A literature review on pain management in swines that undergone experimental surgery has found that only 37% (87/233) articles have mentioned the use of postoperative analgesic agents (Bradbury *et al.*, 2016) [3].
Several combinations of medicine are used for the management of pain in animals; this includes local anaesthetic agents as well as alpha adrenergic receptor agonists.
The advantage of local anaesthetic is that it is widely available and inexpensive. World small animal veterinary association global pain council has recommended the use of incisional as well as intraperitoneal administration of local anaesthetics. Intraperitoneal and incisional analgesics are recommended for controlling pain in cats and dogs as an additional technique for pain relief (Steagall *et al*., 2020) [27].
Ropivacaine is an amide group long-acting local anaesthetic agent. It has improved sensory and motor blocking ability with reduced toxicity potential (Kuthiala and Chaudhary, 2011) [15]. Dexmedetomidine is a strong α-2 adrenoceptor agonist and it provides adequate analgesia, anxiolysis as well as anaesthesia sparing action (Mahmoud and Mason, 2015) [14]. By considering these factors the present study was under taken to evaluate the haemato-biochemical changes associated with intraperitoneal application of ropivacaine and dexmedetomidine during the herniorrhaphy of pigs.

Materials and Methods
The research work was conducted in Teaching Veterinary Clinical Complex and Department of Veterinary Surgery and Radiology, College of Veterinary Sciences and Animal Husbandry,

Central Agricultural University, Selesih, Aizawl, during the period of 2020-2021. The research was performed after the approval by the institutional animal ethics committee. The study was conducted in 18 Clinical cases of pigs which were operated for the correction of either umbilical or ventral hernia. The mean body weight of studied pigs was 20.64±6.43 kg and the mean age was 3.08±0.97 months. Pigs of different breeds and either sex were included in this study.

The animals were randomly divided into three groups *viz*. Group A, Group B and Group C comprising six animals in each. Feed was withheld overnight (12 hours) and water was restricted 4 hours before anaesthesia in all the animals. Routine clinical examinations were carried out before surgery in all the groups. All the three groups of animals were premedicated with meloxicam (Melonex injection, 5 mg/ml) at the dose of 0.4 mg/kg intramuscularly. Ten minutes after premedication anaesthesia was induced and maintained with diazepam (Lori, 5 mg/ml) at the dose of 2 mg/kg and ketamine (Aneket, 50 mg/ml) at the dose of 10-15 mg/kg intravenously through the superficial ear vein in all groups. Intra peritoneal administration of the drug was done immediately after opening of peritoneal layer. In Group A animals normal saline was administered intraperitoneally. Volume of administered normal saline in Group A animals were calculated as double the volume of 0.5% ropivacaine, if used @ 3 mg/kg body weight in those animals. In Group B animals, ropivacaine (Ropin 0.5%) at the dose of 3 mg/kg mixed with equal volume of normal saline and administered intraperitoneally. Whereas in Group C animals, ropivacaine at the dose of 3 mg/kg and dexmedetomidine (Dextomid, 100 mcg/ml) at the dose of 10 µg/kg mixed with equal volume of normal saline in a single syringe and administered intraperitoneally. The blood samples were collected from superficial ear vein in dry vials containing EDTA and sterile clot-activator vials before pre medication (zero minute), after induction of anaesthesia (30 minutes), after intraperitoneal infusion (1 hour) and postoperatively after 24 hours. Samples were analyzed by using automated haematology cell counter MS4e for the estimation of haemoglobin (g/dL), packed cell volume (%), total erythrocyte count (millions/cu.mm), total leukocyte count (thousands/cu.mm) and differential leukocyte count (%). Serum biochemical analysis was done with automated serum biochemical analyzer DRI-CHEM 4000i (Fuji Film) for the estimation of gamma glutamyl transferase (U/L), creatinine (mg/dL), creatine kinase (U/L). The blood glucose (mg/dL) level was estimated by using glucometer (One touch select plus simple). Serum cortisol was estimated by using porcine cortisol ELISA kit (Bioassay Technology Laboratory, Cat.No. E0235Po) and the values were expressed in microgram per deciliter.

Data was analyzed by using statistical package for social sciences (SPSS) version 25. One way analysis of variance (ANOVA) along with post hoc test using Duncan's multiple range tests were used for the data analysis. The results were presented as mean±Standard error (mean±SE) and differences were considered statistically significant when $P<0.05$.

Result and Discussion

The mean level of haemoglobin (Fig.1) and packed cell volume (Fig.1) were significantly decreased from the base level at 30 minutes and 60 minutes of observation in Group A and Group B animals, whereas a non-significant decrease was noticed in Group C animals. The total erythrocyte count (Fig.1) was significantly decreased at 30 minutes and 60 minutes observation in all the three groups. The level of Hb, PCV and TEC reached near the base line value after 24 hours in all the groups. There was no significant difference in mean level of Hb, PCV and TEC between groups throughout the observation period. Ketamine-diazepam anaesthesia might have caused RBC pooling in the spleen and extravascular compartments this might be the reason for the reduction in Hb, PCV and TEC level. Vasodilation of micro-circulation would have lead to the migration of RBC from circulation and there by a decrease in Hb level at peripheral veins (Naghibi *et al*., 2002) [21]. Decrease in PCV during the anaesthesia might be due to the shifting of fluid from extravascular space to intravascular compartment for maintaining normal cardiac output (Kilic, 2008) [11]. Intravenous administration of fluids also might have influenced the changes in haematological parameters. The decrease in Hb and PCV level were also reported with ketamine-diazepam in buffalo calves by Kumar *et al.* (2014b) and in buffalo with epidural dexmedetomidine and ropivacaine by Kamble *et al*. (2016) [9]. Ahmad and shukla (2013) also observed significant reduction in PCV in goat after ropivacaine-xylazine administration.

The total leukocyte (Fig.1), lymphocyte (Fig.2), monocyte (Fig.2) and granulocyte (Fig.2) counts were also showed a non-significant fluctuation within the physiological range during the observation period. There was no significant change in these values between the treatment groups. The decline in TLC and DLC might be due to the pooling of blood cells in spleen and other reservoirs as a result of decreased sympathetic activity (Kilic, 2004) [10]. TLC level was also influenced by changes in autonomic nervous system, endocrine system and immune system due to anaesthetic agents (Dhumeaux *et al*., 2012) [5]. Elevation in TLC after 24 hours might be because of the normal inflammatory response associated with surgery or as a sign of beginning of infection (Jung *et al*., 2019) [7]. The anti-inflammatory effect of ropivacaine might have caused a decrease in the production of inflammatory mediators, which also can affect the total leukocyte count (Wu *et al*., 2019). Similar fluctuation of granulocyte in horse after ketamine anaesthesia was observed by Malik and Singh (2007) [17]. Munthe Kaas, (2018) [20] also observed granulocyte elevation in pigs that undergone inguinal hernia surgery. Change in granulocyte count might be associated with adrenocortical stimulation and the subsequent effect of glucocorticoid on circulating granulocyte. Adrenaline and cortisol release during stress can also cause elevation in leukocyte count mainly neutrophils in the blood (Weiser, 2012) [28].

The glucose level (Fig.2) was non-significantly increased from the base value in all the groups at 30 minutes and 60 minutes of observation. There was no significant difference in glucose level between groups at any time period. The increase in glucose level might be due to the inhibition of insulin production from pancreas along with an increase in gluconeogenesis from the liver due to the effect of anesthetic agents (Mate and Aher, 2018) [18]. Hyperglycemia might also happen due to the traumatic stress as well as stress associated with handling of animals, that result in increased release of glucocorticoid hormones which aid in the gluconeogenesis (Reeder and Kramer, 2005) [25]. The non-significant variation of glucose level at 24 hours observation might be because of the feeding of pigs.

In all the animals mean GGT and Creatinine level (Fig.3)

were within the physiological range. A non-significant change in GGT after xylazine-ketamine-diazepam anaesthesia in goat was observed by Ismail *et al*. (2010) [6]. Similarly a non-significant variation in creatinine within the physiological range was observed by Kumar *et al.* (2014a) after midazolam-ketamine anaesthesia in calves. Variation in GGT and creatinine within the physiological range could be suggestive of least hepatobiliary as well as renal effect of anaesthetic agents. The non-significant elevation of GGT might be because of the metabolic disturbance associated with anaesthetic agents as well as the altered blood circulation to the liver (Ram *et al*., 2016). The non-significant fluctuation in creatinine level might be because of the changes in renal blood flow due to anaesthetic agents and perhaps not because of renal damage (Celestine Okwudili *et al*., 2014) [4].

Creatine kinase (Fig.3) value showed non-significant increase from the base level at 30 minutes, 60 minutes and 24 hours of observation. There was no significant change in CPK value between the treatment groups at any time period. In all groups the base level of creatine kinase was elevated from the physiological limit. Elevated CPK level might be attributable to the tissue damage (Arts *et al.*, 2007) [2] associated with hernia as all the animals included in the present study were operated for the correction of either umbilical or ventral hernia. Similar observations were also reported in umbilical hernia affected calves by Peiro *et al.* (2009) [23] and by Saidu *et al*. (2020) [26] in goat after surgery.

The elevated level of cortisol (Fig.3) in all animals at zero minute might be due to the stress associated with transportation (Pavicic *et al*., 2003) [22]. In all groups, a non-significant elevation in cortisol level was observed at 30 minutes. Group A animals showed a significant increase in cortisol level at 60 minutes and it reduced significantly at 24 hours than 60 minutes level. In Group B and Group C animals, a non-significant increase was noticed at 60 minutes and it decreased non-significantly at 24 hours than the 60 minutes level. The decreased cortisol level in Group B and Group C animals when compared to Group A might be due to the effect of intra peritoneal infusion of ropivacaine and ropivacaine-dexmedetomidine respectively. A decrease in cortisol level was observed by Morgaz *et al.* (2021) [21] after preperitoneal infusion of ropivacaine in dog. Kim *et al.* (2012) also observed a reduced cortisol level up to 24 hours after intra peritoneal application of bupivacaine in dog. Non-significant reduction in cortisol after intra peritoneal local anaesthetic application was also reported by Kahokehr *et al.* (2011) [8]. There was no significant difference in mean cortisol level between the groups throughout the observation period. Sympathomimetic effect of ketamine can also trigger the release of cortisol by its antagonistic effect on NMDA receptors which are involved in the regulation of hormone release from hypothalamo-pituitary-adrenal axis (Celestine Okwudili, 2014) [4].

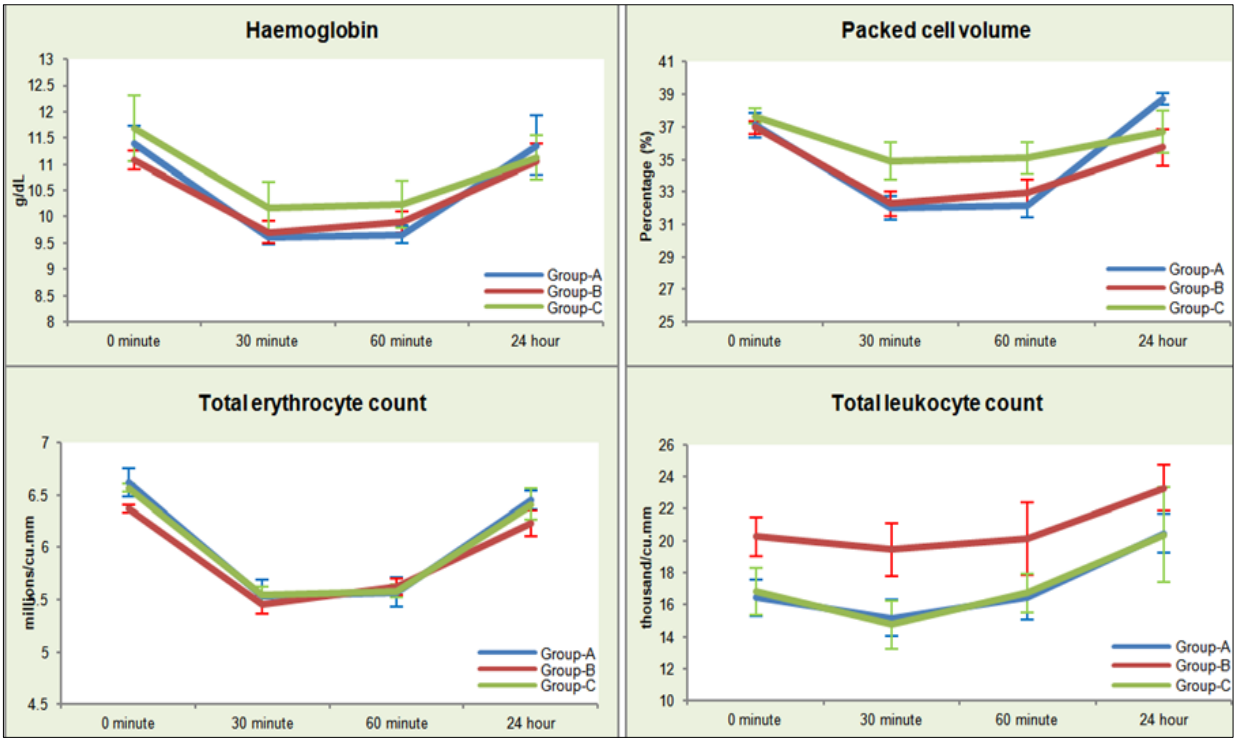

Fig 1: Haemoglobin, packed cell volume, total erythrocyte count, total leukocyte count in Group A, Group B and Group C.

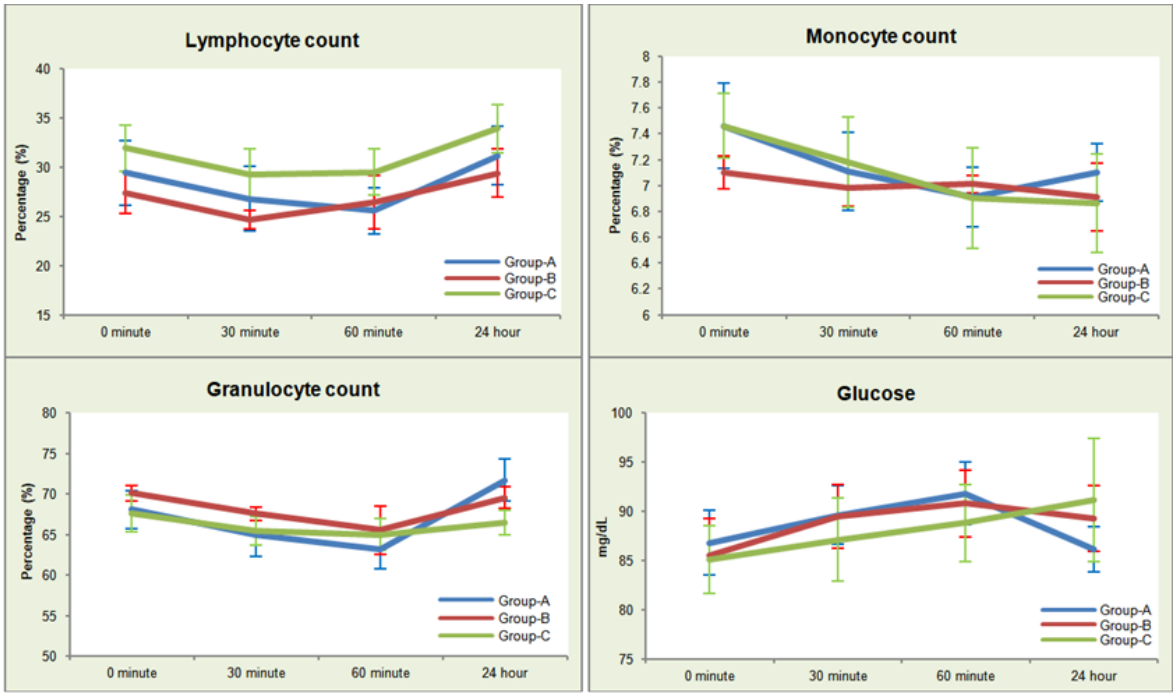

Fig 2: Lymphocyte count, monocyte count, granulocyte count and blood glucose level of Group A, Group B and Group C.

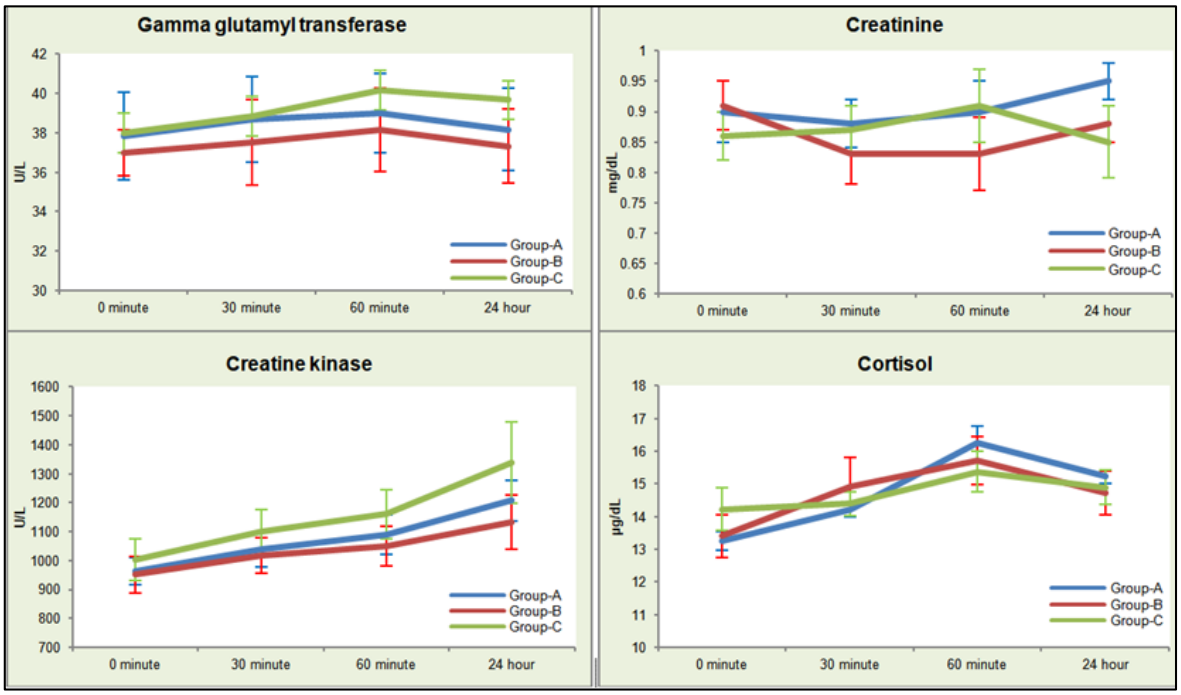

Fig 3: Gamma glutamyl transferase, creatinine, creatine kinase and cortisol level of Group A, Group B and Group C.

Conclusion

The changes observed in haemato-biochemical parameters were associated with the combined effect of anaesthetic agents. Higher level of glucose and lower level of cortisol was recorded in both the treatment groups as compare to the control group which might be due to the effect of the intraperioneal infusion which caused effective pain control. The higher creatine kinase observed in all the groups might be due to the tissue trauma in hernirraphy procedures. The intraperitoneal administration of ropivacaine as well as the combination of ropivacaine-dexmedetomidine did not cause any kind of haemato-biochemical adverse changes in the animals. So both the treatments are safe and effective for the management of pain in pigs.

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