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A Study on Intra-operative and Post-operative Analgesia with Intraperitoneal Ropivacaine and Dexmedetomidine in Pigs

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ABSTRACT

Background: 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 care and analgesia. The purpose of this study was to introduce an effective treatment method for the management of surgery related pain in pigs.

Methods: Study was conducted in 18 clinical cases of pigs 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 animals were observed till 24 hours for the recording of clinical parameters such as time for induction, depth of anaesthesia, perioperative analgesia, muscle relaxation, quality of recovery, recovery time, post-operative analgesia and physiological parameters such as heart rate, respiratory rate, temperature and blood pressure.

Result: Enhanced intraoperative and postoperative analgesia was observed following intraperitoneal infusion of ropivacaine and ropivacaine-dexmedetomidine combination in pigs. Clinical and cardio-respiratory changes were within the physiological limit after intraperitoneal administration of the drugs.

Key words: Dexmedetomidine, Hernia, Intraperitoneal analgesia, Pigs, Ropivacaine.

INTRODUCTION

Pigs are used as an experimental animal model for translational research due to their similarity with human anatomy and physiology than other animal species. Laparotomy procedure involving caesarean sections, spaying and hernia correction are also common in swine. But these animals are not receiving good standard perioperative as well as post-operative care and analgesia equivalent to humans. One literature review of 233 articles on pain management in swine that undergone experimental surgery has found that only 37% (87/233) articles have mentioned the use of postoperative analgesics (Bradbury *et al.,* 2016).

Management of pain in the animal is a challenge for veterinarians. The fundamental cause of this problem is the inability of animals to verbally communicate about pain. In majority of the animals, pain causes delay in recovery along with prolonged hospital stands (Lamont *et al*., 2000). During the painful condition, hypothalamo-pituitary-adrenal axis gets activated and produces many physiological responses.

Several combinations of medicines including local anaesthetics are used in human and animal surgery for alleviating pain. The advantage of local anaesthetic is that it is inexpensive and widely available. Uses of incisional as well as intraperitoneal administration of local anaesthetics have been recommended by the world small animal veterinary association global pain council. Intraperitoneal and incisional analgesics are recommended for controlling pain in cats and dogs which are undergoing laparotomy, as an additional technique for pain relief (Steagall *et al*., 2020).

Ropivacaine is an amide group long-acting local anaesthetic, which is structurally S (-) enantiomer. It has a reduced toxicity potential along with a relatively improved sensory and motor blocking ability (Kuthiala and Chaudhary, 2011). Dexmedetomidine is a strong α-2 adrenoceptor agonist. It provides adequate analgesia, anxiolysis and anaesthesia sparing action (Mahmoud and Mason, 2015). Considering these factors the present study was under taken to evaluate the effectiveness, as well as to study the clinical and physiological changes associated with intraperitoneal ropivacaine and dexmedetomidine application for the intraoperative and postoperative pain management in pigs.

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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 operated for the correction of either umbilical or ventral hernia. The age, sex, breed and weight of pigs under study were recorded. 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 for 4 hours before anaesthesia in all the animals. Routine clinical examinations were carried out before surgery in all the groups.

All the animals in Group A, Group B and Group C were premedicated with meloxicam at the dose of 0.4 mg/kg intramuscularly. Ten minutes after premedication, anaesthesia was induced and maintained in all the three groups of animals with diazepam at the dose of 2 mg/kg and ketamine at the dose of 10-15 mg/kg intravenously through the superficial ear vein. In Group A animals, normal saline was administered intraperitoneally. Volume of administered normal saline in Group A animals was calculated as, double the volume of 0.5% ropivacaine, if used @ 3 mg/kg body weight in those animals. In Group B animals, ropivacaine 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 at the dose of 10 µg/kg mixed with equal volume of normal saline in a single syringe and administered intraperitoneally. In all the groups the Intra peritoneal administration of the agents were done immediately after opening of peritoneal layer.

All the animals were observed till 24 hours for the recording of clinical and physiological parameters. Induction time was recorded in seconds from administration of the induction agent to the loss of reflex. Recovery time was recorded in minutes elapsed from discontinuation of anaesthesia to the time when the animal walked unassisted. Anaesthetic depth was assessed as palpebral reflex by touching the medial canthus of eye as per the method described by Ahmad *et al*. (2013). The quality of analgesia was evaluated through needle-pricked reflexes and the muscle relaxation was scored by the degree of relaxation of the muscles of leg and jaw as per the methods described by Lu *et al*. (2010). Quality of recovery was assessed as per the method described by Linkenhoker *et al*. (2010). UNESP-Botucatu pig composite acute pain scale was used for assessing postoperative pain in the animals (Luna *et al*., 2020). Evaluation of postoperative pain was done after complete recovery (zero minute) and then 6 hours, 12 hours and 24 hours after recovery. Heart rate (beats/minute), respiratory rate (breaths/minute), rectal temperature (^{o}C), systolic and diastolic blood pressure (mmHg) were evaluated in all the groups before pre medication (zero minute), after induction of anaesthesia (30 minutes), after intraperitoneal infusion (1 hour).

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 $P<0.05$.

RESULTS AND DISCUSSION

Studied pigs were weighed in a range of 13-32 kg with a mean body weight of 20.64±6.43 kg and the age ranged from 2.5-5 months with a mean age of 3.08±0.97 months. Pigs of different breeds and both sex were included in this study.

There was no significant difference in the induction time (Table 1) among the three groups of animals. The induction was rapid and smooth in all the animals. Intravenous administration of diazepam and ketamine provided fast and smooth induction in all the animals which might be due to the rapid distribution of the drugs. Shorter induction time with intravenous injection of ketamine-diazepam was also reported by Konwar and Saikia (2006).

All the three groups showed similar depth of anaesthesia (Table 1) and no statistically significant difference in score was observed among the groups. In all the three groups, out of six animals one animal showed very weak and occasional palpebral reflex, analgesic and sedative effect of ketamine-diazepam combination might

Table 1: Mean±SE values of clinical parameters.

Parameter	Group A	Group B	Group C	F value
Time for induction (seconds)	81.67±1.99	82.17±4.68	81.83±3.21	0.995^{NS}
Depth of anaesthesia	2.83±0.16	2.83±0.16	2.83±0.09	1^{NS}
Perioperative analgesia	2.67±0.21	3.00±00	3.00±00	0.119^{NS}
Muscle relaxation	2.83±0.16	2.67±0.21	3.00±00	0.322^{NS}
Quality of recovery	3.00±00	3.00±00	3.00±00	1^{NS}
Recovery time (minutes)	$58.33±3.05^{a}$	$61.83±3.57^{a}$	$104.33±3.12^{b}$	0.00**

Values in the same row with different superscripts differ significantly.

**: ($P< 0.01$) and ^{NS}: Non-significant.

have led to abolished palpebral reflex. Sensitivity to ketamine in pigs varies with the breed and age of the animal hence some animals might show pain reflex at higher dose of ketamine, this might be the reason for occasional weak palpebral reflex (Boschert *et al.,* 1996).

Sufficient perioperative analgesia (Table 1) was observed in all the groups and no statistically significant changes were observed among the groups in mean pain score. However in Group A, out of six animals two animals showed slight response during needle-pricked reflex evaluation, whereas in Group B and Group C, no reflex was observed in any of the six animals. Ketamine provided analgesia by its action on opiate receptors in brain (Pai and Heining, 2007) and also through the monoaminergic receptor interaction (Hirota and Lambert, 1996). The intraperitoneal ropivacaine can also provide anti nociceptive effect by its selective action on A-delta nerves and C-nerve fibers (Hansen, 2004). Perioperative analgesia might be enhanced by dexmedetomidine through its α-2 adrenergic receptor agonist activity (Hoy and Keating, 2011). The use of meloxicam might also contribute to decrease the surgical stress and to provide analgesia. Meloxicam provide peripheral anti inflammatory activity through the blockage of prostaglandin synthesis (Keita *et al.,* 2010).

All the animals showed adequate relaxation of jaw and leg muscles. There was no statistically significant difference in muscle relaxation score (Table 1) among the three groups of study. In Group A and Group B, one animal showed moderate relaxation of leg and jaw muscle whereas other five animals in the groups showed profound muscles relaxation. All the six animals in Group C showed profound muscle relaxation. Diazepam exerts its sedative, anticonvulsant and the muscle relaxation by enhancing $GABA_A$ receptor affinity towards the inhibitory neurotransmitter gamma amino butyric acid in the central nervous system (Kumar *et al*., 2014). Variation in the muscle relaxation score might be due to the effect of ketamine. Dissociative anaesthetics can cause hypertonus and occasional movement unrelated to nociceptive stimuli (Pai and Heining, 2007).

All the three groups received 'acceptable level' scoring during the evaluation of quality of recovery (Table 1). All the six animals in each group regained the sternal recumbency as well as the ability to stand and walk with some struggling. During recovery, the animals showed drowsiness and it was more noticeable in Group C animals when compared to other groups. The Similar quality of recovery was observed by Momin *et al*. (2012) as well as Konwar and Saikia (2006) in pigs anaesthetised by ketamine-diazepam combination.

A significantly prolonged recovery time (Table 1) was observed in Group C animals when compared to other two groups. Group A and Group B animals had similar recovery time. Similar finding was noticed after diazepam-ketamine anaesthesia in buffalo calves by Kumar *et al*. (2014). A prolonged recovery time was also observed by Kamble *et al*. (2016), when ropivacaine-dexmedetomidine combination used epidurally in buffalo calves.

During post-operative pain scoring (Fig 1) in Group A animals, a significantly higher pain score was noticed at 6 hour (moderate pain) and 12 hours (mild pain) of observation, which gradually decreased and reached near the zero minute value after 24 hours (no pain).

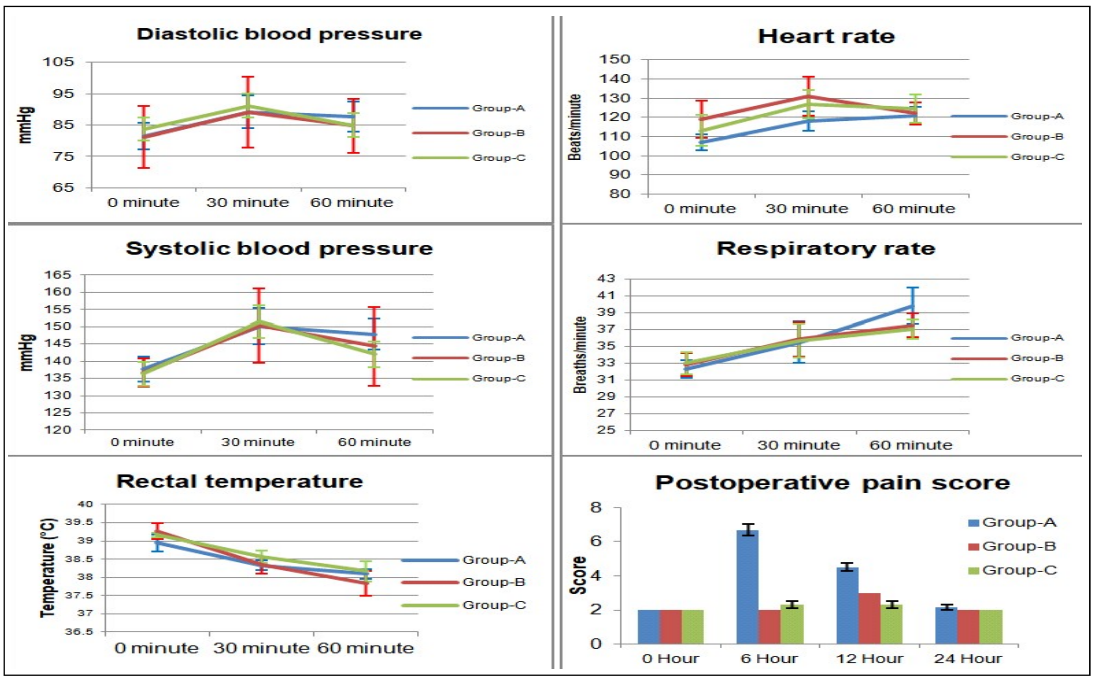


Fig 1: Heart rate, respiratory rate, rectal temperature, systolic blood pressure, diastolic blood pressure and postoperative pain score in Group A, Group B and Group C.

Group B animals showed significantly higher pain score (mild pain) at 12 hours observation and there was no significant change in pain score at 6 and 24 hours observation from the zero minute score (no pain). Group C animals came in 'no pain' category during entire period of observation.

A local anaesthetic agent when applied intraperitoneally can cause the blockage of peritoneal afferent nerve endings and it might result in hindrance of visceral nociceptive transmission. Systemically absorbed local anaesthetic agents from the peritoneal cavity might also provide analgesic effect (Perniola *et al*., 2014). A similar decrease in postoperative pain after intraperitoneal application of local anaesthetics was reported by Kahokehr *et al*. (2010) and Shukla *et al.* (2015). An improved analgesia in dogs postoperatively up to 6 hours after intraperitoneal application of ropivacaine was also observed by Lambertini *et al*. (2018).

The heart rate (Fig 1) was in physiological limit throughout the observation period in all the groups however a non-significant increase from base line value was recorded in all the groups at 30 minutes and 60 minutes of observation. In Group B and Group C, the heart rate showed a non-significant decrease at 60 minutes than the 30 minutes value. The elevation of heart rate in ketamine administered animals might be due to the inhibition of catecholamine uptake by sympathetic nerve ending or might be because of increased catecholamine release (Kumar *et al.,* 2014). Non-significant reduction of heart rate in Group B and Group C animals might be due to the reduction in acute pain due to the effect of intraperitoneal ropivacaine and dexmedetomidine. Reduction in nociceptive stimuli might cause decreased catecholamine release as well as sympathetic nervous system activation (Terkelsen *et al.,* 2005). Dexmedetomidine might also play a role in reduction of heart rate, as it can cause a decreased central sympathetic out flow. A reduction in heart rate was also observed in cat undergoing overiohysterectomy after application of ropivacaine-dexmedetomidine combination by De OL Carapeba *et al*. (2020).

A non-significant increase in respiratory rate (Fig 1) from the base level was recorded at 30 minutes and 60 minutes in all the groups. Similar increase in respiratory rate after ketamine-diazepam anaesthesia was observed by Konwar and Saikia (2006) in pigs. Ozba *et al*. (2003) also observed identical finding with xylazine-zolazepam-tiletamine combination in calves. The respiratory depression due to ketamine-diazepam combination can cause a compensatory increase in rate of respiration (Hall *et al*., 2001).

The rectal temperature (Fig 1) was reduced significantly from the base level during 30 minutes and 60 minutes of observation in all the groups. Reduced metabolic activity and muscular activity after anaesthesia or the peripheral vasodilation due to the effect of diazepam (Wixson *et al.,* 1987) or depression of the thermoregulatory center due to the effect of alpha$_2$-adrenoceptor agonists (Mahmoud and Mason, 2015) might be the cause of reduction in body temperature.

A non-significant increase in systolic and diastolic blood pressure (Fig 1) from the base level within the physiological range was recorded at 30 minutes and 60 minutes of observation in all the treatment groups however during 60 minutes observation blood pressure non-significantly reduced than 30 minutes value. A reduction in blood pressure after intraperitoneal infusion of ropivacaine in human was also reported by Meena *et al.* (2019). The initial rise in blood pressure in all the groups might be due to the action of ketamine that might have caused activation of sympathetic nervous system (Tranquilli and Grimm, 2015). In the present study the mild decrease in blood pressure at 60 minute might be because of the reduced use of ketamine as supplemental dose or might be due to the analgesia obtained after intraperitoneal application of ropivacaine and dexmedetomidine.

Conclusion

Enhanced intraoperative and postoperative analgesia can be achieved following intraperitoneal administration of ropivacaine and ropivacaine-dexmedetomidine combination in pigs. Intraperitoneal administration of ropivacaine and ropivacaine-dexmedetomidine combination in pigs does not alter clinical and cardio-respiratory parameters from the physiological limit. Ropivacaine-dexmedetomidine combination provided better postoperative analgesia than ropivacaine. However, ropivacaine-dexmedetomidine combination prolonged the recovery time.

Conflict of interest

All authors declare that they have no conflict of interest.

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