



EVALUATION OF ANAESTHETIC AND ANALGESIC EFFECTS OF KETAMINE-DIAZEPAM AND KETAMINE-XYLAZINE FOR CHEMICAL RESTRAINT IN GROWER PIGS UNDERGOING SURGICAL CASTRATION.

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ABSTRACT

Pain response during pig handling is aggravated due to difficulty in restraining them for surgical procedure and thus gives rise to more welfare concerns. This study evaluated the comparative advantage of either combination of ketamine/xylazine (KX) or Ketamine/diazepam (KD) for surgical castration in pigs. Ten client-owned grower pigs, scheduled for orchidectomy were randomly assigned to two treatment groups containing five pigs were used for the study. Group 1 were anaesthetized with simultaneous intramuscular injection of 0.3 mg/kg diazepam and 10 mg/kg ketamine while group 2 were simultaneously injected with 2mg/kg Xylazine and 10 mg/kg ketamine, intramuscularly. Orchidectomy was thereafter performed on each pig using standard procedures. Cardiopulmonary parameters and anaesthetic indices were measured before and after anaesthetic induction. Castration was successfully done in all the grower pigs and the recovery from anaesthesia was uneventful. There was no significant change in all the cardiopulmonary parameters measured throughout the procedure. Also there was no significant difference ($P>0.05$) in respiratory rate, heart rate and body temperature between the two groups. There was faster but insignificant ($p=0.15$) loss of righting reflex in pigs in group KX compared to KD group. Also, the induction time, time of standing and duration of surgery was faster in KX group than KD group although not statistically significant. Following skin incision, all the pigs in the KD and non in KX group were found to require subcutaneous lidocaine infiltration. Ketamine-Xylazine combination provided better anaesthesia and analgesia sufficient for a 30 minutes surgical procedure like castration in grower pigs.

Keywords: Ketamine, xylazine, diazepam, analgesia, anaesthesia, pain, pig, castration.

INTRODUCTION

Orchidectomy in piglet is a routine procedure in swine husbandry aimed at reducing the incidence of aggressive behaviours as well as to prevent the development of very unpleasant boar taint in meat (Saller *et al.*, 2020; Söbbeler *et al.*, 2022). It is a procedure common in many commercial pig farms around the world including Africa with varying degree of level of practice such that nearly 100% of all male pigs are castrated in the United States of America while approximately 80% are castrated in European Union (Bradford and Mellencamp, 2013). Surgical castration can lead to poor body condition and death as a result of the associated pain and distress (Sutherland *et al.*, 2012). This has increased the negative public perception of castration without adequate use of analgesics and/or anaesthetics (Giersing *et al.*, 2006). Castration in boar has already been abolished in some countries while it is declining in others (Backus *et al.*, 2014). Countries such as Ireland and United Kingdom have disallowed their farmers from surgically castrating male pigs without adequate analgesia due to welfare concerns (Rault *et al.*, 2011). There is a leading debate to ban castration of boar without analgesia within the European Union with complaint of violation of animal welfare, wellbeing, right and integrity (Scollo *et al.*, 2021). The difficulty in handling of pigs due to their behavior tend to aggravate their pain during handling for surgical procedure and thus gives more welfare concern (Lehmann *et al.*, 2017). Moreover, handling of pigs on farms with limited access to appropriate handling facilities and trained personnel require the use of chemical restraint. Therefore, there is always the need for chemical restraints to facilitate handling of pigs, especially outside hospital locations for routine clinical and surgical procedure such castration or

claw trimming. Several drug combinations have been reported for use in pigs for various procedures (Ajadi *et al.*, 2008; Linkenhoker *et al.*, 2010; Rana *et al.*, 2013; Wellington *et al.*, 2013; Albrecht *et al.*, 2014; Gottardo *et al.*, 2016; Lautenbacher *et al.*, 2017; Lehmann *et al.*, 2017; Viscardi and Turner, 2018; Saller *et al.*, 2020; Sixtus *et al.*, 2021; Scollo *et al.*, 2021; Coutant *et al.*, 2022; Söbbeler *et al.*, 2022; Link *et al.*, 2023). The ideal drug combination for chemical restraint in pigs should be small in volume, safe for both animals and handlers, provide adequate analgesia and predictable anaesthesia, facilitate a smooth recovery, have specific reversal agent and be readily accessible to veterinary practitioners (Lehmann *et al.*, 2017). In swine anaesthesia, drug combinations for sedation include α -2 adrenoreceptor agonists, benzodiazepines and opioids (Martín *et al.*, 2015; Santos *et al.*, 2013). There are several previously reported clinical trials of α -2 adrenoreceptor agonist agents medetomidine, dexmedetomidine and xylazine in various combinations or as a sole agent for sedation of pigs (Santos *et al.*, 2013; Ugarte and O'Flaherty, 2005) and xylazine, is being used routinely as a premedicant for surgical procedures in pigs (Lee *et al.*, 2010). Ajadi *et al.* (2008) has reported that ketamine hydrochloride is suitable for sedation, induction of anaesthesia and analgesia. There is common combination of dissociative anaesthetic drugs like ketamine with sedative agents like xylazine, detomidine, medetomidine, and butorphanol (Gaertner *et al.*, 2008; Lee *et al.*, 2012; Martín *et al.*, 2015) for surgical anaesthesia in pigs and this combined sedative protocols help in reducing the volume of drug for administration aside improving the anaesthetic outcome (Martín *et al.*, 2015).

The addition of muscle relaxants and analgesics in anaesthesia for animal handling and surgical procedure, provide balanced anaesthesia typified by muscle relaxation, analgesia and unconsciousness (Kleine *et al.*, 2015). Benzodiazepines, such as diazepam, provides muscle relaxation and sedation (Lacoste *et al.*, 2012). Previous reports suggest that benzodiazepine like midazolam or diazepam may provide reasonable sedation in pigs when used alone or in combination with other agents including ketamine (Linkenhoker *et al.*, 2010). Surgical castration is a painful procedure in pigs and prevention and alleviation of pain in livestock is a key welfare issue (Sutherland, 2015). Despite availability of reports on the various combinations of ketamine, xylazine and diazepam for anaesthesia during surgical castration in pig, there is paucity of information on comparative advantage of either combination of ketamine/xylazine or Ketamine/diazepam for surgical castration in piglets. Therefore, this study was carried out to determine the drug combination that provides better anaesthesia and analgesia during surgical castration in piglets and to determine which of the combination will require lidocaine for local analgesia.

MATERIALS AND METHODS

Animals: Ten male, large white pigs, presented for castration were used for the study. The pigs were randomly assigned to two treatment groups containing five pigs each. The pigs were between 5 and 6 months of age with mean weight of 25kg. This research was approved by the Research and Ethics Committee of the college of veterinary medicine, Federal University of Agriculture, Abeokuta Ogun State with ethical approval number FUNAAB/COLVET/CREC/2022/02/02.

Induction of anaesthesia: In group 1 (KD group), anaesthesia was induced with intramuscular injection of 0.3 mg/kg 1% diazepam (Bleorpan, Norris Medicine Ltd, Gujarat India) and 10 mg/kg 5% ketamine (Ketamine hydrochloride, Rotexmedica, Trittau, Germany). The pigs in group 2 (KX group) were injected with 2mg/kg, 2% Xylazine hydrochloride (Xylased, Bioveta, Ivanovice, Czech Republic) and 10 mg/kg 5% ketamine (Ketamine hydrochloride, Rotexmedica, Trittau, Germany) intramuscularly. The anaesthetic agents in each group were injected simultaneously. Pigs in either group that struggled upon commencement of scrotal skin incision were given additional local infiltration 5mls of 2% Lidocaine hydrochloride (Labcalin[®] Laborate Pharmaceutical, India).

The following anaesthetic parameters were determined:

Induction time: Time from end of anaesthetic drugs injection to onset of total lateral recumbency.

Loss of righting reflex: Time from end of anaesthetic drug administration to loss of consciousness.

Time to sternal: Time from end of anaesthetic drug administration to the animal regaining consciousness and balance on sternal recumbency.

Time to standing: Time from end of anaesthetic drug administration to the animal gaining consciousness and standing.

Duration of Surgery: Time from beginning of surgery till end of surgery.

Physiological Parameters

Baseline readings of heart rates (HR), Rectal

Temperatures (T) and respiratory rates (RR) of the pigs were obtained at 0 minute before anaesthetic induction. The parameters were measured at 10, 15, 20, 25, 30, 35 and 40minutes post anaesthetic induction. Heart rate were determined with cardiac stethoscope. Respiratory rate was determined by using abdominal excursion, and rectal temperature using a clinical thermometer.

Orchidectomy: The pigs were castrated using standard surgical procedure.

Data Analysis

All data were expressed as Mean ± Standard

deviation. The cardiopulmonary and anaesthetic data obtained in the KD group were compared respectively with those of KX group using independent sample T-test on SPSS (Statistics Package for the Social Sciences, version 11.0; SPSS Inc., Chicago, IL, USA). Values of $P \leq 0.05$ were considered significant.

RESULTS

Castration was successfully done in all the grower pigs and the recovery from anaesthesia were uneventful. The changes in respiratory rate, heart rate and rectal temperature are shown in Figs 1–3 respectively.

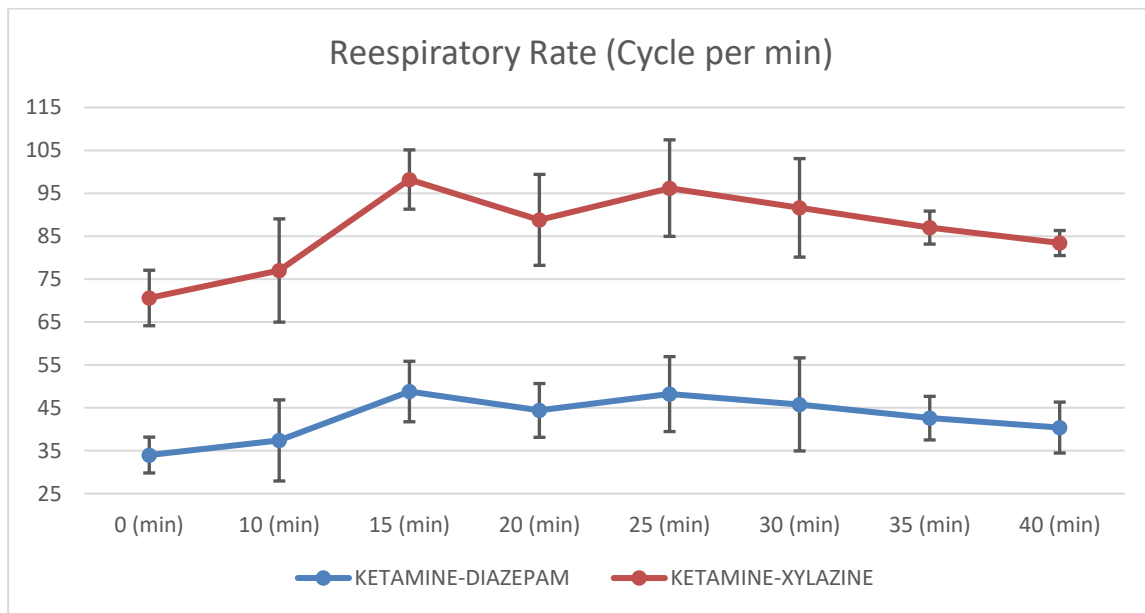


Figure 1: The Mean±SD of Respiratory rate obtained following administration of either KD or KX for anaesthesia in grower pigs undergoing surgical castration.

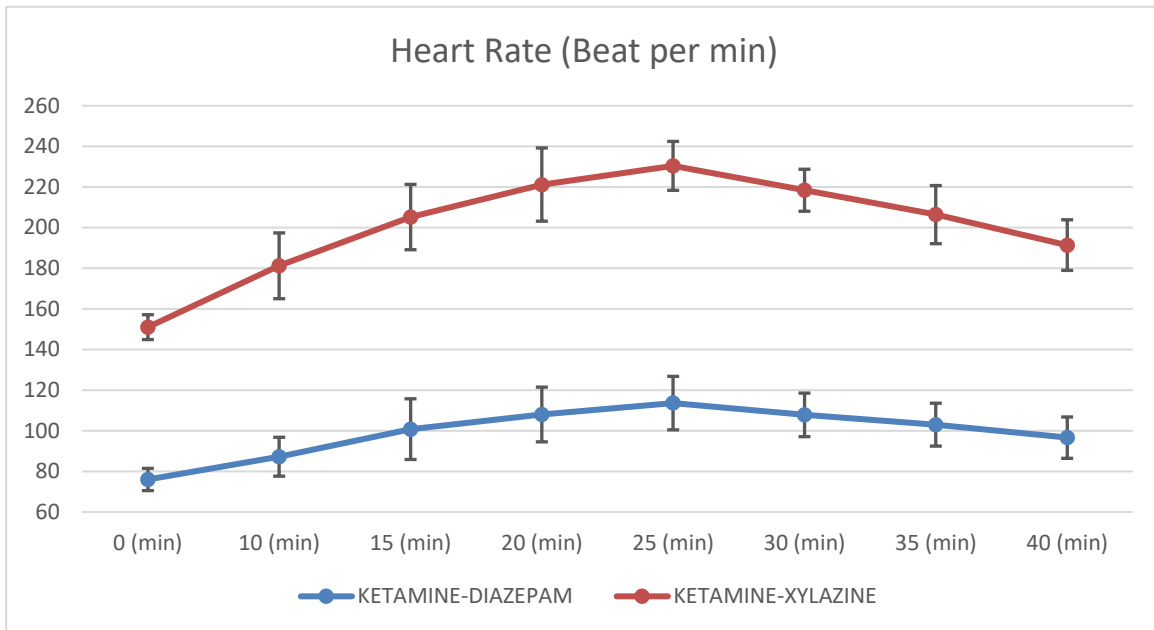


Figure 2: The Mean±SD of Heart rate obtained following administration of either KD or KX for anaesthesia in grower pigs undergoing surgical castration.

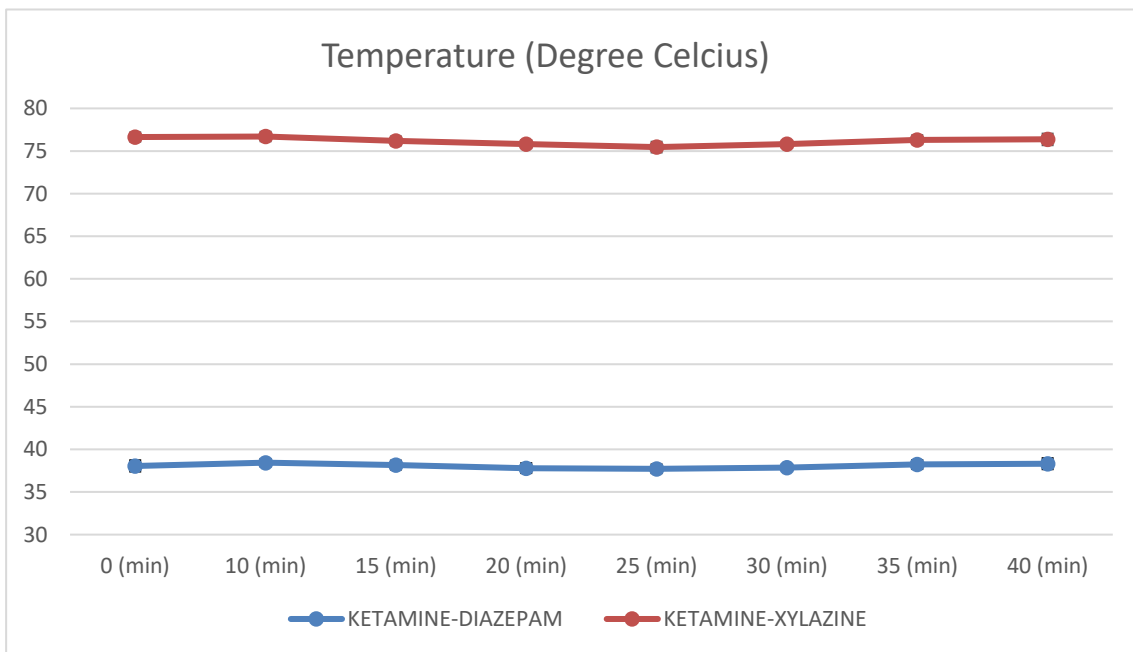


Figure 3: The Mean±SD of Temperature rate obtained following administration of either KD or KX for anaesthesia in grower pigs undergoing surgical castration.

Throughout the procedure, there was no significant difference ($P>0.05$) in respiratory rate, heart rate and rectal temperature between the two groups. The respiratory rate and heart rate rose to maximum levels at 15minutes and 25minutes post anaesthetic induction and then fell to the baseline towards the recovery period in all groups, although these values were not statistically significant ($P>0.05$). In both groups, the rectal temperature remained stable during anaesthesia and within acceptable limits (Figure 3) and there was no statistically significant difference in the measured readings. As shown in Table 1, the pigs in group KX lost righting reflexes faster than the pigs in KD group, although the difference was not statistically significant ($p=0.15$). Also the induction time, time to standing and duration of surgery were faster in KX group than KD group. Upon scrotal skin incision, all the pigs in KD group got agitated and reacted to pain of scalpel blade incision. Following this reaction, scrotal skin incisional infiltration with lidocaine hydrochloride. However, all the pigs in the KX group did not require additional scrotal incisional lidocaine infiltration.

TABLE I: The Mean \pm SD of anaesthetic variables obtained following administration of either KD or KX for anaesthesia in grower pigs undergoing surgical castration.

	Induction Time (Min)*	Loss of Righting Reflex (Min)*	of Time to Sternal (Min)*	to Time to Standing (Min)*	to Duration of Surgery (Min)*
Ketamine-Diazepam	13.6 \pm 4.16 ^a	4.6 \pm 2.51 ^b	31.6 \pm 6.88 ^c	40 \pm 12.10 ^d	7 \pm 1.22 ^e
Ketamine+Xylazine	12.8 \pm 5.54 ^a	2.6 \pm 0.55 ^b	33.6 \pm 5.68 ^c	36 \pm 4.85 ^d	6.6 \pm 1.34 ^e

Key: Means \pm standard error in the same column with different superscripts are significantly different ($P\leq 0.05$).

DISCUSSION

This study examines the comparative advantage of the combination of ketamine-xylazine and ketamine-diazepam for anaesthesia in grower pigs undergoing surgical castration. Our results indicated that KX and KD provided a comparable level of anaesthesia. Also, the addition of lidocaine to KD showed a comparable analgesic effect to that of KX. Due to the nature of pigs, it is desirable that ideal anaesthetic protocol should provide fast and reliable immobilization, adequate analgesia and sufficient muscle relaxation without excessive cardiovascular and respiratory depression (De Monte *et al.* 2015). Xylazine acts on both the peripheral and central nervous systems to produce sedation, analgesia and muscle relaxation (Ali and Al-Qarawi, 2002). Ketamine being a centrally acting, dissociative general anesthetic agent, provides amnesia, analgesia, and immobility (Plumb, 2011) and it is used as an adjunct anaesthetic, due to its limited ability to provide adequate skeletal muscle relaxation (Barletta *et al.*, 2011; Buitrago *et al.*, 2008). However, when combined with other agents like xylazine and diazepam, it provides a profound anaesthesia and muscle relaxation (Struck *et al.*, 2011; Wellington *et al.*, 2013). Combination of ketamine and Xylazine (KX) provides analgesic, muscle relaxation, and sedative effects which are great and desirable supplemental effects (Wellington *et al.*, 2013). Benzodiazepines like midazolam or diazepam are centrally acting anaesthetic agents which provide reasonable sedation in pigs when used alone (Bustamante and Valverde, 1997) or in combination with other agents including ketamine (Linkenhoker *et al.*, 2010). The anaesthetic drugs used in this study including ketamine, diazepam and xylazine, have been reported to cause cardiopulmonary side effects in animals (Icen *et al.*,

2019). Although little cardiopulmonary side effects were encountered in previous study in grower pigs administered with xylazine, ketamine and midazolam (Ajadi *et al.*, 2008). In this study, there was initial insignificant increase in respiratory rate which was followed by insignificant decrease in the respiratory rate fifteen minutes after induction and during maximum depth of anaesthesia which later returned to initial value after recovery in group KD and KX. These results correspond with previous studies where respiratory depression was observed with a decrease in tidal volume and respiratory rate in pigs anaesthetized with KX or KD (Lee *et al.*, 2010; Rana *et al.*, 2013). Ketamine is also known as a potent respiratory depressant (Schifilliti *et al.*, 2010). Xylazine-ketamine and Xylazine-Diazepam anaesthesia have been found to decreased respiratory rate (Kaya *et al.*, 2019). This decreased respiratory rate might be due to depression of respiratory centers either by diazepam, xylazine, ketamine alone or their combination. During anaesthesia with KX or KD, there was insignificant and mild increase in heart rate up to 25minutes post induction and insignificantly decreased to initial level towards the recovery period. This is in contrast to the findings of Rana *et al.* (2013) and Alkattan (2012) who observed a decrease in heart rate throughout the anaesthetic period in pig anaesthetized with KX. Ketamine has been observed to produce a mild to moderate transient increase in blood pressure, heart rate, and cardiac output due to increase in sympathetic activity (Goddard *et al.*, 2021). This effect is balanced out in combination with xylazine or diazepam. Xylazine, an alpha-2 agonist causes a variety of adverse effects, including bradycardia, respiratory depression, hypotension and reversible arrhythmias.

Xylazine, like other alpha-2 agonists diminishes sympathetic tone and increases systematic vascular resistance to produce its effects on the cardiovascular system (Sinclair 2003). Ketamine is often paired with an alpha-2 agonist (e.g., xylazine, medetomidine) to counter the effects of ketamine on cardiopulmonary system, muscle tone and movement (Farag et al., 2018). It is known that anaesthetics alter thermoregulation, although decrease in rectal temperature due to KX anaesthesia was observed by *Rana et al., (2013)* and was attributed to decrease in metabolic rate, and increase in heat loss, inhibition of skeletal muscle, peripheral vasodilatation and inactivation of the hypothalamic thermoregulatory centres. In this study, there was no significant change in rectal temperature throughout the duration of anaesthesia. The duration of anaesthesia observed in this study is as expected for both groups. The KX combination had a rapid onset of action demonstrated with faster loss of righting reflex and shorter induction time compared to the group injected with ketamine-diazepam combination. This makes this combination very good for adequate restraint in pigs. The KX group had a longer time to sternal compared to the KD group. Xylazine has profound muscle relaxation effect which could lead to prolonged anaesthesia (Link et al., 2023). It has been reported that xylazine-ketamine combination usually lasts approximately 20–30 minutes similar to what was seen in this study (Holtgrew-Bohling, 2016). This is ideal for surgery of short duration like castration as seen in this study. Pigs in either the KD or KX group responded to stimulus with pedal withdrawal throughout the duration of anaesthesia. This is in contrast to Link et al., (2023) and Tanaka et al. (2009) who reported that piglets used in their experiments did not show pedal withdrawal and nasal reflex and opined that the use of ketamine

in combination with other anaesthetic drugs like diazepam, xylazine etc provides deep sedation with adequate muscle relaxation. This observed difference could however be due to the age of the pigs. In their own study, less than 1 month old (18–20days old) piglets were used, whereas, this study was carried out on 5–6months old grower pigs. Lautenbacher et al., (2017) had reported that pain perception and pain threshold in humans and animals is affected by age with low pain perception and threshold in the young. So, it is thus advised that castration is done in piglets at a younger age, preferably 2–3weeks, in order to reduce pain responses and behavioural changes due to pain in pigs. This is because pigs have sufficient cognitive and emotional capacity to experience negative affective states such as pain (Herskin and Giminiani 2018) and pigs are very sensitive to both visceral and somatic pains (Kluivers-Poodt et al., 2012, Viitasaari et al., 2013). Moreso, Ketamine and xylazine combination have been found to be more suitable sedative/chemical restraint for pigs but poor anaesthetic induction agents in pigs (Ajadi et al., 2008). This could also be the reason for the observed longer time to standing in the KD group than the KX group due to deep anaesthetic effect of ketamine-diazepam combination compared to ketamine-xylazine combination. The duration of surgery was faster in KX group than KD group. This could be due to KX providing more profound anaesthesia and analgesia which makes the animal struggle less during the surgery, thus reducing the operation time. Combination of ketamine and Xylazine (KX) provides analgesic, muscle relaxation, and sedation effects which are very desirable. Ketamine has proprioceptive and somatic analgesic effect and xylazine has also been reported to provide somatic analgesic effect (Ali

and Al-Qarawi, 2002; Wellington et al., 2013), although Gómezde Segura et al. (1997) reported that xylazine did not induce adequate sedative or analgesic effects in pigs at any dosage tested. Ketamine has proprioceptive and somatic analgesic effect and xylazine has also been reported to provide somatic analgesic effect (Ali and Al-Qarawi, 2002; Wellington et al., 2013), although Gómezde Segura et al. (1997) reported that xylazine did not induce adequate sedative or analgesic effects in pigs at any dosage tested. In contrast, the longer operation time in KD group could be due to lack of profound nociceptive analgesia. This is evident in the fact that upon incision of the scrotum, all the pigs in KD group got agitated and reacted to pain of scapel blade incision. However, this pain perception was lost upon administration of subcutaneous lidocaine which provided adequate surgical anaesthesia similar to the KX group. It has been reported that subcutaneous or intrascrotal lidocaine administration provides adequate analgesic effect during castration in pigs and this analgesic effect was believed to be due to blockade of nociception during castration (Saller et al., 2020; Söbbeler et al., 2022).

CONCLUSION

Castration is a painful surgical procedure in pigs and thus requires adequate anaesthesia and analgesia. This study showed that administration of Ketamine-Xylazine and Ketamine-Diazepam for castration in grower pigs provided comparable levels of anesthesia sufficient for a 30 minutes surgical procedure. However, Ketamine-Xylazine combination provided better analgesia and anaesthesia for castration in growing pigs. Ketamine-Diazepam showed poor somatic and nociceptive analgesic effects and thus should be

used in combination with analgesics especially local anaesthetic agents like lidocaine as used in this study.

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