Increasing ketamine dose enhances the anaesthetic properties of ketamine-xylazine-midazolam combinations in growing pigs

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ABSTRACT

The influence of increasing the dosage of ketamine on anaesthesia induced by a combination of ketamine, xylazine and midazolam in pigs was determined by assessing the onset of action (OAN), duration of analgesia (DAN), anaesthesia time (ANT), and recovery time (RCT) in 10 growing pigs (Mean weight: 18.2 ± 1.65 kg) receiving either 10 mg/kg intramuscular (i.m) injection of 10 % ketamine, 2 mg/kg i.m injection of 2 % xylazine and 0.25 mg/kg i.m injection of 0.1 % midazolam (K_{10}XM) or 20 mg/kg i.m injection of ketamine and 2 mg/kg i.m injection of xylazine and 0.25 mg/kg i.m injection of 0.1 % midazolam (K_{20}XM). In addition, the heart rates (HR), respiratory rates (RR) and rectal temperatures (RT) were determined immediately after drug administration and at 10 minute intervals over a period of 60 minutes. Analgesia was assessed by the response of the pigs to artery forceps applied at the interdigital space. Recovery was determined as pigs' ability to stand without ataxia. Data were expressed as mean ± SEM while anaesthetic indices were compared using Student's *t*-tests. A *P* value of 0.05 was accepted as significant in all cases. In this study, both the OAN and RCT were significantly ($P < 0.05$) shorter in K_{10}XM (1.4 ± 0.2 min; 7.8 ± 2.2 min) than in K_{20}XM (2.2 ± 0.2; 18.6 ± 1.4 min) respectively. Similarly, the duration of anaesthesia was significantly ($P < 0.05$) shorter in K_{10}XM (55.4 ± 8.4 min) than in K_{20}XM (92.0 ± 13.6 min). The pigs that received K_{20}XM combination had analgesia of duration of 41.4 ± 12.6 min while those that received K_{10}XM combination had no analgesia. However, the HR, RR, and RT were not significantly ($P > 0.05$) different between K_{10}XM and K_{20}XM. It was therefore concluded that the lower dose ketamine combination is better for the induction of anaesthesia, while the higher dose ketamine combination is preferable for surgery of short duration in pigs.

Key words: anaesthesia, pigs, ketamine, midazolam, swine, xylazine.

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Ketamine is the most widely used anaesthetic in almost all the species, including humans, non-human primates, cats, laboratory rodents and wildlife[5]. This is because the drug is considered to be relatively safe, as it generally causes minimal cardiovascular depression and may actually stimulate cardiovascular function *via* its sympathomimetic effect[5,8]. The other advantage is that ketamine can be administered intramuscularly as well as intravenously, making it practical for use in animals in which venous access is difficult.

No single anaesthetic agent has been found ideal in providing adequate anaesthesia for surgery in pigs. Thus 2 or more drugs are often combined for the purpose[4,6,7]. Drug combinations that have been used for anaesthesia in swine include telazol-ketamine, telazol-xylazine, telazol-ketamine-xylazine[5], ketamine-xylazine-butorphanol and ketamine-mede-tomidine-butorphanol[6]. However, most of these drugs have not been found to be satisfactory. For example, xylazine and ketamine combinations have been evaluated in pigs and combinations were reported with short-lived duration of analgesia[2,3].

The properties of ketamine-xylazine-midazolam combination have been evaluated in growing pigs (unpubl. data). The combination was found to be associated with rapid onset, smooth induction and recovery with some duration of analgesia. However, the recovery time and duration of anaesthesia was found to be relatively long. In this study, we aimed to evaluate the effect of halving the dosage of ketamine on the anaesthetic properties and the recovery characteristics of ketamine-xylazine-midazolam anaesthesia in pigs.

Ten grower pigs (Niger hybrid and Large white breeds) of both sexes and mean body weight (18.2 ± 1.65 kg) were used for the study. Prior to the study, all the pigs were assessed to be in good general health based on findings at complete physical examination and full blood counts. The protocol for the study was approved by the Pig Management Committee of the University of Agriculture, Abeokuta.

Two series of trials were carried out. The 1st series involved pigs anaesthetised with intramuscular injection of 10 mg/kg of 10 % ketamine hydrochloride (Kepro, Holland), 2 mg/kg of 2 % xylazine hydrochloride (Kepro, Holland) and 0.25 mg/kg of 0.1 % midazolam (Claris Life, India) (K_{10}XM). The 2nd series involved pigs anaesthetised by intramuscular injections of 20 mg/kg of 10 % ketamine hydrochloride and 2 mg/kg of 2 % xylazine hydrochloride and 0.25 mg/kg of 0.1 % midazolam (K_{20}XM). All the pigs were pre-treated with atropine sulphate at the rate of 0.04 mg/kg body weight.

Following induction of anaesthesia, each pig was intubated with a size 6.0 cuffed endotracheal tube and then positioned in lateral recumbency. Analgesia was assessed by the pigs' response to the pain perception from artery forceps applied at the toe. In this study, the onset of action (OAN), duration of analgesia (DAN), duration of anaesthesia (DAN) and recovery time (RCT) were determined. Onset of action was determined as the time interval in minutes between the end of drug administration and the time taken for the pig to assume lateral recumbency. The duration of analgesia was determined as the interval in minutes between the disappearance and reappearance of pedal withdrawal reflex.

Duration of anaesthesia was determined as the time interval in minutes between the pigs' assumption of lateral recumbency and return to sternal posture. The recovery time is the time interval in minutes between assumption of sternal posture and when the pigs finally assume

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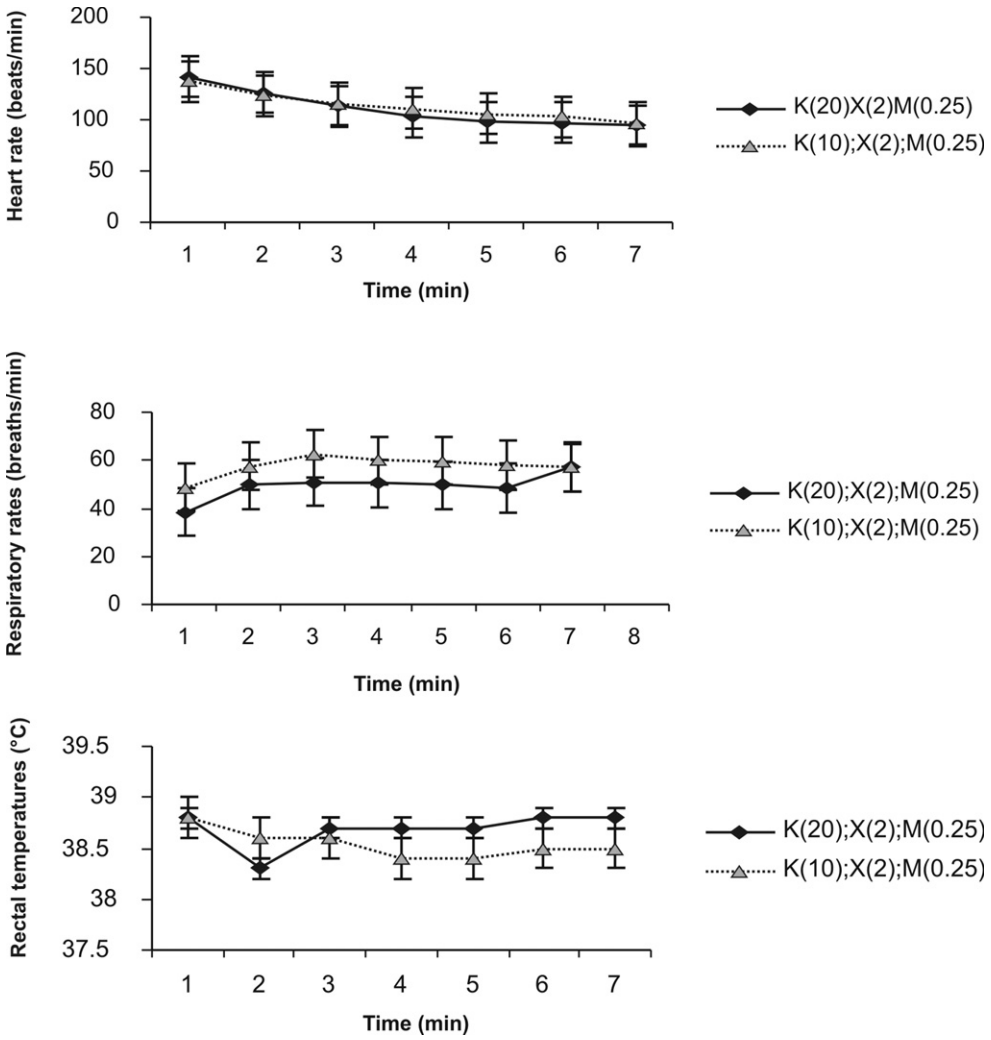

Fig. 1: **Changes in heart rates, respiratory rates and rectal temperatures following either 20 mg/kg or 10 mg/kg intramuscular injections of ketamine in midazolam-xylazine premedicated pigs.**

standing position without ataxia.

The pigs' heart rates (HR), respiratory rates (RR) and rectal temperatures (RT) were also determined immediately after the induction of anaesthesia and at 10-minute intervals until the pigs recovered from anaesthesia. Heart rates were counted in beats/min with the aid of a precordial stethoscope. Respiratory rates were counted in breaths/min by visual observation of chest excursion, while the rectal temperatures were measured in °C using a clinical thermometer. In addition, observable adverse effects of the drugs such as apnoea, cyanosis, and malignant hyperthermia were noted. Data are presented as mean ± standard error of mean. Anaesthetic indices were compared using Student's paired *t*-tests, while physiological variables were compared using analysis of variance (ANOVA) for repeated measures. A *P*-value of 0.05 was accepted as significant in all cases.

There were no observed adverse effects in either K_{10}XM or K_{20}XM anaesthetised pigs. Similarly, there were no significant ($P > 0.05$) differences in the HR, RR, and RT between K_{10}XM and K_{20}XMM anaesthetised pigs (Fig. 1). Table 1 shows the results of the anaesthetic indices of the pigs anaesthetised with either K_{10}XM or K_{20}XM. Both OAN and RCT were significantly ($P < 0.05$) shorter in K_{10}XM (1.4 ± 0.2 min; 7.8 ± 2.2 min) than K_{20}XM (2.2 ±0.2; 18.6 ± 1.4 min) respectively. Similarly, the duration of anaesthesia was significantly ($P < 0.05$) shorter in K_{10}XM (55.4 ± 8.4 min) than K_{20}XM (92.0 ± 13.6 min). The pigs that received K_{20}XM combination had analgesia of duration of 41.4 ± 12.6 min while those that received K_{10}XM combination had no analgesia.

Table 1: **Anaesthetic indices following administration of either 2 mg/kg or 10 mg/kg intramuscular injections of ketamine in xylazine and midazolam combinations in pigs.**

Anaesthetic indices (min)	K_{20}XM (n = 10)	K_{10}XM (n = 10)
Onset of analgesia	2.2 ± 0.2	1.4 ± 0.2*
Duration of analgesia	41.4 ± 12.6	Nil*
Anaesthesia time	92.0 + 13.6	55.4 ± 8.4*
Recovery time	18.6 ± 1.4	7.8 ± 2.2*

*$P < 0.05$

K_{20}, dosage of ketamine = 20 mg/kg; K_{10}, dosage of ketamine = 10 mg/kg; X, dosage of xylazine = 2 mg/kg; M, dosage of midazolam = 0.25 mg/kg.

This study was a follow up to an initial study in which we evaluated the anaesthetic features of ketamine-xylazine-midazolam combination in swine. The aim of this study was to determine the dosage of ketamine that produces the best anaesthetic effects with minimal adverse reactions. In this study, both doses of ketamine produce anaesthesia characterised by rapid onset, smooth induction and recovery with virtual lack of adverse reaction. In addition, the lower ketamine dose is not associated with analgesia, while the larger dose was characterised by longer

recumbency and recovery periods.

The efficacy and safety of anaesthetic agents have been related to the dose of the drug administered[1,4,7]. Although lower dosages are often associated with minimal adverse reactions, the low dosage also reduces the efficacy of such drug. The aim of any anaesthetic protocol is to administer the minimum dose of drug that can produce the desired anaesthetic depth with minimal side-effects. Ketamine and xylazine combinations have been evaluated in pigs[4], but the combination was found only to be suitable for chemical restraint and not for induction of anaesthesia in pigs. Therefore midazolam was added at the rate of 0.25 mg/kg to improve the quality of anaesthesia produced by ketamine-xylazine combination in the pigs.

In this study, the K_{20}XM group was characterised by analgesia (loss of toe pinch reflex) with a duration of 41.4 ± 12.6 minutes, while the K_{10}XM was not associated with loss of toe pinch. This finding suggests that the low dose ketamine may only be useful for induction of anaesthesia, to be followed then by administration of a volatile anaesthetic agent. However, the use of volatile anaesthetic agent may not be feasible in a field setting; this might then necessitate the need for opioid analgesics to make the combination useful. On the other hand, the addition of opioid analgesic to the K_{10}XM may make this combination too laborious. Furthermore, both the recovery period and duration of anaesthesia were significantly longer in K_{20}XM than K_{10}XM. Although this finding is expected, the implication is that the higher ketamine dose will require an extended period of patient monitoring compared with the low ketamine dose.

Finally, the HR, RR and RT did not differ significantly between K_{20}XM and K_{10}XM. This finding is similar to that reported earlier[4]. This suggests that increasing the dosage of ketamine does not have any significant adverse effect on the physiological status of the anaesthetised pigs. In conclusion, K_{10}XM appears to be a better combination for induction of anaesthesia in pigs owing to its shorter duration of recumbency and recovery. However, K_{20}XM will be preferred for surgery of short duration because of the presence of analgesia. The higher ketamine dosage is therefore recommended when the combination is to be used as the sole anaesthetic agent. It also remains to be determined which of the 3 drugs could be added and at what incremental dosage if the duration of the analgesia produced by the combination were to be increased without any serious adverse effects.

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