Quality of restraint and the ease of intubation of intramuscular midazolam and medetomidine with ketamine or alfaxalone in swine

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ABSTRACT

Swine often require sedation or general anaesthesia for various medical procedures. The aim of this study was to compare the effects of low doses of alfaxalone and ketamine on the quality of sedation and conditions for endotracheal intubation when midazolam and medetomidine are co-administered.

Sixteen female Large White swine, aged 6 months and weighing 28.4 ± 4.0 kg, were divided into two groups: all animals received medetomidine (7 µg/kg) and midazolam (0.4 mg/kg), with Group MMK receiving ketamine (7 mg/kg) and Group MMA receiving alfaxalone (2 mg/kg). All drugs were administered in the same syringe intramuscularly. The time from injection to recumbency was noted and defined as the onset time. A semiquantitative scale scored sedation quality at 5 and 10 minutes from injection. Intubation was then attempted, and if not feasible, additional alfaxalone was administered intravenously every 2 minutes until successful intubation was achieved. The total alfaxalone dose needed was noted, along with the assessment of the ease of endotracheal intubation.

Clinical variables evaluated at intubation time (Tpre), after 5 (T5) and 10 (T10) minutes included pulse rate, systemic arterial blood pressure, respiratory rate, arterial haemoglobin oxygen saturation (SpO_2), end-tidal carbon dioxide ($EtCO_2$), and body temperature. Both protocols induced effective restraint and smooth induction, with all animals reaching recumbency within four minutes, and no significant differences were observed between the groups. However, for successful intubation, both groups required additional boluses of alfaxalone. Muscle twitches were observed in seven swine in MMA group, but these were transient and did not adversely affect the induction period. No significant differences were found between groups in terms of sedation scores at 5 minutes or 10 minutes, induction scores, or the total dose of additional alfaxalone boluses. Respiratory rate, heart rate, and systemic arterial blood pressure and temperature also showed no significant differences between the two groups. However, $EtCO_2$ was higher at T0, T5, and T10 compared to Tpre, and four swine experienced a decline in SpO_2 below 90% after intubation.

In conclusion, low doses of alfaxalone and ketamine, in combination with medetomidine and midazolam, were effective in achieving predictable sedation in swine. The intramuscularly administered protocols allowed for the insertion of an intravenous catheter but proved insufficient for successful orotracheal intubation without additional boluses of alfaxalone. Both protocols demonstrated minimal and clinically non-relevant effects on cardiovascular and respiratory parameters. Some swine experienced hypoxaemia, emphasizing the potential need for supplemental oxygen in similar procedures.

KEY WORDS

Alfaxalone; Ketamine; Swine; Restraint; Intubation.

INTRODUCTION

Swine is a common biomedical preclinical model undergoing procedures and often requires sedation or general anaesthesia. Due to the anatomical conformation of the animal and its temperament, venous access is generally challenging in the awake animal. Nevertheless, intravascular access is commonly necessary to administer anaesthetic induction agents, facilitating the induction of anaesthesia and tracheal intubation. Vein cannulation is crucial for prolonged anaesthetic procedures, but this process can be challenging if the patient is not adequately sedated. Consequently, the intramuscular route is frequently preferred for chemical immobilisation. Intramuscular general anaesthetics, such as ketamine and alfaxalone, induce restraint in swine, with minimal cardiovascular depression. However, when used alone at elevated doses, they may result in muscle rigidity, twitches, or excitement at recovery [1-3]. Coadministration of sedatives can mitigate these effects, although

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there is a potential for enhanced cardiovascular and respiratory depression.

In swine, benzodiazepines or alpha-2 agonists are commonly used to induce muscle relaxation and are frequently co-administered with ketamine or alfaxalone [1-9]. Furthermore, the co-administration of benzodiazepines and alpha-2 agonists leads to a reduction in the dose and injection volume of both injectable anaesthetics, positively influencing heart and respiratory rates [4, 7].

For the intramuscular restraint in swine, doses of ketamine with medetomidine typically range from 5 to 10 mg/kg and 100 or 80 µg/kg, respectively. Intramuscular alfaxalone at 5 mg/kg provides mild to moderate sedation when used alone [6]. Bigby and colleagues reported moderate to profound sedation with alfaxalone at 4 mg/kg co-administered with medetomidine at 40 µg/kg and butorphanol at0.4 mg/kg [10]. In swine, intramuscular midazolam at 0.5 mg/kg as a single agent induces moderate sedation within 4 minutes with minimal alteration of cardiovascular function and respiratory rate [11].

No reports have investigated the clinical effects of low dose of alfaxalone, or ketamine combined with benzodiazepine and alpha-2 agonists in swine. Therefore, the aim of this study was to assess and compare the quality of restraint and the ease of intubation using intramuscular midazolam and medetomidine with either ketamine or alfaxalone in swine. It was hypothesised that alfaxalone might induce more muscle relaxation than ketamine, thereby improving the quality of sedation and conditions for endotracheal intubation.

MATERIALS AND METHODS

Animals

Sixteen female Large White swine, aged 6 months and weighing 28.4 ± 4.0 kg, were included in a prospective opportunistic experimental study. The pigs were housed in stalls, fed a commercial swine diet twice daily, had access to hay and water ad libitum, and underwent an 8-hour fasting period before anaesthesia.

The study was performed with the approval of the Animal Welfare Body of the University of Padua and of the Italian Ministry of Health (authorization number 694/2017-PR), and in compliance with European Directive (2010/63/EU) and Italian regulation (Legislative Decree 26/2014). Animals were anaesthetised for an unrelated laparoscopic nephrectomy surgery as part of a terminal medical training procedure.

Anaesthesia protocol

Swine were randomly allocated into two even groups (Research Randomizer Version 4.0; www.randomizer.org). Animals received: medetomidine (Domitor, Orion Corporation, Finland) 7 µg/kg, and midazolam (Midazolam-Hameln, Hospira Italia, Italy) 0.4 mg/kg mixed with ketamine (Ketavet 100, Intervet, Italy) 7 mg/kg (group MMK) or alfaxalone (Afaxan CD; Jurox Pty Ltd, Australia) 2 mg/kg (group MMA). All the drugs were drawn in the same syringe by an operator not involved in the data collection and quality scoring. The syringe was connected to a needle (BD Microlance 3, 21 gauge × 1 ½"; Becton Dick-

Tabella 1 - Semiqualitative scale to score sedation (sedation score) and ease of intubation (intubation score) in swine.

Sedation score		
Posture	Normal	0
	Sitting with head up	1
	Lying sternally head down	2
	Lying laterally	3
	Lying laterally, responding to stimuli	4
	Lying laterally, not moving when stimulated	5
Resistance to being rolled in dorsal recumbency	Normal resistance	0
	Moderate resistance	1
	Slight resistance	2
	No resistance	3
Jaw muscle tone	Normal	0
	No resistance	1
Palpebral reflex	Normal	0
	Decreased	1
	Absent	2
Intubation score		
Jaw relaxation	Relaxed	1
	Acceptable relaxation	2
	Poor relaxation	3
Ease of moving soft palate	Easy to dislodge epiglottis	1
	Needed > 1 attempt	2
	Difficult to dislodge; >3 attempts	3
Visibility	Excellent (saw vocal cords)	1
	Fair (saw part of vocal cords)	2
	Difficult (saw vocal cords with difficulty)	3
Vocal cord movement	Abducted; no movement	1
	Intermediate; moving	2
	Closed; closing	3
General difficulty of intubation	Easy (straightforward; intubation on first attempt using stylet; no swallowing)	1
	Fair (some difficulty; 1 or 2 attempts; no swallowing)	2
	Difficult (several attempts; repositioning required; swallowing)	3

inson U.K. Limited, UK) via an extension tube (Original-Perfusor line, 150 cm; B. Braun, Germany). The intramuscular (IM) injection was administered in the epaxial muscles of the neck and, the remaining solution in the extension tube was flushed with 2.5 mL of Lactate Ringer's solution (Ringer lattato SALF; SALF Laboratorio Farmaceutico, Italy). The animals were then observed, and the moment when each animal reached sternal recumbency was recorded. After 10 minutes, the swine were transferred to the pre-surgery room and placed on a surgical table in sternal recumbency. A 24 gauge over-the-needle catheter (Delta Ven 1; DeltaMed Spa, Italy) was inserted into the auricular vein. Orotracheal intubation was then attempted and, if endotracheal tube (Rüsch Endotracheal tube; Teleflex Medical, PA, USA) insertion was not possible, alfaxalone at the dose of 0.5 mg/kg was administered intravenously (IV), with a repeated dose of 0.2 mg/kg after 2 minutes if necessary. This last dose was repeated every 2 minutes until successful endotracheal tube (ETT) insertion.

Measurements

The time from IM injection to recumbency was noted as the onset time (T_{onset}). The quality of restraint was scored at 5 minutes (Rest5) and 10 minutes (Rest10) after the IM injection. Table 1 shows the scoring system used and adapted from previous scales [9, 12, 13]. The quality of restraint was assessed by two operators who collaborated to combine their scores. A scale (table 1), as reported by Duke-Novakovski and colleagues, was used to score the ease of intubation in the swine [14]. This intubation score was assessed by the same operator at the first attempt to insert the orotracheal tube and then reassessed after each redosing of alfaxalone until the successful intubation was achieved. For swine weighing less than 30 kg, intubation was performed using an ETT with an internal diameter (ID) of 6.5, otherwise with a tube with an ID of 7. To facilitate intubation, 0.5 mL of lidocaine (Lidocaine 2%; Ecuphar Italia S.r.l., Italy) was sprayed on the larynx. The intubation score was recorded at the first attempt and at the time of successful endotracheal tube insertion.

After intubation, the endotracheal tube was connected to a mainstream capnograph (EMMA Mainstream Capnometer; Masimo Corporation, California, USA) to record the respiratory rate (RR) and the end-tidal carbon dioxide ($EtCO_2$). A portable pulse oximetry (EDAN VE-H100B; EDAN USA, CA, USA) was placed on the tongue to measure the pulse rate (PR) and the haemoglobin oxygen saturation (SpO_2). Systemic arterial blood pressure was measured using an oscillometric monitor (PetTrust Blood Pressure Monitor, BioCare, Aster Electrical Co. Ltd., Taiwan), with the cuff placed on the metatarsal region. Cuff size was selected with a ruler provided by the manufacturer. Rectal temperature (T°C) was measured using an electronic thermometer. Upon the animal's arrival in the pre-survey room (Tpre), RR, PR, SpO_2, T°C, and systemic blood pressure were measured. The same variables, along with $EtCO_2$, were collected at endotracheal tube insertion (T0), and again at 5 minutes (T5) and 10 minutes (T10). Following the last measurement, the observation period concluded, and the animals were transferred to the surgery room.

Statistical analysis

Continuous normally distributed data assessed with a D'Agostino & Pearson test were expressed as a mean ± standard deviation. Ordinal variables or data not distributed normally were reported as median (minimum-maximum). A Student's t-test or a Mann-Whitney test were used to detect differences between groups, as appropriate. Analyses were performed using GraphPad Prism 8.0 (CA, USA) and $p < 0.05$ was considered statistically significant.

RESULTS

All swine completed the observation period without complications. In all animals, the onset of recumbency was smooth, achieving recumbency within 4 minutes with no differences between groups (p = 0.419) (Table 2). In group MMA, seven swine showed muscle twitches that appeared after 6 minutes form injection. There were no significant o differences between groups in the restraint score at 5 and 10 minutes (Table 2). The intravenous catheter was easily placed in all animals, although in group MMA, 3 swine reacted during insertion. At least one bolus of 0.5 mg kg was needed to insert the ETT. No significant differences between groups were detected in the induction score (p = 0.298), the number of additional boluses of alfaxalone (p = 0.612), or the total amount of the additional dose injected (p = 0.586).

No statistical differences were observed between groups in terms of respiratory rate, pulse rate, rectal temperature, and systemic arterial blood pressure (Table 3). The respiratory rate at T0 was

Tabella 2 - Mean ± standard deviation or median (min-max) and results of the unpaired Student's t test or Mann-Whitney test between swine that received intramuscularly medetomidine 7 µg/kg, midazolam 0.4 mg/kg and ketamine 7 mg/kg (group MMK) or alfaxalone 2 mg/kg (group MMA). Sedation score was evaluated 5 minutes and 10 minutes after drug administration.

Variables		MMK	MMA	*p*-value
Weight (kg)		28 ± 4	29 ± 5	0.519
T_{onset} (seconds)		174 ± 50	198 ± 64	0.419
Sedation score				
	Rest5	9 (5-10)	9 (3-10)	0.582
	Rest10	10 (9-11)	10 (9-11)	0.492
Number of boluses		2 (1-5)	4 (1-4)	0.612
Total alfaxalone dose (mg/kg)		1.0 ± 0.4	0.9 ± 0.3	0.586
Intubation score				
	at first attempt	14 (10-15)	14 (11-15)	0.946
	at successful attempt	5 (5-11)	8 (5-13)	0.298

T_{onset}, time from intramuscular injection to recumbency; Rest5 and Rest10: quality of sedation scored at 5 minutes and 10 minutes after the IM injection, respectively.

Tabella 3 - Mean ± standard deviation or median (min-max) for heart rate, systemic arterial blood pressure, respiratory rate, end tidal carbon dioxide ($EtCO_2$) and haemoglobin oxygen saturation (SpO_2) in swine that received intramuscularly medetomidine 7 µg/kg, midazolam 0.4 mg/kg and ketamine 7 mg/kg (group MMK) or alfaxalone 2 mg/kg (group MMA). Measurements were recorded the animal arrived in the pre-survey facility (Tpre), at endotracheal tube insertion (T0), and 5 (T5) and 10 (T10) minutes after endotracheal intubation.

Variables		MMK	MMA	*p*-value	
		Tpre	T0	T5	T10
Pulse rate (beats minute)					
	MMK	121 ± 5	142 ± 32	126 ± 38	124 ± 44
	MMA	130 ± 14	123 ± 15	120 ± 13	111 ± 10
Systolic arterial blood pressure (mmHg)					
	MMK	112 ± 13	127 ± 27	122 ± 21	111 ± 13
	MMA	112 ± 14	104 ± 31	124 ± 26	127 ± 25
Mean arterial blood pressure (mmHg)					
	MMK	82 ± 6	94 ± 35	97 ± 33	79 ± 8
	MMA	81 ± 14	79 ± 26	98 ± 27	97 ± 23
Diastolic arterial blood pressure (mmHg)					
	MMK	67 ± 7	78 ± 40	73 ± 16	66 ± 10
	MMA	66 ± 15	66 ± 27	85 ± 27	82 ± 23
Respiratory rate (breath minutes)					
	MMK	37 ± 14	24 ± 10	32 ± 11	31 ± 14
	MMA	39 ± 14	24 ± 11	31 ± 16	35 ± 10
$EtCO_2$ (mmHg)					
	MMK	44 ± 9	53 ± 14*	54 ± 11*	53 ± 10*
	MMA	32 ± 10	44 ± 15*	49 ± 15*	48 ± 15*
SpO_2 (%)					
	MMK	99 (93-100)	95 (88-100)	99 (88-100)	99 (96-100)
	MMA	98 (95-100)	93 (80-100)	98 (90-100)	97 (91-100)

* indicates a statistically significant difference ($p<0.05$) between T0, T5 and T10 and the baseline Tpre.

lower than that measured at Tpre, T5, and T10. Although there were no statistically significant differences between groups in $EtCO_2$, this variable was higher at T0, T5 and T10 compared to Tpre. At T0, two animals in each group had an SpO_2 lower than 90%, and in group MMK, one of those swine maintained a persistent value below 90% at T5.

DISCUSSION

Both protocols provide effective restraint and ensure a smooth induction; however, intubation was only achievable with additional boluses of alfaxalone. Adding 2 mg/kg of alfaxalone to medetomidine and midazolam does not enhance the ease of intubation compared to ketamine at 7 mg/kg.

Santos and colleagues (2016) compared the intramuscular restraint achieved with alfaxalone or ketamine with dexmedetomidine [2]. As observed in our study, recumbency was achieved between 150 and 240 seconds. However, at 10 minutes after the IM injection, swine that received ketamine showed a sedation score lower than those that received alfaxalone. No difference in the sedation score was observed in the current study and the scores recorded were higher at 10 minutes than at 5 minutes, regardless of the protocol used. The similarity in scores may be attributed to the effect of midazolam administered in both groups, which potentially improved the quality of sedation. In pigs, the maximum effect of intramuscularly administered midazolam at a dose of 0.5 mg/kg is typically observed at 10 minutes [11]. Furthermore, in our study, the dose of ketamine was lower than that used by Santos et al. (2016), potentially contributing to preventing signs of muscle rigidity and facilitating restraint without twitches or limb movement [2]. In contrast, alfaxalone was associated with muscle twitches in 7 swine, despite the low dose administered and the use of midazolam. The twitches were observed in each animal only once, for a few seconds within 6 minutes after administration, and did not interfere with the subsequent induction period. Other studies have reported similar muscle reactions with alfaxalone, which do not disappear with the concurrent use of benzodiazepine or dexmedetomidine [3, 9].

In none of the groups, sedation achieved allowed the insertion of the orotracheal tube, and at least one bolus of alfaxalone was administered to all animals. Similar results were described in other studies that utilised different alfaxalone-based protocols. Bigby and colleagues reported that 50% of the piglets receiving alfaxalone at 4 mg/kg, medetomidine at 40 µg/kg, and midazolam at 0.4 mg/kg required at least 0.9 mg/kg of IV alfaxalone before orotracheal intubation was possible, with a maximal dose of 2.3 mg/kg [10]. A lower dose of alfaxalone (2 mg/kg) with dexmedetomidine at 20 µg/kg and azaperone at 0.2 mg/kg allowed the insertion of an IV catheter into the auricular vein, but intubation was achieved only after an IV bolus of 1.6 mg/kg of alfaxalone [7]. Moreover, only one out of seven swine could be intubated after intramuscular administration of high dose of alfax-

alone combined with low dose of dexmedetomidine, specifically 5 mg/kg and 10 μg/kg, respectively [2]. In swine, orotracheal intubation is challenging due to the anatomical conformation and the laryngeal sensitivity; this procedure requires deep muscle relaxation of the jaw muscles to facilitate the visualisation of the arytenoids and to allow for the displacement of the epiglottis [15]. The myorelaxation achieved by the doses used in the current study was not optimal, and reducing the dose of ketamine was also ineffective in obtaining an adequate condition for orotracheal intubation. Increasing the dose of midazolam and medetomidine [16] or the use of neuromuscular blocking agents [14] may be considered to facilitate the insertion of an endotracheal tube.

Pulse rate and systemic arterial blood pressure did not show statistical differences between groups, and the measured values are consistent with those reported in studies using similar protocols [1, 2, 6, 7, 17]. The doses of alfaxalone, ketamine, and medetomidine in our study were lower than those reported by other authors, and this may have contributed to the higher rate observed in our study [5,10]. Specifically, the doses of alpha-2 agonists and alfaxalone administered in swine were 4 mg/kg and 10 to 80 μg/kg [10, 16], respectively, resulting in a decreased pulse rate below 100 beats/minutes 10 minutes after drug injection. Systemic arterial blood pressure remained within clinically acceptable limits for the species, and the measurements obtained in the current study align with those reported by other authors that used an alfaxalone-based protocol [10].

Some animals become hypoxemic, with SpO_2 values falling below 90% after successful intubation. Both ketamine and alfaxalone induce respiratory depression in swine and other species when co-administered with sedatives [12,13]. In swine, a study investigated the effects of medetomidine (40 μg/kg) and midazolam (0.2 mg/kg) co-administration on arterial blood gas [18]. The authors concluded that the combination caused non-clinically relevant effects. Despite in our study the doses of alfaxalone or ketamine were lower than commonly reported, they still appear to negatively impact ventilation especially if additional boluses of alfaxalone are needed. Close SpO_2 monitoring and a readily available source of oxygen are essential to promptly identify hypoxia and initiate treatment. Moreover, the current study was designed to investigate the ability of our protocols to safely secure the airway with an orotracheal tube. In species where endotracheal tube insertion is challenging, the laryngeal mask may represent an alternative, as it requires a lower dose of sedation or anaesthesia for insertion [19].

A limitation of this study is that recovery quality was not evaluated. As mentioned before, this was an opportunistic study, and the animals underwent a terminal non-recovery procedure. Alfaxalone causes a smooth recovery in several species, especially if administered with alpha-2 agonists [9, 12]. Further studies are required to investigate if our protocol led to a reasonably smooth recovery.

CONCLUSION

Low doses of alfaxalone and ketamine, when combined with medetomidine or midazolam, may be used to achieve reliable sedation. The chemical restraint obtained allows for the insertion of an IV catheter but not orotracheal intubation. Cardiovascular changes are minimal and clinically non-relevant across the protocols. Additional oxygen may be required.

Author contributions

Conceptualization, methodology, investigation, writing original draft preparation GMDB, LB
Formal analysis and data curation: LB
Writing, review, editing FZ, GMDB, LB, MC
Review final paper: MC

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