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Comparison of ketamine–dexmedetomidine–methadone and tiletamine–zolazepam–methadone combinations for short-term anaesthesia in domestic pigs

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ABSTRACT

Cardiorespiratory effects, quality of induction, depth of anaesthesia and quality of recovery were compared in pigs anaesthetised with 8 mg/kg ketamine, 20 μg/kg dexmedetomidine and 0.2 mg/kg methadone (KDM, $n = 18$) or 8 mg/kg tiletamine–zolazepam and 0.2 mg/kg methadone (TZM, $n = 9$). Anaesthesia with KDM was partially reversed in nine animals with 0.2 mg/kg atipamezole (KDM*at*). Sedation was observed earlier in the TZM group (47.2 ± 25.3 s) than the KDM group (91.5 ± 37.4 s). Sternal and lateral recumbency were achieved earlier in the TZM group (76.3 ± 36.5 s and 132.1 ± 30.5 s, respectively) than in the KDM group (149.1 ± 58.7 s and 249.2 ± 84.0 s, respectively). PaO_2, SaO_2 and PaO_2:FiO_2 were lower in the TZM group (68.7 ± 4.1 mmHg, 93.4 ± 1.4% and 327.2 ± 19.9 mmHg, respectively) than in the KDM group (80.4 ± 5.9 mmHg, 95.7 ± 1.0% and 380.4 ± 25.6 mmHg, respectively). Fshunt and $P_{(A-a)}O_2$ were higher in the TZM group (24.0 ± 11.8% and 31.4 ± 3.8 mmHg, respectively) than in the KDM group (13.4 ± 3.2% and 20.7 ± 7.4 mmHg, respectively). Times from drug injection to first head movements, sternal recumbency and standing/walking were significantly shorter in the KDM group (45.1 ± 10.5, 48.4 ± 12.6 and 54.4 ± 17.8 min, respectively) than in the TZM group (57.8 ± 11.4, 93.1 ± 14.2 and 165.7 ± 56.6 min, respectively). The median recovery score was higher in the TZM group than in the KDM*noat* and KDM*at* subgroups. Both drug combinations provided adequate anaesthesia for minor procedures lasting about 30 min, but TZM was associated with a poor recovery and oxygenation.

Introduction

Short-term anaesthesia of domestic pigs is often required in biomedical research for minor surgical or diagnostic procedures (Hastings et al., 1982; Swindle et al., 1994; Nunes et al., 2007; Grasso et al., 2009; Staffieri et al., 2012; Jordan et al., 2014). The ideal anaesthetic protocol in pigs should provide fast and reliable immobilisation, minimal cardiovascular and respiratory depression, and adequate analgesia and muscle relaxation.

Pigs are difficult to handle and restrain due to their temperament and resistance to sedative drug combinations (Brodbelt and Taylor, 1999; Heinonen et al., 2009; Lee et al., 2010; Linkenhoker et al., 2010). Restraint for IM administration of drugs seems to be less stressful than for intravenous (IV) injection (Henrikson et al., 1995). The combination of two or more drugs (balanced anaesthesia) targeting specific clinical effects (hypnosis, analgesia and muscle relaxation) represents the current best standard for injectable IM anaesthesia in pigs in terms of safety and efficacy (Nishimura et al., 1992).

Cyclohexane anaesthetic drugs (ketamine and tiletamine) are commonly used for sedation and anaesthesia in pigs, since they produce rapid and reliable immobilisation after IM administration, with a high margin of safety and few cardiopulmonary side effects (Lin et al., 1993; Boschert et al., 1996). These drugs produce a state of dissociative anaesthesia resulting from an electrophysiological dissociation between the limbic and cortical system, do not usually depress the cardiovascular or respiratory systems and have significant analgesic effects (Reves et al., 2005; Craven, 2007). Tiletamine is more potent than ketamine and is commercially available in combination with the benzodiazepine tranquiliser zolazepam (Telazol) in a 1:1 combination. The major collateral effects of dissociative drugs are muscle rigidity, ataxia and excitatory effects during recovery (Lin et al., 1993). To counteract these side effects, α2 agonists (xylazine, detomidine and medetomidine) and opioids (butorphanol and buprenorphine) are commonly combined with dissociative drugs for short-term anaesthesia in pigs (Nishimura et al.,

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1992; Sakaguchi et al., 1992, 1995, 1996; Brodbelt and Taylor, 1999; Heinonen et al., 2009; Lee and Kim, 2012; Santos González et al., 2013). However, there are few reports of the use of dexmedetomidine and methadone in this species (Hermansen et al., 1986; Sano et al., 2010; Santos et al., 2015).

Dexmedetomidine is the latest α2 adrenoceptor agonist available for veterinary use; it is an enantiomer of medetomidine and provides sedative and analgesic effects (Pypendop et al., 2011). α2 agonists exert their sedative effects through stimulation of α2 adrenoceptors in the brain, decreasing release of noradrenaline (norepinephrine). Sedation results from decreased activity of ascending neural projections to the cerebral cortex and limbic system (Stenberg, 1986). Analgesia appears to be the result of both cerebral and spinal effects, possibly in part mediated by serotonin and the descending endogenous analgesia system (Sinclair, 2003).

Methadone is a synthetic μ opioid agonist with potent and short acting (about 4 h) analgesic and sedative effects (Lamont and Mathews, 2007). Methadone has pharmacological properties qualitatively similar to those of morphine, the prototypical opioid analgesic, but possessing additional antagonistic affinity for N-methyl-D-aspartate (NMDA) receptors, thus contributing to analgesia by minimising central nervous system sensitisation (Ebert et al., 1995).

Considering the unique and advantageous characteristics of dexmedetomidine and methadone, the aim of this study was to evaluate the physiological effects of an anaesthesia protocol that includes these drugs in comparison with a traditional protocol to produce short-term anaesthesia in pigs undergoing skin and mucosal biopsies. Ketamine–dexmedetomidine–methadone and tiletamine–zolazepam–methadone combinations were evaluated in terms of quality of induction, depth of anaesthesia, quality of recovery, and cardiovascular and respiratory effects. The study did not consider situations in which pigs are intended for food production, since only ketamine is licensed for food producing animals among the drugs tested.[1]

Materials and methods

Animals

Twenty-seven Landrace × Large white pigs (22 female, 5 male) were used in this study. Food was withheld for 24 h and water was withheld for 2 h before the administration of drugs to prevent any possible adverse effects, such as vomiting during the anaesthetic or recovery periods. The study protocol was approved by the Ethics Committee of the University of Perugia (approval number 2013-027R; date of approval 6 September 2013). Pigs were involved in another experimental study in which four skin biopsies (dorsal thoracic area) and two mucosal biopsies (ventral aspect of the tongue) were collected with a cutaneous punch (0.6 mm diameter) under general anaesthesia. The aim of the surgical study was to compare the quality of incisions and degree of thermal injury produced by different surgical instruments and their effects on reepithelialisation. The number and allocation of the pigs among groups were based on the main surgical experimental study. Physical examination carried out the day before the experiment, including measurement of rectal temperature (T, °C), heart rate (HR, beats/min) and respiratory rate (RR, breaths/min), had shown the pigs were healthy. The experiments were carried out at room temperature (18–20 °C). The mean body weights (TZM 41.0 ± 6.1 kg; KDM 40.5 ± 6.6 kg) and ages (TZM 86.6 ± 7.4 days; KDM 85.2 ± 6.6 days) were similar in both groups.

Study design

Eighteen animals (KDM group) were anaesthetised IM with a combination of ketamine (8 mg/kg; Ketavet 100, 100 mg/mL, Intervet), dexmedetomidine (20 μg/kg; Dexdomitor, 0.5 mg/mL, Elanco Animal Health) and methadone (0.2 mg/kg; Eptadone, 10 mg/mL, Molteni Farmaceutici). Nine animals (TZM group) received a combination of tiletamine–zolazepam (8 mg/kg; Zoletil 100, 100 mg/mL, Virbac) and methadone (0.2 mg/kg) IM. Pigs in the KDM group were further divided in two subgroups of nine animals each based on the administration (KDM*at*) or not (KDM*noat*) of atipamezole (0.2 mg/kg; Antisedan, 5 mg/mL, Elanco Animal Health) during recovery. All animals were injected into the neck muscles caudal to the base of the ear (splenius and brachiocephalic muscles). Randomisation of pigs among treatment groups was performed using Research Randomizer.[2]

The times from injection of drugs to the first signs of sedation, and to sternal and lateral recumbency, were recorded. The quality of induction was assessed using a descriptive score ranging from 1 (excellent) to 4 (poor; see Appendix: Supplementary Table S1). Ten minutes after administration of drugs, pigs with inadequate induction (scores 3–4; one pig in the KDM group) received an additional dose of ketamine (1 mg/kg, IV; KDM group) or tiletamine–zolazepam (1 mg/kg, IV; TZM group); these animals were excluded from the study. When the induction was adequate (scores 1–2), pigs were approached, blindfolded and placed in left lateral recumbency; animals were not intubated and breathed room air (fraction of inspired oxygen, FiO_2 0.21).

Depth of anaesthesia (anaesthesia score) (Laricchiuta et al., 2012) was assessed by checking palpebral, pedal, auricular and anal reflexes, jaw tone, presence of voluntary movements and reaction to painful stimuli (blood sampling, ear notching), scored from 1 (deep anaesthesia) to 6 (very light sedation; see Appendix: Supplementary Table S2). If the anaesthesia score was 5–6 (one pig in TZM group), pigs received an additional dose of ketamine (1 mg/kg, IV; KDM group) or tiletamine–zolazepam (1 mg/kg, IV; TZM group) and these animals were excluded from the study.

Monitoring and data collection

Heart rate, RR, T, oxygen haemoglobin saturation (SpO_2, %), non-invasive systolic, diastolic and mean arterial pressures (SAP, DAP, MAP, respectively, mmHg; HB100 multiparametric monitor, Foschi) and depth of anaesthesia were recorded at the time of the first approach (T0) and after 10 (T10), 20 (T20) and 30 (T30) min. Skin and tongue biopsies were collected between T10 and T30; no other surgical interventions were performed. An arterial (femoral artery) blood sample was collected at T20 (3 mL BD Preset syringe, BD). Arterial samples were analysed immediately using a portable blood gas analyser (i-STAT Portable Clinical Analyzer, Abbott). The measured and calculated parameters were pH, partial arterial pressure of carbon dioxide ($PaCO_2$, mmHg), partial arterial pressure of oxygen (PaO_2, mmHg), base excess (BE, mmol/L), haematocrit (Hct, %), bicarbonate concentration (HCO_3^-, mmol/L), haemoglobin concentration (tHb, g/dL), oxygen haemoglobin saturation (SaO_2,%), concentrations of Na^+, K^+ and Ca^{2+} (mmol/L), arterial CO_2 (TCO_2, vol%), and concentration of glucose (mg/dL). The alveolar to arterial oxygen gradient [$P_{(A\text{-}a)}O_2$], PaO_2:FiO_2 ratio (mmHg) and estimated shunt fraction (Fshunt,%) were calculated (Araos et al., 2012). All parameters were corrected for the rectal temperature measured at the time of sampling.

The $P_{(A\text{-}a)}O_2$ was calculated as:

$$P_{(A-a)}O_2 = ([P_B - PH_2O] \times FiO_2 - PaCO_2/R) - PaO_2$$

where P_B is the barometric pressure, PH_2O is the water vapour pressure, FiO_2 is the inspired oxygen fraction and R is the respiratory exchange ratio, assumed to be 0.9 (Cohen et al., 1995). The PH_2O was corrected for the rectal temperature recorded at the time of arterial blood collection (Mackenzie, 1963).

The *F*shunt was calculated as:

$$F\text{shunt}: ([Cc'O_2 - CaO_2]/[Cc'O_2 - CaO_2 + 3.5\,\text{mL/dL}]) \times 100$$

where $Cc'O_2$ is the pulmonary end-capillary oxygen content, CaO_2 is the arterial oxygen content and 3.5 mL/dL is an approximate fixed value of the arterial-to-mixed venous oxygen content difference.

The $Cc'O_2$ and CaO_2 were calculated as follows:

$$Cc'O_2 = Hb \times 1.31 \times Sc'O_2 + 0.0031 \times Pc'O_2$$

$$CaO_2 = Hb \times 1.31 \times SaO_2 + 0.0031 \times PaO_2$$

where Hb is the haemoglobin concentration (g/dL), 1.31 is the oxygen-carrying capacity of haemoglobin (mL/g) (Larimer, 1959), $Sc'O_2$ is the pulmonary end-capillary oxygen saturation, 0.0031 is the solubility coefficient of oxygen in porcine plasma and $Pc'O_2$ is the pulmonary end capillary partial pressure of oxygen (mmHg).

Pulmonary end-capillary partial pressure of oxygen was assumed to be equal to PAO_2 (alveolar partial pressure of oxygen); for $PAO_2 > 100$ mmHg, pulmonary end capillary oxygen saturation was assumed to be 100% (i.e. 1), whereas for $PAO_2 \leq 100$ mmHg, pulmonary end capillary oxygen saturation was calculated from the actual PAO_2 via the same method. FiO_2 was always assumed to be 0.21 because pigs were breathing room air.

Recovery from anaesthesia

At T30, pigs were moved to a recovery box to observe recovery from anaesthesia; pigs in the KDM*at* subgroup received 0.2 mg/kg atipamezole IM. Times between injection of anaesthetic drugs and the first head movements, sternal recumbency and standing/walking were recorded. Times between atipamezole administration

[1] See: http://ec.europa.eu/health/files/eudralex/vol-5/reg_2010_37/reg_2010_37_en.pdf (accessed 28 December 2014).

[2] See: http://www.randomizer.org (accessed 28 December 2014).

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and the first head movements, sternal recumbency and standing/walking were also recorded in the KDM*at* subgroup. Quality of recovery was assessed using a scoring system from 1 (excellent) to 4 (poor; see Appendix: Supplementary Table S3). Any side effects noted during the procedure and during the following 24 h were recorded.

Statistical analysis

Data were tested for normal distribution with the Kolmogorov–Smirnov test, and the means, standard deviations (SDs) and ranges (parametric data: physiological, blood gas and haematological parameters) or median values and ranges (non-parametric data: induction, anaesthesia and recovery scores) were calculated. Parametric physiological data were compared among study times (T0, T10, T20 and T30) and groups using one-way analysis of variance (ANOVA) for repeated measures, while non-parametric data were compared using the Kruskal–Wallis test, followed by Dunn's test (significant at $P < 0.05$, MedCalc Software).

Results

The study was completed without any major complication in all pigs. Two pigs were excluded from the study; one case in the KDM group was excluded because of a non-adequate induction (score 3–4) and one case in the TZM group was excluded because of inadequate anaesthesia (score 5–6). The first signs of sedation after injection of drugs were observed significantly earlier in the TZM group (47.2 ± 25.3 s) than the KDM group (91.5 ± 37.4 s; $P < 0.01$). Sternal and lateral recumbency were achieved earlier in the TZM group (76.3 ± 36.5 s and 132.1 ± 30.5 s, respectively) than the KDM group (149.1 ± 58.7 s and 249.2 ± 84.0 s, respectively; $P < 0.01$). The median induction scores were similar in both groups (KDM score 1, range 1–3; TZM score 1, range 1–1; $P = 0.15$).

The mean time required to approach the animal after injection was significantly shorter in the TZM group (3.08 ± 1.15 min) than the KDM group (7.3 ± 3.3 min; $P < 0.01$).

The mean values of HR, RR, SAP, DAP, MAP, SpO_2 and T, and the median anaesthesia scores, are presented in Table 1. The mean values of T and SpO_2 were lower ($P = 0.004$) in the TZM group than the KDM from T10 to T30.

The mean values of pH, PaO_2, $PaCO_2$, SaO_2, $P_{(A-a)}O_2$, Fshunt, PaO_2:FiO_2, tHb, HCO_3^-, BE, glucose, TCO_2, Hct, Na^+, K^+ and Ca^{2+} are shown in Table 2. The PaO_2 ($P < 0.01$), SaO_2 ($P < 0.01$) and PaO_2:FiO_2 ($P < 0.01$) were lower and the $P_{(A-a)}O_2$ ($P < 0.01$) and Fshunt ($P < 0.01$) were higher in the TZM group than the KDM group. Animals did not show any evident motor reaction during the biopsies under either protocol.

Times from drug injection to first head movements ($P < 0.01$), sternal recumbency ($P < 0.01$) and standing/walking (deambulation) ($P < 0.01$) were significantly shorter in the KDM group (45.1 ± 10.5, 48.4 ± 12.6 and 54.4 ± 17.8 min, respectively) than the TZM group (57.8 ± 11.4, 93.1 ± 14.2 and 165.7 ± 56.6 min, respectively). Pigs that received atipamezole during recovery (KDM*at* subgroup) had significantly shorter times for first head movement, sternal recumbency

Table 1
Physiological parameters (means ± standard deviation) and anaesthesia scores (medians and ranges) in pigs anaesthetised intramuscularly with ketamine (8 mg/kg), dexmedetomidine (20 μg/kg) and methadone (0.2 mg/kg) (KDM group; $n = 17$ pigs) or with tiletamine–zolazepam (8 mg/kg) and methadone (0.2 mg/kg) (TZM group; $n = 8$ pigs).

Parameters	Groups	Time points in the study			
		T0	T10	T20	T30
HR	KDM	101.2 ± 12.1	94.6 ± 14.2	86.0 ± 14.8	81.0 ± 14.2
	TZM	117.2 ± 22.7	95.0 ± 26.6	85.2 ± 23.3	77.8 ± 17.1
RR	KDM	41.3 ± 15.5	44.0 ± 15.0	43.6 ± 20.0	49.2 ± 16.5
	TZM	28.3 ± 13.9	31.4 ± 13.9	33.2 ± 15.9	34.2 ± 17.7
SAP	KDM	158.0 ± 31.3	149.2 ± 19.9	144.3 ± 18.0	143.6 ± 23.8
	TZM	147.3 ± 22.8	148.7 ± 4.5	157.5 ± 31.4	141.0 ± 12.1
MAP	KDM	114.4 ± 22.0	111.5 ± 17.4	111.0 ± 18.8	115.0 ± 19.7
	TZM	112.7 ± 16.6	110.3 ± 20.3	124.7 ± 37.8	118.3 ± 14.4
DAP	KDM	91.8 ± 23.9	92.5 ± 15.1	90.4 ± 18.8	91.3 ± 21.3
	TZM	86.3 ± 16.6	81.1 ± 21.6	106.7 ± 42.7	98.0 ± 20.1
SpO_2	KDM	92.3 ± 3.9	92.9 ± 2.2	94.3 ± 2.5	95.7 ± 3.2
	TZM	89.6 ± 2.8	89.8 ± 2.7*	90.5 ± 3.6*	90.6 ± 3.6*
T	KDM	38.2 ± 0.7	38.0 ± 0.6	37.7 ± 0.6	37.3 ± 0.8
	TZM	37.0 ± 0.7	36.6 ± 0.94*	36.3 ± 0.8*	36.1 ± 0.6*
AS	KDM	2 (2-6)	2 (2-4)	3 (2-5)	3 (2-5)
	TZM	2 (2-3)	2 (2-3)	2 (2-5)	2 (2-5)

T0, time between drug administration and approach to the animal; T10, 10 min after T0; T20, 20 min after T0; T30, 30 min after T0; HR, heart rate (beats/min); RR, respiratory rate (breaths/min); SAP, systolic arterial pressure (mmHg); MAP mean arterial pressure (mmHg); DAP diastolic arterial pressure (mmHg); SpO_2, saturation of haemoglobin with oxygen (%); T, rectal temperature (°C); AS, anaesthesia score (median and range).
* Significant statistical differences between groups ($P < 0.05$).

Table 2
Blood gas analysis (T20) and calculated oxygenation indexes (means ± standard deviations) in pigs anaesthetised intramuscularly with ketamine (8 mg/kg), dexmedetomidine (20 μg/kg) and methadone (0.2 mg/kg) (KDM group; $n = 17$ pigs) or with tiletamine–zolazepam (8 mg/kg) and methadone (0.2 mg/kg) in TZM group (8 pigs).

Groups	Parameters							
	pH	PaO_2	$PaCO_2$	SaO_2	$P_{(A-a)}O_2$	Fshunt	PaO_2:FiO_2	tHb
KDM	7.4 ± 0.0	80.4 ± 5.9	48.2 ± 2.8	95.7 ± 1.0	20.7 ± 7.4	13.4 ± 3.2	380.4 ± 25.6	9.8 ± 0.3
TZM	7.4 ± 0.0	68.7 ± 4.1*	49.8 ± 2.1	93.4 ± 1.4*	31.4 ± 3.8*	24.0 ± 11.8*	327.2 ± 19.9*	13.51 ± 9.0
	HCO_3^-	BE	Glucose	TCO_2	Hct	Na^+	K^+	Ca^{2+}
KDM	33.5 ± 3.3	9.3 ± 3.9	111.8 ± 20.0	35.6 ± 3.9	28.9 ± 1.0	140.9 ± 1.78	3.7 ± 0.1	1.3 ± 0.0
TZM	32.9 ± 2.1	7.1 ± 2.4	95.8 ± 12.0	34.2 ± 2.2	29.3 ± 1.6	141.0 ± 0.6	3.83 ± 0.1	1.35 ± 0.0

T20, 20 min after the animal approach; PaO_2, partial arterial pressure of oxygen (mmHg); $PaCO_2$, partial arterial pressure of carbon dioxide (mmHg); SaO_2, oxygen haemoglobin saturation (%); $P_{(A-a)}O_2$, alveolar to arterial oxygen gradient (mmHg), Fshunt, estimated shunt fraction (%); PaO_2:FiO_2, ratio of partial pressure arterial oxygen and fraction of inspired oxygen (mmHg); tHb, haemoglobin concentration (g/dL); HCO_3^-, bicarbonate concentration (mmol/L); BE, base excess (mmol/L); TCO_2, total carbon dioxide content (vol%); Hct, haematocrit (%).
* Statistical differences between groups at given time points ($P < 0.05$).

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and standing/walking (39.1 ± 6.0, 40.2 ± 6.2 and 42.5 ± 6.3 min) compared with the TZM group and KDM*noat* subgroup (51.7 ± 9.6, 58.6 ± 8.9 and 68.8 ± 14.9 min, respectively). In the KDM*at*, after atipamezole administration (37.5 ± 6.0 min), the mean time to first head movement was 90.3 ± 64.7 s, to sternal recumbency was 157.4 ± 86.3 s and to standing/walking was 4.7 ± 2.6 min. The median recovery score was higher ($P < 0.01$) in the TZM group (median 3, range 2–4) than in the KDM*noat* (median 2, range 1–2) and KDM*at* (median 1, range 1–3) subgroups. The quality of recovery was similar between the KDM*noat* and KDM*at* subgroups.

Discussion

The results of this study suggest that the combinations of tiletamine–zolazepam–methadone and ketamine–dexmedetomidine–methadone, with or without atipamezole, are both suitable protocols for providing short-term anaesthesia for minor surgical procedures in pigs. The TZM combination provided shorter induction times, but also caused a greater derangement of gas exchange and poorer recovery quality than the KDM protocol. Administration of atipamezole at the end of the procedure, in animals receiving dexmedetomidine, shortened the recovery time.

The time for induction of anaesthesia may play a critical role for the quality of the anaesthesia in domestic pigs, since they are 'easy to stress' and become restless if the lapse of time between injection of intramuscular drugs and induction of anaesthesia is too long (Henrikson et al., 1995). The increase in sympathetic tone that occurs in this phase may interfere with the onset of the sedative effect of the drugs administered (Fournier et al., 1995; Sweitzer et al., 1997; Caulkett and Arnemo, 2007). The protocols tested in this study provided reasonable (within 5 min) induction times (Lu et al., 2010; Lee and Kim, 2012), but the TZM combination was superior, since it produced lateral recumbency in almost half the time compared to the KDM group. As a consequence, the time to approach the animal was shorter, making this combination more suitable for fractious animals.

The quality of induction of anaesthesia was good in both groups, with the animals making from one to three attempts to lie in sternal or lateral recumbency, with or without mild signs of excitement (induction scores 1 or 2; see Appendix: Supplementary Table S1). In one case, the KDM protocol failed to produce adequate induction and an extra dose of ketamine was required in order to continue with the procedure. Misplacement of the needle or a different individual sensitivity to the drug could have been responsible for an abnormal effect in this animal.

The depth of anaesthesia was adequate (anaesthesia scores 4–5; see Appendix: Supplementary Table S2) during the period of observation in both groups. In all pigs, skin and mucosal biopsies were collected without any complications. Experimental subjects did not show any sign of nociception, indicating that the combinations of tiletamine and methadone in the TZM group, and of ketamine, dexmedetomidine and methadone in the KDM group, provided an adequate level of analgesia for cutaneous or mucosal biopsy.

Many factors are responsible for decreases in body temperature during general anaesthesia (Díaz and Becker, 2010). Agitation and stress during induction of anaesthesia may contribute to the development of hyperthermia (Parrott and Lloyd, 1995). In our study, pigs in the TZM group had a lower rectal temperature than pigs in the KDM group from T10 to T30. The main factors that could have contributed to the better maintenance of body temperature in the KDM group are the longer induction time (which could have increased the body temperature of the animals) and the peripheral vasoconstriction induced by dexmedetomidine, which reduces peripheral heat loss (Sinclair, 2003).

Blood pressure was high (mean MAP > 110 mmHg) with both protocols from T0 to T30. Dissociative anaesthetic drugs cause central activation of the sympathetic nervous systemic, an increase in blood pressure and cardiac inotropism (Wong and Jenkins, 1974). α2 agonist drugs induce a transitory initial phase of peripheral vasoconstriction that usually results in systemic hypertension (Sinclair, 2003). We speculate that the effects of the dissociative drugs were mainly responsible for the hypertension observed in our pigs. Moreover, it seems that dexmedetomidine did not have an additive effect on haemodynamic conditions, since there was no significant difference in blood pressures between the KDM and TZM groups.

PaO_2:FiO_2 and Fshunt are two common indicators of venous admixture (Araos et al., 2012). There was a moderate degree of impairment of oxygenation and ventilation with both protocols, but the impairment was greater in the TZM group. PaO_2 and the PaO_2:FiO_2 were lower than physiological ranges (90–100 mmHg and 400–500 mmHg, respectively) in room air (Haskins et al., 2005; McDonnel and Kerr, 2007), particularly in the TZM group, where most pigs had PaO_2 values < 70 mmHg, PaO_2:FiO_2 < 350 mmHg and Fshunt values higher than those in the KDM group. We assume that the TZM combination induced a greater impairment of gas exchange due to a greater amount of intrapulmonary shunt fraction. The SaO_2 was lower in TZM than the KDM group, but it was never <90% in both protocols. However, it is strongly recommended to provide oxygen supplementation (e.g. flow-by, nasal cannula, face mask) to compensate for the mild derangement of lung function induced by these protocols (Haskins, 1992).

Ketamine and, to a greater extent, tiletamine, as well as dexmedetomidine, increase the pressure of the pulmonary circulation (Lagutchik et al., 1991; Sano et al., 2010; Pypendop et al., 2011). Pulmonary hypertension may also have influenced gas exchange in our animals, but we did not measure this parameter. In the TZM and KDM groups, a moderate degree of hypoventilation was observed, indicated by increased values of $PaCO_2$ (>45 mmHg) and respiratory rates (>30 breaths/min). Dissociative anaesthetic drugs, as well as α2 agonists, have minor respiratory effects (Sinclair, 2003; Craven, 2007); the hypoventilation observed in this study might be attributed to the effects of methadone.

The results of this study demonstrated that the TZM protocol was associated with longer recovery times than the KDM protocol; moreover, administration of atipamezole at the end of the surgical procedure further shortened the recovery in the KDM*at* protocol. Atipamezole did not affect the recovery score in the KDM*at* subgroup compared to the KDM*noat* subgroup. This result could be related to the low number of animals and/or because atipamezole was administered at a time (30–40 min after dexmedetomidine administration) when the sedative effects of the α2 agonist had almost disappeared. Times for sternal recumbency and standing/walking were almost doubled in the TZM group compared with the KDM group, suggesting that, despite a similar time of immobilisation, the TZM protocol produced a prolonged recovery. Moreover, the quality of recovery was worse in the TZM group, with the pigs making numerous attempts and frequent transitions from lateral to sternal recumbency and severe ataxia. These findings may be related to the longer duration of action of tiletamine and zolazepam compared to ketamine (Kumar et al., 2006; Lin, 2007).

Conclusions

The results of this study suggest that TZM and KDM produce adequate anaesthesia for minor surgical procedures in domestic pigs for about 30 min. However, the KDM protocol appeared to be superior to the TZM protocol, which, although producing faster immobilisation, resulted in a more prolonged and poorer quality of recovery, and a greater impairment of lung function. In animals treated with the KDM protocol, administration of atipamezole 30–40 min after anaesthetic drugs shortened the recovery time, but did not affect the quality of recovery.

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Conflict of interest statement

None of the authors has any financial or personal relationship that could inappropriately influence or bias the content of the paper.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.tvjl.2015.05.011.

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