Review

Pig sedation and anesthesia for medical research

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Review

Pig Sedation and Anesthesia for Medical Research

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Simple Summary: Anesthesia plays a crucial role in ensuring the ethical treatment of research animals and obtaining reliable and accurate data. Pig anesthesia is a significant aspect of clinical veterinary practice, especially when performing surgical procedures, diagnostic imaging, various medical interventions, and scientific research procedures. Anesthesia is essential to minimize pain and distress in research animals. Proper anesthesia protocols ensure that the animals are kept unconscious and do not experience pain or distress, which is not only ethically responsible but also required by regulatory bodies and animal welfare standards. Pig anesthesia safeguards animal welfare, enables accurate data collection, facilitates standardized experiments, ensures the safety of both animals and researchers and supports the development and validation of medical interventions. This article presents the considerations for sedation and anesthesia of pigs, highlighting species particularities and reviewing the agents and protocols commonly used for medical and scientific research.

Abstract: Anesthesia ensures the welfare of the animal, enables safe and effective procedures, and allows accurate data collection [1]. In clinical veterinary practice, proper training and expertise in anesthesia administration and monitoring are essential. Pigs are commonly used in medical and scientific research as models for studying various aspects of human health, physiology, and disease due to their physiological and anatomical similarities to humans [2–4]. Pigs are suitable experimental animals for many surgery techniques because they are similar in size to humans and have a short reproductive cycle. This makes them ideal for research concerning organ transplantation, cardiovascular surgery, and other procedures that require a large animal model. Pigs also have a similar anatomy to humans, which makes them a good choice for studying diseases and developing new treatments [5]. Sedation and premedication should be administered at the lowest dose to be effective with predictable results and reduced adverse effects, to ensure the safety of both the animal and the team involved in the procedure, with a fast onset and optimizing the induction and maintenance of anesthesia. The goal of induction is to achieve a safe and effective level of anesthesia that ensures the patient's safety and facilitates the research. Most of the time, inhalation anesthesia with endotracheal intubation is the ideal choice for maintenance., allowing efficient anesthetic management. The difficulties related to the endotracheal intubation of pigs can be overcome by knowing the anatomical peculiarities related to the species and the multiple methods cited in the literature. Effective analgesia tailored to the specific procedure, the pig's condition, and individual responses to medications should complete the maintenance and recovery protocols, reducing perioperative complications.

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1. Physical examination

Pigs are known to be highly sensitive to stress, thus it is best to transport and accommodate them to allow stress reduction before anesthesia, at least a few days before the start of the experiment [6,7]. Physical pre-anesthetic examination must be performed in a low-stress environment emphasizing respiratory and cardiovascular functions [8]. Age and maturity criteria should also be taken into account when choosing a model, the majority of pigs utilized in research projects weigh 15 to 30 kg, aged 8 to 12 weeks old with gains in weight at this time ranging from 2 to 5 kg per week [5]. Patient preparation before general anesthesia requires fasting for 6-12 hours, although the regurgitation risk is reduced, accidents can occur and can result in aspiration pneumonia [8]. Piglets, who are prone to hypoglycemia, should be denied suckling for only 1-2 hours before anesthetic induction [9]. Aspiration of acidic stomach fluid causes immediate reflex airway closure and destruction of type II alveolar cells and pulmonary capillary lining cells. Consequently, pulmonary edema and

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hemorrhage may develop along with bronchospasm, dyspnea, hypoxemia, and cyanosis. Recovery from aspiration pneumonia depends on the pH since swine tend to have very acidic stomach fluid with a pH as low as 1.5–2.5 [10]. Alfalfa and other types of hay can delay gastric emptying time, which means that vomiting and aspiration may still occur even after a 12-hour fasting period. To avoid this, alfalfa or other forms of hay should be eliminated from their regular diet 2-3 days before general anesthesia [11]. Following the pre-anesthetic physical examination, pigs can be included in a corresponding anesthetic risk classification system according to the American Society of Anesthesiologists (ASA) physical status classification system modified for veterinary medicine, which is a valuable prognostic tool, recommended to identify an increased risk of anesthetic complications and mortality [12,13].

2. Recommendations for injectable administration

Injections must be performed under slow pressure because otherwise the injection pain would increase unnecessarily and tissue damage might occur. The dimensions of the needle have to be adapted to the size of the animal and the liquid consistency of the injection (aqueous or oily). For subcutaneous (SC) or intramuscular injections (IM), a flexible hose can be used to connect the syringe and cannula to reduce the risks associated with the possible occurrence of evasive movements of the pig [14]. The skin of swine can only be shifted to a minor degree and is hardly removable, and consequently, only small-volume SC injections can be delivered [15]. Two spots are suitable for SC injections and recommended: the knee fold (body weight under 20 kg) or caudal to the ear base for bigger pigs [14,16]. The muscles of the caudal thigh region, semimembranosus and semitendinosus, and the gluteal muscles of the cranial thigh are generally selected as a suitable site for large-volume intramuscular injections (IM), while for small volumes to be injected, it is preferred to access the dorsolateral neck region. The injection can be done in a less stressful way for the pig if it is possible to feed it simultaneously [16,17]. Intravenous access (IV) can be challenging because pigs resist restraint and they have very few superficial veins accessible for IV injection or catheterization [9,17]. The auricular veins, jugular vein, and femoral vein are all commonly used for drawing blood or administering fluids in pigs. The auricular veins located on the lateral and medial dorsal ear margins offer the easiest access for intravenous injection. Puncture of the ear vein requires a tight fixation of the swine or sedation. After blocking blood flow at the ear base, the vessels are easy to detect. Puncturing the jugular or femoral vein can be challenging and should only be done by experienced personnel [14,15].

3. Anatomical features

Pigs have relatively thick, muscular, long tongues and narrow oropharyngeal spaces, compared to many other animals. The elongated soft palate can hide the epiglottis and partially obstruct the airway, making breathing more difficult, especially in brachycephalic breeds of pigs [18]. The pharyngeal diverticulum is an anatomical structure found in pigs, that protrudes from the wall of the pharynx, above the esophagus. The presence and length of the pharyngeal diverticulum (3-4 cm in adults, 1 cm in piglets), can vary among individuals and affect the ease of intubation [19]. The porcine larynx is tubular and lies caudal to the intermandibular space. The structural elements are divided into the thyroid cartilage, the cricoid cartilage, and some primitive arytenoid cartilage. This organ creates a characteristic obtuse angle with the trachea [19]. This anatomical characteristic, along with the existence of the lateral laryngeal ventricles, or ventricles of Morgagni, has been cited as the cause of the difficulty that may be encountered when intubation is attempted for the induction of inhalation anesthesia [19,20]. The vocal cords are positioned caudoventrally [18] and can be easily traumatized if too much pressure is applied during tracheal intubation [20].

4. Sedation and premedication

Sedation is often suitable for minor procedures, such as physical examinations, and diagnostic imaging or it represents the premedication for anesthesia. The choice of an appropriate sedative

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protocol should be based on the procedure's type, animal health status, age, and size. Other factors such as the desired level of sedation, the duration of the procedure, and the pig's response, influence the selection of medication. Sedatives should be administered at the lowest effective dose to minimize the risk of adverse effects and calculated based on the pig's weight. After sedation, pigs may still need some level of physical restraint to ensure the safety of both the animal and the people involved in the procedure [12,15].

Premedication refers to the administration of medications preliminary to the induction, preparing the patient for anesthesia, minimizing stress and anxiety, providing pain relief, and optimizing the induction and maintenance of anesthesia. The ideal premedication agent must be effective with predictable results and fast onset, easy to administer, reversible, and offer analgesia and muscle relaxation with minimum cardiovascular and respiratory depression. Medication and protocols will be decided based on the pre-anesthetic evaluation (ASA status, temperament, procedure, level of pain expected), anesthetist's level of experience, and equipment available [13]. Detailed considerations regarding the dosage, route of administration, and relevant data for sedation and premedication are exposed in Table 1.

Agent	Dose	Route	Considerations, References
Azaperone	1-8 mg/kg (2-5 mg/kg mean)	IM	20 minutes to effect, sedative [21]
Acepromazine	0.03 - 1.1 mg/kg	IM, IV	tranquilizer [22,23]
Alfaxalone	5 mg/kg	IM	sedation [24]
Diazepam	0.2-1 mg/kg	IV	mild sedative [23,24]
Midazolam	0.1-0.5 mg/kg	IM, IV	sedation [23,24]
Xylazine	1- 2mg/kg	IM, IV	pigs are the least sensitive to xylazine [11]
Medetomidine	0.03-0.08 mg/kg	IM, IV	sedation and muscle relaxation [11,22]
Ketamine	2-30 mg/kg	IM, IV	poor muscle relaxation and analgesia [23,24]
Buprenorphine	0.01-0.05 mg/kg q 8-12 hrs.	IM, SC	significant respiratory depression [14,26]
Butorphanol	0.1-0.3 mg/kg q 4-6 hrs.	IM, IV	analgesia, short duration [23]
Tiletamine/Zolazepam Telazol®	2-8.8 mg/kg	IM, IV	sedation or anesthesia for minor surgery, 20-30 minutes, reversed with flumazenil 0.08 mg/kg [23]
Naloxone	0.5-2 mg/kg	IV	[8,23]
Maropitant	1 mg/kg q 24 hrs.	IM	[25]
Glycopyrrolate	0.005-0.01 mg/kg	IM, IV	correct bradycardia, decrease salivation [9,15]
Atropine	0.02-0.04 mg/kg	IM, IV	correct bradycardia, decrease salivation [9,26]
Combinations			
Azaperone Midazolam	4 mg/kg azaperone 1 mg/kg midazolam	IM	[27]
Azaperone Xylazine	2 mg/kg azaperone 2 mg/kg xylazine	IM	[28]
Azaperone Butorphanol Ketamine	5 mg azaperone, 0.2 mg butorphanol 15 mg ketamine	IM	[29]
Azaperone Xylazine Ketamine	6 mg/kg azaperone 2mg/kg xylazine 15 mg/kg ketamine	IM	[30]
Azaperone	2 mg/kg azaperone	IM	[23]

Midazolam Ketamine	0.3 mg/kg midazolam 15 mg/kg ketamine		
Acepromazine Ketamine	1.1 mg/kg acepromazine 33 mg/kg ketamine	IM	[23]
Alfaxalone Butorphanol Medetomidine	4 mg/ kg alfaxalone 0.4 mg/ kg butorphanol 40 µg/kg medetomidine	IM	[31]
Dexmedetomidine Ketamine Methadone	10 µg/kg dexmedetomidine 10 mg/kg ketamine 0.25–0.4 mg/kg methadone	IM	Premedication, minor surgery [32]
Xylazine Ketamine	1-2 mg/kg xylazine 10-20 mg/kg ketamine	IM	Premedication, short-term anesthesia [12,33]
Medetomidine Ketamine	0.04 mg/kg medetomidine 10 mg/kg ketamine	IV	Premedication, short-term anesthesia [34]
Medetomidine Ketamine	0.08 mg/kg medetomidine 10 mg/kg ketamine	IM	Premedication, short-term anesthesia [34]

4.1. Butyrophenones

Azaperone is a neuroleptic sedative medication that belongs to the class of butyrophenone derivatives. It is widely used in pigs to provide sedation, reduce anxiety, calm animals, and combat aggression and stress in pigs [35]. It is considered to be the most effective tranquilizer for pigs [36]. Azaperone works toward central adrenergic dopamine D2 receptors located in the reticular activating system, leading to its sedative and anti-anxiety effects [37]. Due to its risk of producing vasodilation, hypotension, and hypothermia, it will not be used in patients debilitated or shocked. It can also be used for maiden sows after their first litter to reduce the rejection of piglets [22]. Azaperone given alone by intramuscular route has a rapid onset of action (5-10 min) with a duration of action of 2-6 hours (maximal effects within 30 min), while intravenous injection often results in excitation [9]. Oral or intranasal administration of azaperone at a dose of 4 mg/kg induces sedation in piglets clinically comparable with an intramuscular administration of 2 mg/kg [38,39]. Deeper sedation with fewer adverse effects can be achieved by combining azaperone with ketamine and butorphanol [22,29] or azaperone with ketamine and an alpha-2 adrenergic agonist [30]. Susceptible Pietrain pigs were 100% protected against malignant hyperthermia with azaperone at doses of 0.5-2 mg/kg IM [11].

4.2. Phenothiazines

Acepromazine (0.11 - 1.1 mg/kg IM, IV, SC) is commonly used alone for sedation [23], and decreases spontaneous motor activity, providing inconsistent sedation in pigs, along with hypotension and hypothermia [9]. Recommended dose of 0.1–0.4 mg/kg IV or IM should be used in different combinations, with a maximum dose of 1.5 mg/kg [40]. Combinations with ketamine or tiletamine/zolazepam produce reliable sedation and muscle relaxation [36]. Acepromazine 1.1-1.65 mg/kg IM has been reported to reduce the incidence of malignant hyperthermia related to anesthesia [41,42].

4.3. Benzodiazepines

Benzodiazepines are a class of sedative and anxiolytic drugs that are commonly used in both human and veterinary medicine. They work by enhancing the effects of a neurotransmitter called gamma-aminobutyric acid (GABA), which leads to sedative, anxiolytic (anti-anxiety), muscle relaxant, and anticonvulsant effects. Midazolam when compared with diazepam is water soluble, is absorbed rapidly, has a higher affinity for receptors, stronger potency, quicker onset with a shorter

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duration of effect [9]. Diazepam and Midazolam can be used in combination with ketamine, alpha-2 adrenergic agonists, and opioids. In association with ketamine, muscle relaxation will be improved during anesthesia [36]. In association with alfaxalone (5 mg/kg IM) muscle relaxation and sedation levels increase [9]. Intranasal administration of midazolam (0.2 mg/kg) determines a good and quick sedation (effect in 3–4 minutes) [43]. With a reduced frequency in use, they are also cited Flurazepam 2 mg/kg IV [44] and Lorazepam 0.1 mg/kg [15]. Flumazenil 0.02-0.08 mg/kg is a selective benzodiazepine antagonist reversal agent that can be used to counteract the effects of benzodiazepines in cases of overdose or adverse reactions [26,45].

4.4. Alpha 2-Adrenergic Agonists

Alpha-2 adrenergic agonists are a class of medications that activate specific receptors in the body called alpha-2 adrenergic receptors. These medications have various effects, including sedation, analgesia, muscle relaxation, and vasoconstriction. Alpha-2 adrenergic agonists are often used for sedation, pre-anesthetic medication, and pain management in pigs, alone or as part of a balanced anesthesia protocol in combination with other medication, such as anesthetics and analgesics. Pigs are more resistant to alpha-2 agonists than ruminants [46]. While alpha-2 agonists have beneficial effects, they can also cause side effects such as bradycardia, decreased respiratory rate, hypotension, decreased gastrointestinal motility, and hypothermia. Reversal agents (e.g., atipamezole, yohimbine, tolazoline, vatinoxan) are available that can rapidly antagonize their effects [47].

4.5. Ketamine

Ketamine is a dissociative anesthetic drug that can be used for sedation in pigs. It works by antagonizing the effects of the neurotransmitter glutamate, resulting in sedation, analgesia, and dissociation from the environment. Ketamine is often used in combination with other medications to achieve the desired level of sedation or anesthesia. Ketamine can cause side effects such as hypersalivation, increased muscle tone or muscle fasciculations [48] and poor muscle relaxation and analgesia when used alone [26]. Occasionally pigs may experience a period of disorientation and ataxia during recovery from ketamine sedation and might need a comfortable environment to prevent injury during this phase. These effects can be managed and minimized through appropriate dosing and the use of ketamine, and other medications. In healthy animals, ketamine has a good analgesic effect and just slightly modifies heart rate. When ketamine is administered alone, the ability the swallowing reflex will be unaffected, but excitation and excessive salivation develop during recovery [22].

4.6. Tiletamine

Tiletamine is a dissociative anesthetic and tranquilizer used in veterinary medicine in combination with zolazepam (Telazol® tiletamine/zolazepam, 4.4 mg/kg), to induce sedation and anesthesia in pigs. Tiletamine is a dissociative agent, about twice as powerful as ketamine, and has a longer duration of action [49]. Telazol® (tiletamine/zolazepam, 4.4 mg/kg) and xylazine (2.2 mg/kg) IM, provides rapid sedation and can be used for sedation and induction. Pigs often experience prolonged and rough recovery characterized by swimming motions with repeated attempts to right themselves when recovering from Telazol anesthesia, similar to that observed when ketamine is used alone [41,50]. Studies have shown that tiletamine and zolazepam are both eliminated more slowly in pigs than in other species and tiletamine has a longer effect than zolazepam in pigs [50]. Telazol® (tiletamine/zolazepam, 4.4 mg/kg) effect can be reversed successfully and safely with flumazenil 0.08 mg/kg [12,47].

4.7. Opioids

Opioids are a class of medications commonly used for pain management and sedation in pigs, acting by binding to specific receptors in the nervous system (opioid receptors), which results in pain relief, sedation, and other effects [12,47]. Opioids can be used for sedation in pigs, particularly for

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pain management and calming effects. Opioids can be used in combination with other sedatives, anesthetics, or analgesics to achieve the desired level of sedation and pain control: μ pure agonists determine a strong analgesic effect, μ partial agonists can be used in protocols for moderate pain along with μ- antagonists /K-agonists. Opioids can cause side effects such as respiratory depression, decreased heart rate, and constipation. Reversal agents available (e.g., antagonist naloxone 0.5-2 mg/kg IV [26]) can counteract these effects and can be used in unexpected reactions or overdose.

4.8. Alfaxalone

Alfaxalone is a neurosteroid anesthetic agent used for sedation, induction, and maintenance of anesthesia, with a rapid onset and relatively short duration of action, beneficial for procedures that require only temporary sedation. Alfaxalone can be administered in both IV and IM in pigs [51,52]. Alfaxalone can cause side effects such as respiratory depression, decreased heart rate, and a decrease in blood pressure. Alfaxalone has been used in pigs to induce and maintain anesthesia with minimal cardiovascular effects [31,53]. A combination of alfaxalone and dexmedetomidine can be used to maintain long-duration total intravenous anesthesia in pigs [32,53].

4.9. Local anesthetics

Lidocaine and bupivacaine are local anesthetic medications commonly used for various purposes in pigs, including local anesthesia for surgical procedures, postoperative pain management, and nerve blocks [8]. While local anesthetics are generally well-tolerated, some pigs may experience hypersensitivity or allergic reactions to the medications [37]. Careful observation of adverse reactions is important [54].

4.10. Neurokinin-1 (NK-1) receptor antagonists- Maropitant

Maropitant is primarily administered before anesthetic premedication and used as antiemetic medication but also for visceral analgesia. The minimum alveolar concentration of sevoflurane is decreased by maropitant, indicating a potential role as an adjunct visceral analgesic [55].

5. Induction

Induction of anesthesia is the process of administering medication to initiate general anesthesia. Preoxygenation with supplemental oxygen via a mask or through a flow by technique can increase the oxygen concentration in the lungs and bloodstream, reducing the risks for hypoxia during induction. The goal of induction is to achieve a safe and effective level of anesthesia that ensures the patient's well-being throughout it and in the maintenance phase of anesthesia. Induction agents are administered by inhalant, intravenous route, or combination (Table 2), depending on the patient and surgical setting. Inhalational induction is not preferred as a method for induction of anesthesia for pigs, due to the lack of predictable effect, the high volume of volatile agents necessary, and increased risks for the personnel. Ketamine, thiopental, propofol, and alfaxalone are the drugs most commonly used for inducing anesthesia in pigs, due to their fast-acting effects and short recovery time. Thiopental is a thiobarbiturate used for maintenance with intubation and positive pressure ventilation available since it can determine apnea. Ketamine administration alone is not recommended but it can be associated with propofol for endotracheal intubation during spontaneous breathing [56].

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Table 2. Induction agents in pigs.

Agent	Dose	Route	Considerations, References
Propofol	2-5 mg/kg	IV	[37,56]
Propofol Fentanyl	2 mg/kg 5 ug/kg	IV	allows intubation [14]
Dexmedetomidine Propofol	20-40ug/kg dexmedetomidine 2-4 mg/kg propofol		[46]
Propofol Ketamine	1-1.5 mg/kg propofol 0.5-1 mg/kg ketamine	IV	sedation, induction, no respiratory depression, good recovery [56,57]
Alfaxalone	0.6-1.1 mg/kg	IV, IM	[46]
Etomidate	2-4 mg/kg	IV	provides cardiovascular stability [46,57]
Thiopental	10-20 mg/kg	IV	apnea, prolonged recovery [40]

6. Endotracheal intubation

Endotracheal intubation is necessary to protect the airway, preventing aspiration and maintaining positive pressure ventilation during anesthesia [58]. Swine intubation is challenging, technically difficult, and requires experience due to anatomical features: the shape of the head, thick tongue, long and narrow oropharyngeal space, small larynx, and an undersized trachea that is very sensitive to excessive manipulation. During endotracheal intubation, it can be very difficult to visualize the larynx. Both dorsal and ventral recumbency are described as positions for endotracheal intubation, but ventral recumbency is crucial in facilitating safe and fast intubation and reduces the risk of airway obstruction determined by an overextension of the head [18,22,41]. To decrease the risk of laryngeal spasm the arytenoids can be sprayed with 2-4 % Lidocaine [46].

A laryngoscope with a long, straight blade and a plastic guide wire (vascular catheter) can be used to facilitate the advance of the endotracheal tube (ETT) [59]. Some techniques are described using a urinary catheter, a rigid stylet through the tube [40], or a rigid semiflexible intubating stylet adapted manually [12]. The laryngoscope should be introduced until the base of the epiglottis, pressing the tongue followed by lifting the soft palate with the tip of the tube. The ETT is advanced under direct visualization and slightly rotated around its longitudinal axis. Straight tubes made of soft material may be advantageous in diminishing the risk of laryngeal trauma. To avoid any aspiration, it is recommended to use cuffed endotracheal tubes and to have available equipment for aspiration if regurgitation appears. Due to the anatomical particularities in many situations, a flexible connector can be added between the endotracheal tube and the circuit.

Ideally is to perform a successful and smooth intubation at the first attempt. If resistance is encountered during intubation at the level of the arytenoid cartilages, a smaller ETT should be used, without forcing. Repeated attempts during a standard intubation procedure can determine laryngospasm and laryngeal trauma [60]. Difficult intubation is frequently encountered. In some situations, emergency tracheotomy and maintaining the anesthesia via the endotracheal tube connected to this level is mandatory [12]. Extubating is performed gently to avoid any traumatization of the tissues; their edema can cause obstructions of the airways during the awakening period. Each time the patient's position changes, the endotracheal tube must first be disconnected from the respiratory circuit.

7. Maintenance

Maintenance (Table 3) of anesthesia can be done by administering intravenous anesthetics (total intravenous anesthesia), volatile or mixed (partial intravenous anesthesia). [61,62]. A hypermetabolic response to potent volatile anesthetic gases such as halothane, sevoflurane, desflurane, and isoflurane can trigger malignant hyperthermia, a pharmacogenetic disorder of skeletal muscle [63]. Maintenance can be completed in a multimodal approach by the use of local anesthesia. Lumbosacral epidural anesthesia is the most commonly used form of regional analgesia in swine [9].

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Effective analgesia, in a preemptive approach tailored to the specific procedure, pig's condition, can prevent the onset of pain and minimize the sensitization of pain pathways, reducing the overall pain experience. Using a combination of different classes of analgesic drugs can provide more comprehensive pain relief [14,64]. Multimodal analgesia involves using opioids, non-steroidal anti-inflammatory drugs (NSAIDs), local anesthetics, and other pain-relieving medications. NSAIDs are commonly used to reduce inflammation and inhibit pain signaling pathways. NSAIDs alone might not provide sufficient pain control for more invasive procedures, so they might be used in combination with other analgesic medications or techniques [65,66]. The specific choice of NSAIDs and its dosing regimen should be determined by the individual pig's health status, the procedure being performed, and other relevant factors, to ensure the safety and well-being of the animals. NSAIDs like meloxicam or flunixin meglumine can help reduce inflammation and provide analgesia [65]. They are particularly useful for managing postoperative pain and are often used in combination with opioids. Opioid medications act on the central nervous system to modulate pain perception. Local anesthetics like lidocaine or bupivacaine can be administered via various nerve blocks or wound infiltration to provide targeted pain relief to specific areas and to reduce the need for systemic analgesics and in some cases, continuous infusion of analgesic medications can maintain a consistent level of pain relief throughout the procedure and into the recovery period [67]. Effective pain management should continue into the recovery period and protocols adjusted based on the pig's response and pain level. Crystalloid fluids during anesthesia are used to maintain homeostasis, to cover losses, to restore blood volume and for stabilization, usually given at a rate of 5-10 ml/kg/h. For patients younger than 12 weeks, Glucose 5% can be given to prevent hypoglycemia [68].

Table 3. Maintenance agents in pigs.

Agent	Dose	Route	Considerations, References
Isoflurane	1.6-1.9% MAC	ETT	[69]
Sevoflurane	2.4-2.66% MAC	ETT	[70]
Propofol	2-3 mg/kg, followed by 0.1-0.2 mg/kg/min	IV	[24]
Alfaxalone	4.8 mg/kg/h	IV	[31]
Fentanyl	50 ug/kg, followed by CRI 30-100 ug/kg/hrs.	IV	[23]
Alfaxalone Dexmedetomidine	5.3 mg/kg/h alfaxalone 3.0µg/kg/h dexmedetomidine	IV	[32]
Alfaxalone Dexmedetomidine Ketamine	5 mg/kg/h alfaxalone 4µg/kg/h dexmedetomidine 5 mg/kg/h ketamine	IV	[53]
Medetomidine Butorphanol Ketamine	0.03-0.08 mg/kg medetomidine 0.2 mg/kg butorphanol 10 mg/kg ketamine	IM	Longer sedation than Xylazine-Butorphanol-Ketamine [71,72]
Xylazine Ketamine Midazolam	2 mg/kg xylazine 0.25 mg/kg midazolam 10-20 mg/kg ketamine	IM	Immobilization in 2 minutes, effect for 50-90 minutes [8]
Tiletamine/Zolazepam Telazol® Xylazine	4.4-6 mg/kg tiletamine/zolazepam **2-** 2.2 mg/kg **xylazine**	IM	Provides rapid sedation and can be used for sedation and induction [45,47]
Tiletamine/Zolazepam Telazol® **Medetomidine**	5 mg/kg tiletamine/zolazepam	IM	Provides rapid sedation and can be used for

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	0.005 mg/kg **medetomidine**		sedation and induction [45,47,56]
Guaifenesin Ketamine Xylazine "Triple drip"	50 mg Guaifenesin 2 mg Ketamine 1 mg Xylazine CRI 2.2 ml/kg/h	IV	Recovery in 30-45 minutes, Guaifenesin-centrally acting muscle relaxant [23,47]
Flunixin Meglumine	1-4 mg/kg q 24 hrs.	IV	managing postoperative pain [23]
Meloxicam	0.4 mg/kg	IM	managing postoperative pain [8]
Carprofen	1-4 mg/kg q 12 hrs. 2 mg/kg q 24 hrs.	IM, IV	managing postoperative pain [8]

8. Peri anesthetic monitoring and complications

Safely managing inhalation anesthesia requires a thorough understanding of the indicators linked to the depth of anesthesia and the continuous surveillance of both the patient and the anesthetic apparatus. Regularly observed indicators should encompass pulse quality and rate, respiratory rate, mucous membrane color, capillary refill time, blood pressure, and electrocardiogram reading [9]. The patient's body temperature should be periodically assessed, and appropriate padding should be applied. The pulse can be detected by feeling the auricular artery, and direct auscultation of the heart should also be performed. In swine, the normal heart rate typically falls within the range of 60 to 90 beats per minute, though it may fluctuate significantly during inhalation anesthesia. During the recovery phase from inhalation anesthesia, diligent and frequent monitoring is imperative as life-threatening complications can arise [41]. Hypotension with mean arterial pressures less than 65 mm Hg or systolic arterial pressures less than or equal to 85 mm Hg is common in miniature pigs and may need intervention with dopamine or dobutamine (1-10 mg/kg/min continuous rate IV infusion for either), colloids, or fluid support [73].

Peri anesthetic complications

When sedating pigs, respiratory obstruction can be a big concern. Oxygen can be supplied via the anesthesia machine or an oxygen demand valve, ideally with the pig placed in a sternal position [22]. Dorsal soft palate displacement, leading to airway obstruction can develop in non-intubated pigs during anesthesia or after extubating [74]. One study on the majority of anesthesia-related complications during experimental invasive surgical procedures on pigs showed that, within the group of individuals at high anesthetic risk for invasive surgical operation, complications occurred in 20.31% of cases [12]. The majority of anesthetic difficulties involved intubation (14.06%), which led to the adjustment of the anesthetic approach by performing an emergency tracheotomy (6.25%) and keeping the anesthesia through an endotracheal tube attached to this level [12]. These types of complications need immediate attention and medical stabilization, as they can become life-threatening. In a liver injury model in pigs, vasopressin, as opposed to fluid resuscitation or saline placebo, resulted in prolonged survival and complete recuperation from uncontrolled and otherwise fatal hemorrhagic shock [75]. However, in experimental surgery, induced heart or organ failure develops frequently [23].

Some complications may appear in correlation with the conditions in which the pigs are housed. Consequently, care should be used for any possible material to be ingested that can determine gastrointestinal foreign body blockages [73]. Limiting the number of pigs in stalls is important because bite wounds are common complications and can be a source of infection for experiments that involve surgical management [76].

Malignant Hyperthermia

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Malignant hyperthermia (MH) is a disorder of skeletal muscle that starts as a hypermetabolic response that can be triggered in susceptible pigs by stress, a warm environment, volatile anesthetic gases, and muscle relaxant succinylcholine [77]. Porcine stress syndrome and malignant hyperthermia can develop in genetically susceptible pigs when they interact with stressors, such as exertion, heat, or social interaction, or when they are exposed to certain medications or anesthetics that stimulate skeletal muscle [78]. MH affects humans, horses, dogs, and certain pig breeds and can be clinically manifested by hyperthermia, tachycardia, tachypnea, increased carbon dioxide production, increased oxygen consumption, acidosis, hyperkalemia, muscle rigidity, and rhabdomyolysis [63]. Halothane is traditionally considered the most likely volatile inhalant to trigger MH, but delayed onset of MH can also occur with exposure to isoflurane and desflurane [41]. Rhabdomyolysis is not a classic symptom of MH, but it can occur as a late complication during MH when muscle tissue breaks down and releases potassium and myoglobin into the bloodstream [77]. The effectiveness of injecting Azumolene into pigs susceptible to MH is not fully understood but, as an analog of dantrolene (which is currently the only drug used to treat MH), Azumolene is effective in reversing MH crisis in pigs in some studies [79,80]. A nanocrystalline dantrolene sodium suspension is also described as effective in the treatment of malignant hyperthermia and comparable to that of standard dantrolene sodium in the pig [81], but more research is needed to confirm their efficacy and safety.

9. Recovery

Proper post-anesthesia care, in a calm environment with the pig positioned in a sternal recumbency as soon as possible, is essential during recovery to ensure that the pig wakes up safely and without complications. It is advisable to retain the endotracheal tube until the pig begins moving its head spontaneously or can no longer tolerate the tube. Ideally is to place the pig with the head elevated and the neck extended to help maintain a patent airway [41]. Continuous monitoring of vital signs, which includes heart rate, respiratory rate, body temperature, and oxygen saturation is crucial during the recovery period and should be assessed for all major procedures at least every 15 minutes during recovery as it regains consciousness [76]. It is advisable to be ready to take action in the event of complications or any adverse reactions to anesthesia. Maintaining a warm and controlled environment to prevent the pig from getting too cold is essential, as pigs are susceptible to hypothermia during anesthesia and recovery. Mild hypothermia improved survival in a clinically relevant pig model of hemorrhagic shock and trauma [82]. Pain should be assessed and managed appropriately during recovery. The recovery area should be kept quiet and free from unnecessary disturbances, allowing a gradual and safe recovery.

9. Conclusions

Pigs share many anatomical, and physiological similarities with humans, allowing extensive surgical procedures and monitoring, making them suitable for complex experiments. Proper anesthesia management is essential when conducting experiments involving animals and researchers must acquire a thorough knowledge of the techniques and protocols to be conducted [83]. Pigs offer a level of consistency and reproducibility in experiments that may be more challenging to achieve with smaller animals. Researchers must adhere to strict ethical guidelines and obtain appropriate approvals. Continuing education and research procedures in terms of the Three Rs (replacement; reduction; refinement) are needed to ensure a minimal use of pigs in research, along with a maximized welfare of those [84].

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