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Effects of anaesthetic qualities of ketamine, propofol and ketofol in horses

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Abstract
To analyse the effects of ketamine, propofol, and ketofol on anaesthetic quality of induction, duration, and recovery. A total of fifteen healthy horses were randomly divided into three Groups as A, B and C and anaesthetised with ketamine (3.0 mg/kg), propofol (3.0 mg/kg) and ketofol (3.0 mg/kg) respectively. The induction time and score of ketamine, propofol and ketofol were not different. Mean disappearance time of palpebral reflex and swallowing reflex of ketamine was significantly longer than that of propofol. Mean disappearance time of corneal reflex in ketamine, propofol and ketofol were not differences. Appearance time of limbs relaxation and jaws relaxation were not difference. In the appearance of tail relaxations, propofol was significantly faster than ketamine. Mean duration and recovery time of ketamine was significantly longer than that of propofol and ketofol. The recovery score of ketamine was significantly rougher than that of ketofol and propofol.

Keywords: Ketamine, propofol, Ketofol, horses

Introduction
Equine anaesthesia carries a relatively high rate of complication. Anaesthesia of healthy horses for elective surgery carries a greater risk of mortality than human anaesthesia or anaesthesia of other companion animals (Clarke and Hall, 1990) [8]. Post anaesthetic colic (PAC) is a well recognised complication of abdominal surgery in horses (Proudman *et al.*, 2002) [29] and a morbidity that may prove fatal or, more commonly, prolong recovery and increase hospitalisation costs (French, 2002) [13].

There are many anaesthetic agents used in equine abdominal surgery. Among them, ketamine is used a safety intravenous anaesthesia in horses. Use of ketamine alone without a co-induction agent, after sedation with an α_2 adrenoceptor agonists has been described in horses (Grandos *et al.*, 2004) [14]. Combination of ketamine with α_2 agonist, produces good to excellent induction of anaesthesia and very quiet recovery (Tranquilli *et al.*, 2007) [35]. Mama *et al.* (2005) [20] also stated that ketamine may be used with xylazine to maintain 60 minutes of anaesthesia in healthy adult horses with oxygen supplementation. On the other hand, ketamine with xylazine infusion significantly improves quality of recovery from sevoflurance anaesthesia in horses (Wagner *et al.*, 2012) [39].

Animals are anaesthetized with ketamine, show varying degrees of muscle hypertonus, and reflexive skeletal muscle movements. Active ocular reflexes coupled with the increases in muscle tone complicate monitoring of anaesthesia are presented. (Lin, 2008) [18]. The use of ketamine with xylazine for short term intravenous (IV) anaesthesia produces an excitement-free induction and recovery, maintenance of normal cardiovascular function, moderate respiratory depression, and adequate muscle relaxation. The average duration of anesthesia was approximately 16 minutes, and horses stood for 12 minutes after a single administration of the anesthetic combination (Muir *et al.*, 1997) [23]. The other publications have confirmed the safety of the technique in horses but have noted some potential problems. Major reported problems associated with the use of xylazine and ketamine in the horse include inadequate

sedation before ketamine administration producing induction failure, inadequate muscle relaxation during recumbency, and too short a duration of anaesthesia (Trim *et al.,* 1987) [36]. Propofol is a suitable ananesthetic agent for intravenous (IV) anaesthesia in horses (Oku *et al.,* 2006) [26]. Rapid onset of action and a short duration are the character of propofol. Propofol is so rapidly metabolized that accumulation does not appear to occur. Propofol has a favorable pharmacological profile, rapid onset and distribution, rapid metabolism. In horses, propofol is also characterized by a smooth and rapid recovery and is suitable for total intravenous anesthesia (TIVA) for more than two hours anesthesia because the degree of cardiovascular depression is less than that for inhalation anesthesia (Oku *et al.,* 2006; Tokushige *et al.,* 2019) [26, 34]. Following IV injection of propofol, hypnosis is induced in a circulation time with anaesthetic depth reaching maximal after around 90 seconds (Wagner *et al*., 2002) [40].

Propofol can be used as an adjunct to ketamine anaesthesia with good results (Wagner *et al*., 2002) [40]. Ketofol is the combination of ketamine and propofol in various concentrations (Pandit, 2011; Amornyotin, 2014) [27, 3]. Ketofol is used as a general anaesthesia in horses are produced without any noted adverse effects (Ohta *et al.,* 2004; Jarrett *et al.,* 2018; Tokushige *et al.,* 2019) [34]. Propofol has a narrow therapeutic range and risks of cardiovascular depression (Amornyotin, 2013) [2]. The use of propofol by non-anesthesiologists is controversial (Vargo *et al.,* 2009; Tan and Irwin, 2010). However, propofol based sedation is safe and highly effective. Mild respiratory adverse events occur frequently, and major complications may happen rarely. Additionally, adverse events do not occur more frequently compared to other sedation regimens (Amornyotin and Aanpreung, 2010; Amornyotin and Kongphlay, 2012) [4, 5]. As a result, the combination of these two drugs has several advantages (Amornyotin, 2014) [3].

Ketofol is the combination of ketamine and propofol in various concentrations. It commonly used for several procedures. Ketamine, a neuroleptic anesthetic agent, works on thalamocortical and limbic N-methyl-D-aspartate (NMDA) receptors (Pandit, 2011; Amornyotin, 2014) [27, 3]. It can be given through intravenous or intramuscular routes. Ketamine stimulates the cardiorespiratory system. A direct effect increases cardiac output, arterial blood pressure, heart rate and central venous pressures. Therefore, it is a valuable agent for hypotensive or hypovolemic patients, but a less desirable agent in patients with ischemic heart disease or raised pulmonary vascular pressure. However, ketamine induces psychomimetic activity and emergence reactions in up to 30% of patients. The combination use of ketamine and propofol can avoid respiratory depression and the occurrence of apnea that could be attributed to the administration of propofol alone (Van Natta and Rex, 2006) [37]. After administration of ketofol (ketamine: propofol) (2: 2 and 1: 15 mg/kg) respectively following xylazine and butaphanol premedication, induction of anaesthesia was rapid and smooth, with good muscle relaxation, no apnoea and no resistance to intubation in foals (Sun *et al.,* 2021) [32]. The combination use of ketamine and propofol (1:2) could reduce the incidence of hypotension and apnoea, and more effective and safer sedoanalgesia regime than propofol – fentanyl in paediatric patients for emergency short surgical producer (Khutia *et al.,* 2012) [16].

Materials and Methods

This research was conducted at the Department of Surgery and Theriogenology, University of Veterinary Science, and Military Veterinary Hospital of Honorable Riding Company, Nay Pyi Taw, during October 2021 to November 2022.

Fifteen healthy horses were randomly divided into three groups, Group A, B, and C. The horses in group A were anaesthetized with intravenous ketamine at a dose rate of 3 mg/kg body weight (Posner *et al.,* 2013) [42]. The horses in group B were anaesthetized with propofol intravenously at a dose rate of 3 mg/kg body weight (Auer *et al.,* 2019) [6]. The horses in group C were anaesthetized with intravenous ketofol which is a combination of ketamine and propofol at a dose rate of 1.5 mg each of drug/kg body weight respectively (Posner *et al.,* 2013) [42]. The anaesthetic qualities of induction, duration and recovery were evaluated according to Dar *et al.* (2013) [9].

For control of secretion, atropine sulphate (Ministry of Industry, Pharmaceutical Factory, Insein, Myanmar) was intravenously administered at the dose rate of 0.06 mg/kg body weight (Wagner *et al.,* 2012) [39]. Diazepam (Square Pharmaceuticals, Ltd., Pabna, Bangladesh) was intravenously administered at a dose rate of 0.05 mg/kg body weight (Wagner *et al.,* 2012) [39], for improving of muscle relaxation. For sedation and muscle relaxation, xylazine (Xyla®, Interchemie werken De Adelaar BV, The Netherlands) was intravenously administered at a dose rate of 0.6 mg/kg body weight (Wagner *et al.,* 2012) [39].

The horses in Group A (A1, A2, A3, A4 and A5) were anaesthetized by intravenous administration of ketamine (Ketalar®, Popular Pharmaceuticals Ltd., Tongi, Bangladesh) at a dose rate of 3 mg/kg body weight, according to Posner *et al.* (2013) [42]. The horses in Group B (B1, B2, B3, B4 and B5) were anaesthetized by intravenous administration of propofol (Fresenius Kabi Austria Gmbh, Austria) at a dose rate of 3 mg/kg body weight according to Auer *et al*. (2019) [6]. The horses in Group C (C1, C2, C3, C4 and C5) were anaesthetized by intravenous administration of ketofol which is a combination of ketamine and propofol at a dose rate of 1.5 mg each of drug/ kg body weight respectively (Posner *et al.,* 2013) [42].

The anaesthetic induction time was evaluated as the time interval between the administration of anaesthetic drugs and attainment of lateral recumbency. It was evaluated as head down time (seconds), ataxia time (seconds), down time (seconds), and induction time (minutes). The anaesthetic induction quality was evaluated as ataxia, barely becomes recumbent, dander or injury to horse and handler (Score 0), down but considerable staggering (Score 1), down easily, but some staggering and poor relaxation initially (Score 2), and down perfectly (Score 3) (Dar *et al.,* 2013) [9].

The quality and depth of anaesthesia were evaluated by time intensities of reflex responses and muscles relaxation after administration of general anaesthesia. Time (minutes) to loss palpebral, corneal, swallowing reflexes and response to noise were evaluated as the different body reflexes and time (minutes) to start relaxation of limb, jaw and tail were evaluated as different muscle relaxation according to Dar *et al.* (2013) [9].

The duration of anaesthesia was evaluated as the time interval between the administration of anaesthesia to the start of limbs and head movements according to Dar *et al.* (2013) [9]. The recovery time was evaluated as the time interval between the start of limbs and head movements to normal gait according to Dar *et al.* (2013) [9]. The recovery time was evaluated by six stages as the time to start to limbs and head movement, attempt to sternal recumbency, successfully attaining and remaining in sternal recumbency, attempt to stand, standing

ataxia, and standing normal gait.

`The anaesthetic recovery score was evaluated as violent ataxia, numerous attempts to stand (Score 0), ataxia, numerous attempts to stand (Score 1), stand up with minimal ataxia, a few attempts to stand (Score 2), and stands perfectly at first attempt (Score 3) (Dar *et al.*, 2013) [9].

Results

The induction time of ketamine (2.00±0.1 minutes (min)), propofol (1.80±0.12 min) and ketofol (1.90±0.19 min) were not differences (p>0.05) (Figure 1). The mean induction scores of all three anaesthesia (2.6±0.25, 3.00±0.00 and 2.8±0.45) were not difference among themselves (p>0.05) (Figure 2).

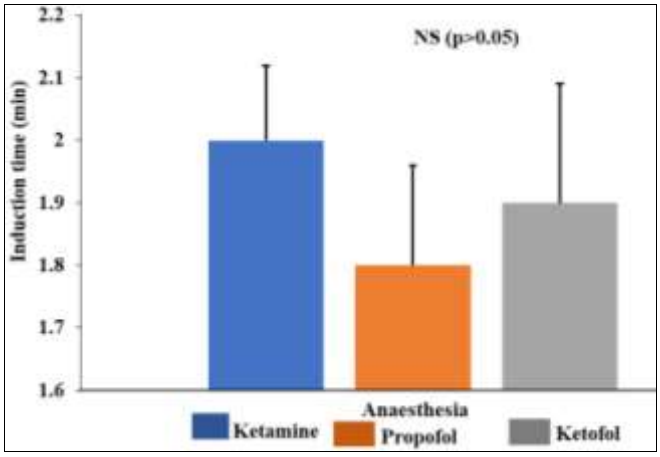

Fig 1: The effect of ketamine, propofol, and ketofol on induction time

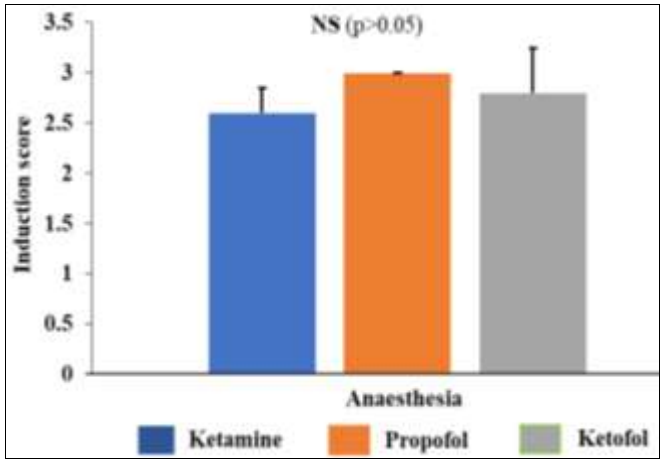

Fig 2: The effect of ketamine, propofol and ketofol on induction score

The effects of anaesthesia on induction qualities, mean disappearance time of palpebral reflex of ketamine (2.64±0.19 min) was significantly (p<0.01) longer than that of propofol (1.7±0.12 min). Propofol (1.7±0.12 min) and ketofol (2.1±0.25 min) were not difference between themselves (Figure 3).

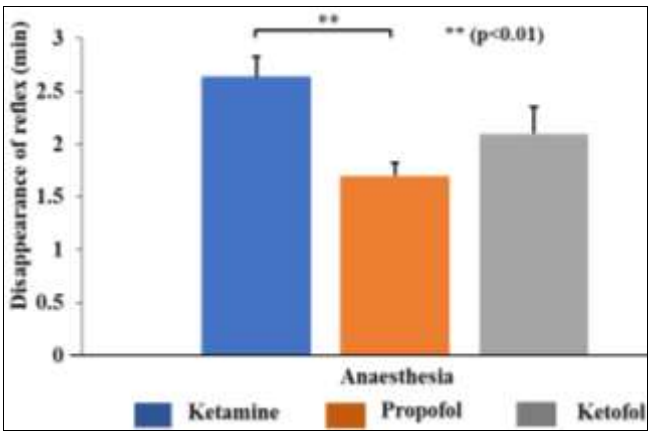

Fig 3: The effect of ketamine, propofol and ketofol on palpebral reflex

Mean disappearance time of corneal reflex in ketamine, propofol, and ketofol (2.9±0.1 min), (2.4±0.25 min) and (2.8±0.2 min) were not differences with each other (Figure 4). Mean disappearance time of swallowing reflex in ketamine was significantly (p<0.01) longer than propofol (1.6±0.19 vs 0.8±0.12 min), and propofol and ketofol were no different (0.8±0.12 vs 1.4±0.42 min) (Figure 5).

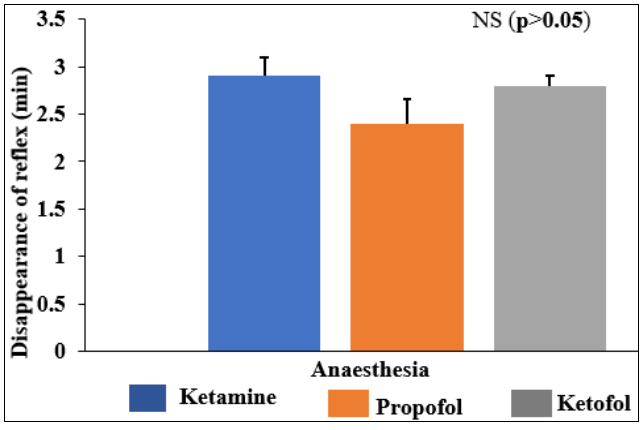

Fig 4: The effect of ketamine, propofol and ketofol on corneal reflex

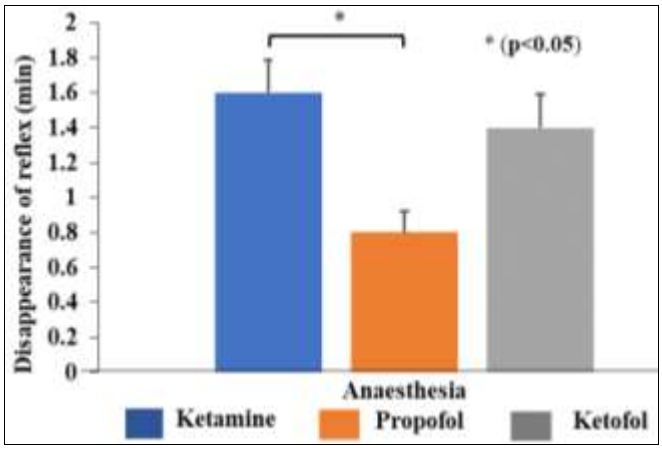

Fig 5: The effect of ketamine, propofol and ketofol on swallowing reflexes

Appearance time of limbs relaxation (3.0±0.27, 2.3±0.2, and 2.6±0.25 min) (Figure 6), jaws relaxation (2.6±0.19, 1.9±0.19 and 2.4±0.19 min) were not difference among themselves (Figure 7). In the appearance of tail relaxation produced by propofol was significantly (p<0.001) faster than ketamine (1.7±0.12 vs 2.8±0.12 min), and significantly (p<0.01) faster than ketofol (1.7±0.12 vs 2.1±0.1min) (Figure 8).

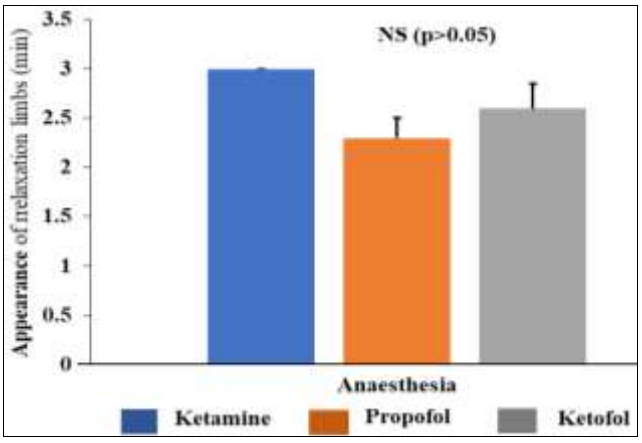

Fig 6: The effect of ketamine, propofol and ketofol on relaxation of limbs

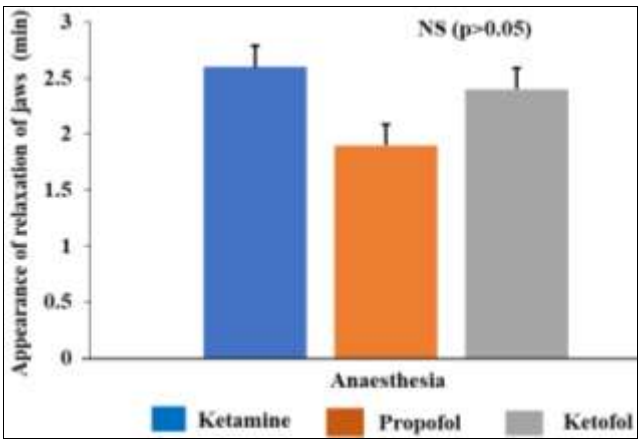

Fig 7: The effect of ketamine, propofol and ketofol on relaxation of jaws

The duration of ketamine (34.0±1.8 min) was significantly (p<0.001) longer than that of propofol (22.0±0.63 min) and ketofol (27.4±0.45 min). The duration of ketofol (27.4±0.45 min) was significantly longer than that of propofol (22.0±0.63 min) (Figure 8).

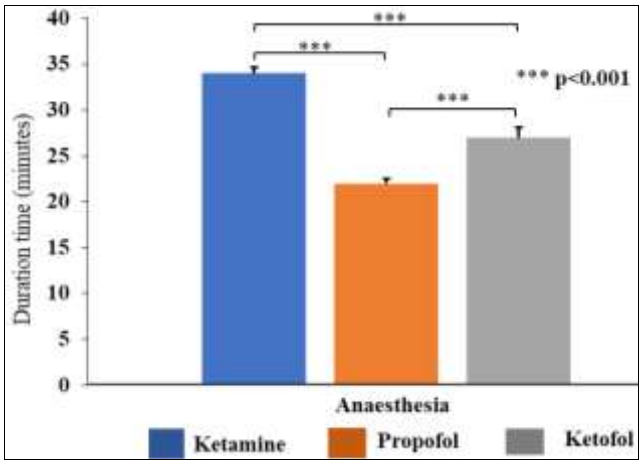

Fig 8: Effect of ketamine, propofol and ketofol on duration

Mean recovery time of ketamine (105.20±0.97 min) was significantly (p<0.001) longer than the recovery times of propofol (54.4±0.92 min) and ketofol (85.60±0.81 min). The recovery time of ketofol (85.60±0.81 min) was significantly (p<0.001) longer than that of propofol (54.4±0.92 min) (Figure 9).

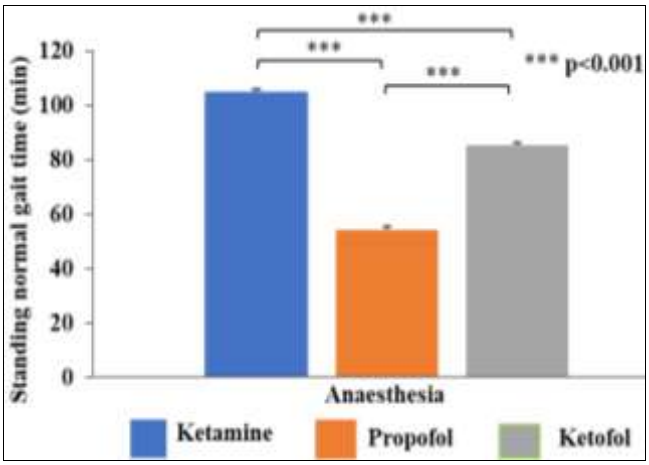

Fig 9: Effect of ketamine, propofol and ketofol on standing normal gait time

The recovery score of ketamine (1.2±0.2) was significantly (p<0.001) rougher than that of ketofol (2.2±0.2) and propofol (2.8±0.2). The recovery score of propofol (2.8±0.2) and that of ketofol (2.2±0.2) were not difference between with each other.

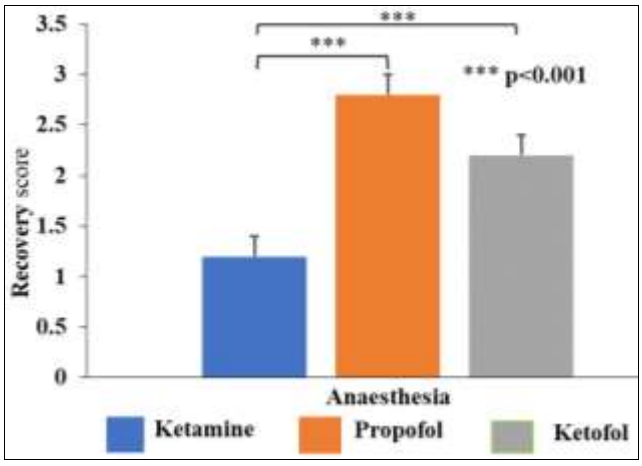

Fig 10: Effect of ketamine, propofol and ketofol on recovery score

Discussions

There were no significant differences in induction time and induction quality among ketamine, propofol and ketofol. All of anaesthesia used in this research produced rapid and smooth induction. The corneal reflex, swallowing reflex and response to noise were without any statistical variation among the three groups. The significant differences were observed for disappearance of palpebral reflex and muscle relaxation of tail. Disappearance of palpebral reflex and appearance of tail muscle relaxation by propofol were significantly rapid than those by ketamine and ketofol (p<0.001). The rapid of induction by propofol is probably due to its ability to cross blood-brain-barrier in one-arm-brain circulation and high plasma free fraction and lipid solubility (Wright, 1982; Mama *et al.*, 2005) [41, 20]. Moreover, propofol enhance the effect of inhibitory transmitter GABA and decreases the brain metabolic activity causing more rapid onset (Li *et al.*, 2009) [17]. The induction quality of propofol has been reported to be considerably variable among horses from good to poor. Moreover, excitation episodes exacerbated muscle activity and paddling limb movement in lateral recumbency were commonly encountered in horses anaesthetized with propofol (Boscan *et al.*, 2006; Rezende *et al.*, 2010) [7, 30]. However, in this research propofol had been associated with high quality anaesthetic induction. Induction quality in this research were likely influenced by the different use of drugs administration for sedation, tranquillizer, anticholinergic agents and dosage differences. Similar findings were reported by Sankar *et al.* (2010) [31], Ferreira *et al.* (2013) [11].

The duration of ketamine (34.0±1.8 min) was significantly (p<0.001) longer than that of propofol (22.0±0.63 min) and ketofol (27.4±0.45 min). The duration of ketofol (27.4±0.45 min) was significantly longer than that of propofol (22.0±0.63 min). Mean recovery time of ketamine (105.20±0.97 min) was significantly (p<0.001) longer than the recovery times of propofol (54.4±0.92 min) and ketofol (85.60±0.81 min). The recovery time of ketofol (85.60±0.81 min) was significantly (p<0.001) longer than that of propofol (54.4±0.92 min). The recovery score of ketamine (1.2±0.2) was significantly (p<0.001) rougher than that of ketofol (2.2±0.2) and propofol (2.8±0.2). The recovery score of propofol (2.8±0.2) and that of ketofol (2.2±0.2) were not different. It was not a difference among themselves. Anaesthetic duration of ketamine was significantly (p<0.001) longer than that of propofol and ketofol whereas the anaesthetic duration of propofol was significantly shorter than that of ketamine and ketofol (p<0.001). This result is in line with Sankar *et al.* (2010) [31], Wagner *et al.* (2012) [39] and Ferreira *et al.* (2013) [11] who reported that propofol produces shorter duration than ketamine. This is because propofol has rapid elimination metabolism from body (Sankar *et al.*, 2010) [31]. In contrast, Wagner *et al.* (2012) [39] and Ferreira *et al*. (2013) [11] documented that there was no significant difference between ketamine and propofol. The qualities of anaesthetic effects may vary depending on species or breed of the animals, susceptibility of the individual patient, health status of animal, the different use of premedication and dosage. Prolong duration of anaesthesia is related to delay recovery and loading to the incidence of hypoxemia and hypothermia as postoperative complications. Hypothermia and consequent shivering caused hypoxemia that involved in the low cardiac output and responsible for cardiac arrythmia in draft horses (Niwa *et al.*, 1998; Dupont *et al.*, 2018) [24, 10].

The combination use of anaesthesia could provide to reduce the doses of anaesthetic drugs as well as to promote the improve recovery by combining advantages of anaesthetic agents. The combination of propofol and ketamine was associated with satisfactory anaesthetic induction and recovery in horses (Ponser *et al.*, 2013) [28]. It has also been reported that ketamine was used successfully as an induction agent before TIVA with propofol (Flaherty *et al.*, 1997) [12]. The combination use of ketamine and propofol can avoid respiratory depression and the occurrence of apnea that could be attributed to the administration of propofol alone (Van Natta and Rex, 2006) [37]. Van Natta and Rex, (2006) [37], and Abdel-Hady *et al.* (2017) [1] also documented that the onset of anaesthesia was more rapid, longer duration and the total recovery time was more smother in horses anaesthetized with the combination of ketamine and propofol. The combination use of ketamine and propofol (1:2) could reduce the incidence of hypotension and apnoea, and more effective and safer sedoanalgesia regime than propofol-fentanyl in paediatric patients for emergency short surgical producer (Khutia *et al.*, 2012) [16]. Recovery quality was influenced by many factors including type of surgery, physical status of animals, out of hours anaesthesia, duration of anaesthesia, age, body mass, temperament, hypoxia and pain (Loomes and Louro, 2021) [19]. In the present research, the mean recovery quality of propofol was the smoothest among three groups (p<0.001), and that of ketofol was significantly (p<0.01) smoother than that of ketamine.

The present research reveals that the combination use of propofol (1.5 mg/kg) and ketamine (1.5 mg/kg) could improve the anaesthetic quality of induction and recovery by reducing risks associated with anaesthesia in horses. This result is in accordance with Sankar *et al.* (2010) [31] and Wagner *et al.* (2012) [39], who reported that propofol produces higher recovery quality than ketamine. The application of propofol for induction of anaesthesia has been associated with increased incidence of excitement and peddling. This complication of propofol could be prevented with the use of anticholinergic drugs (Mama *et al.*, 1995; Mama *et al.*, 1996; Ferreira *et al.*, 2013) [21, 22, 11]. Ferreira *et al.* (2013) [11] and Mama *et al.* (2005) [20] reported that there were no significant differences in recovery quality in ketamine and propofol. This discrepancy may be due to individual horse temperament, premedication routine and dosage differences. In additionally route dependent in plasma drug concentrations might also be account for some effects differences. The longer duration of anaesthesia resulted in longer recovery. However, propofol plasma concentration could decline rapidly after the cessation of anaesthesia. Recovery quality can be improved by the administration of an α_2 adenoceptor agonist immediately prior to recovery (Loomes and Louro, 2021) [19]. The mean for the differences in the quality of anaesthesia due to the different pharmacological induction of the different combination of induction agents used and the doses of medication used.

Conclusion

The satisfactory anaesthetic quality of induction, duration and recovery were successfully achieved after administration of ketamine, propofol, and ketofol at the dosage of 3 mg/kg body weight in horses sedated with atropine, xylazine, and diazepam. It was possible to confirm that the anaesthetic protocol applied in this research could improve the quality of anaesthesia and the most satisfactory anaesthetic effects were successfully achieved by the combination use anaesthesia ketamine and propofol for flank laparotomy in horses.

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