Original Article

Sahel Journal of Veterinary Sciences

Sahel J. Vet. Sci. Vol. 20, No. 1, Pp 44-49 (2023)
http://dx.doi.org/10.54058/saheljvs.v20i1.347

Article History
Received: 14-11-2022
Revised: 09-03-2023
Accepted: 14-03-2023
Published: 31-03-2023

Evaluation of Anaesthetic Indices and Physiological Variables following Total Intravenous Anaesthesia with Acepromazine-Butorphanol-Propofol Combination in Dogs

[1*]Gapsiso, R. H., [2]Umar M. A. and [2]Mohammed, A.

[1]Department of Animal Health and Production, School of Agricultural Technology, Federal Polytechnic Mubi, Adamawa State
[2]Department of Veterinary Surgery and Radiology, Faculty of Veterinary Medicine, University of Maiduguri, Borno State

[*] Author for Correspondence: papiray.rg@gmail.com

ABSTRACT

The study determined the anaesthetic and physiological effects of Acepromazine-Butorphanol-Propofol (ABP-combination) and propofol alone (PRO alone) in dogs. Ten clinically healthy dogs were randomly assigned to two groups to evaluate the anaesthetic and physiological effects following ABP-combination and PRO-alone anaesthesia administered intravenously (iv). Acepromazine at 0.02mg/kg and Butorphanol at 0.05mg/kg iv were used to premedicate the dogs and Propofol at 4mg/kg for induction five minutes after premedication in ABP-combination group while Propofol alone at 6mg/kg for total intravenous anaesthesia (TIVA) induction without premedication. Onset of anaesthesia, duration of anaesthesia time to standing, onset and duration of analgesia and duration of intubation were measured, whereas temperature, heart rate and respiratory rates were measured before induction of anaesthesia and at five minutes interval during anaesthesia. All the anaesthetic indices were significantly ($p<0.05$) different between groups while onset and duration of analgesia was recorded in ABP group only. Significantly ($p<0.05$) longer duration of anaesthesia was produced by ABP-combination compared with PRO-alone. Time to standing were significantly different ($p<0.05$) between the two treatments. The onset and duration of analgesia was 5.0±2.0 and 33.6±3.2 min. following ABP-combination but no analgesia recorded with PRO-alone. There was significant decrease ($p<0.05$) in rectal temperature and respiratory rate from the baseline in ABP-combination group but not significant in PRO-alone group. There was significant ($p<0.05$) difference in heart rates between groups. ABP-combination TIVA provided longer duration of anaesthesia and analgesia with minimal effects on vital parameters. The dogs recovered from the anaesthesia uneventfully. The ABP-combination can be evaluated for clinical procedures in dog.

Keywords: Acepromazine; Anaesthesia; Butorphanol; Dogs; Propofol

INTRODUCTION

Anaesthesia as a state of induced temporary loss of sensation manifesting as a controlled/ reversible unconsciousness, analgesia, and muscle relaxation, with minimal adverse effects (Thurmon and Short, 2007), is a basic and an indispensable prerequisite for most surgical procedures in both human and animals to enhance accuracy during surgical and medical procedures, diagnostic examinations and maximise personal safety (Yamashita *et al.,* 2006; Branson, 2007; Mohammed *et al.,* 2009; Elks, 2014). The use of intravenous anaesthetics in veterinary practice over the years has become popular and an acceptable way of achieving ideal surgical anaesthesia, especially with the availability of propofol which has rapid action, redistribution and clearance, making it possible to induce and maintain adequate depth of general anaesthesia therefore allowing prolonged smooth anaesthesia and efficacy of surgical procedure (Cicek *et al*., 2005; Umar *et al*., 2006; Yamashita *et al*., 2006; Umar *et al.,* 2007). Total Intravenous Anaesthesia (TIVA) therefore allows for the continuous administration of anaesthetic agents solely by intravenous routes for inducing and maintaining anaesthesia (Cicek *et al*., 2005; Umar *et al*., 2007; Morton and Hall, 2012), usually aimed to achieve balanced anaesthesia by combining drugs with analgesic, muscle relaxant and sedatives properties, which are rarely provided by single anaesthetic drug (Branson, 2007; Matthews, 2007; Umar *et al*., 2007; Morton and Hall 2012). Appropriate selection of premedications in TIVA tend to improve intraoperative cardiovascular stability; perioperative analgesia and quality of recovery since the dosage of drugs used to produce general anaesthesia are often reduced (Radney and Smith, 2018; Waelbers *et al*. 2009). Continuous research to find suitable drugs, drug combinations and techniques to meet changing demands of advance diagnostic and therapeutic modalities necessitated the selection of propofol (phenolic anaesthetic), acepromazine (phenothiazine tranquilizer) and butorphanol (morphine-type synthetic agonist–antagonist opioid analgesic) administered via total intravenous anaesthesia

(TIVA) route to achieve balanced anaesthesia in this study. Furthermore, combination of these agents (acepromazine and butorphanol) has been demonstrated in dogs as premedication intramuscularly, while propofol for induction intravenously (Bufalari *et al*., 1997; Bolaji-Alabi and Adeniji, 2018). Due to paucity of information and clinical use regarding Propofol alone and the acepromazine-butorphanol-propofol (ABP) combination for anaesthesia in dogs in Nigeria necessitated the search for ultra-fast balanced anaesthesia with smooth onset of action, longer duration of anaesthesia, smooth recovery with minimal adverse effect on cardiopulmonary system. The study was aimed to evaluate the effect of ABP combination and Propofol alone TIVA on anaesthetic indices and physiological variables in dogs.

METHODOLOGY

Experimental Animals

Ten healthy dogs with means ± Standard deviation (SD) body weight of 15.5 ± 1.96 kg and age 1.59 ± 0.77 years old were used for the study. The dogs were kept at the kennels of the Department of Veterinary Surgery and Radiology, University of Maiduguri two weeks to acclimatise to the environment and ascertained to be healthy based on physical and laboratory evaluations. The dogs were randomly assigned to two groups; Acepromazine-butorphanol-propofol (ABP) combination group and Propofol (PRO) alone groups using a random sampling technique (RST). The animals were fasted of food for 12 hours but not water prior to each experiment.

Experimental Drugs

The drugs used for the study were: Acepromazine (Neurotranq® 10mg/ml Virbac, RSA Pty. Ltd. South Africa), Butorphanol (Dolorex® 10mg/ml Intervet SA Pty. Ltd. South Africa) and Propofol (Propofol® 1% Frensenius Kabi SA Pty. Ltd. South Africa).

The two treatment groups that the dogs were assigned consist of: Acepromazine-Butorphanol-Propofol (ABP) combination and Propofol-alone (PRO). The dosages for ABP combination and PRO were based on experimental trials and literature reviewed. Animals assigned to ABP group, were premedicated with acepromazine (0.02mg/kg iv) and butorphanol (0.05mg/kg iv). The calculated doses of the two drugs for premedication were drawn from their separate vials using insulin syringes and mixed in a single 5ml syringe; water for injection was then added to make up to 1ml of the mixture before iv injection via cannula placed in the cephalic vein. An intravenous fluid (5% dextrose saline by Unique Pharmaceuticals Ltd, Sango Ota Nigeria) was administered at 5ml/10kg through the cannula. Five minutes later, anaesthesia was induced with propofol (4mg/kg) through the cannula. Blood samples were collected through the cannula before premedication and during the anaesthesia. Dogs assigned to PRO-alone group were not premedicated but anaesthesia was induced using propofol (6mg/kg) through the cannula placed in the cephalic vein. An intravenous fluid (5% dextrose saline) was started at 5ml/10kg.

Following the induction of anaesthesia, each dog was intubated via orotracheal intubation and extubation was done once swallowing reflex returns in the dogs.

Measurement of Parameters

Anaesthetic indices (onset of anaesthesia, duration of anaesthesia and time to standing) were measured as described by Adetunji *et al*., (2002). The physiological variables were measured before the injection of the drugs for baseline values and were repeated at intervals during and after anaesthesia. Analgesia (onset and duration of analgesia) was assessed after premedication and during anaesthesia by using haemostatic clamp on the skin of the flank and the distal part of the hind-limb at intervals. Positive response to haemostatic clamp was defined by a gross movement of the head or leg withdrawal.

Physiological Parameters

Physiological parameters (heart rate, respiratory rate and rectal temperature), were measured before the anaesthesia and then at 5 minutes interval in both groups during anaesthesia.

Heart rate (beats/minute) was measured using a stethoscope placed between the 2^{nd} – 5^{th} left intercostal spaces and the heart beats counted for 1 minute. Respiratory rate (breathes/ minute) was measured by visual observation of the thoraco-abdominal movement for 1 minute. Rectal temperature (^oC) was measured using a digital thermometer placed in the rectum touching rectal mucosa for 1 minute.

Data Analyses

Data obtained are expressed as Mean ± Standard Deviation (SD) using One Way Repeated Measure Analysis of Variance (ANOVA) to analyse data within groups and an Independent Sample T-test to analyse data between groups. Dunnett's Multiple Comparison Test was carried out to determine level of significance and analyses were considered significant at $p<0.05$. IBM SPSS software version 20.0 was used.

RESULTS

The onset of anaesthesia recorded for ABP-combination was 24.0±0.1 seconds, while for PRO-alone was 27.0±1.0 seconds. The onset of anaesthesia was not significantly ($p>0.05$) different between the two treatments (Table 1). The duration of anaesthesia for ABP-combination was 30.0±5.8 minutes while that of PRO-alone was 13.6±4.8 minutes. The duration of anaesthesia between the two treatments was significantly ($p<0.05$) longer with ABP-combination (Table 1). Time to standing recorded for ABP-combination was 31.8±6.9 minutes while that of PRO-alone was 16.0±6.8 minutes. There was a significant ($p<0.05$) difference between the two treatments (Table 1). The onset of analgesia using ABP-combination was 5.0±2.0 minutes while the duration of analgesia was 33.6±3.2 minutes. There was no analgesia observed with PRO-alone (Table 1). Duration of intubation observed in this study differ significantly ($p<0.05$) between the two groups (Table 1). It was 15.2±7.7 minutes for ABP-combination and 9.0±6.4 minutes for PRO-alone.

Physiological Variables

There was no significant ($p>0.05$) difference in heart rates compared with the baseline values using ABP-combination and PRO-alone (Table 2). However, the ABP-combination produced increased heart rate compared with PRO-alone. The effects of ABP-combination and PRO-alone on respiratory rate did not show any significant ($p>0.05$) difference between the two treatments during anaesthesia (Table 2). PRO-alone recorded non-significant ($p>0.05$) decrease of 25.8±9.7 and

21.8±5.4 at 5 minutes and 10 minutes respectively from baseline while ABP-combination recorded 24.8±6.5 and 22.8±8.6 at 5 minutes and 10 minutes respectively (Table 2). There was significant ($p<0.05$) decrease in respiratory rates from the baseline to 30 minutes during anaesthesia following ABP-combination (Table 2). Significant ($p<0.05$) decrease in the rectal temperature was recorded from the baseline to 5 minutes and 25 minutes following the ABP treatment. PRO-alone treatment has no significant effect on temperature (Table 2). The effects of the two treatments on rectal temperature did not show any significant ($p>0.05$) difference between the groups during anaesthesia (Table 2).

Table 1: Anaesthetic indices following administration of Acepromazine (0.02mg/kg) - Butorphanol (0.05mg/kg) - Propofol (4mg/kg) combination and Propofol (6mg/kg) -Alone TIVA in Dogs

Anaesthetic Indices	ABP-Combination	PRO-Alone
Onset of Anaesthesia (seconds)	24.0±0.1^{a}	27.0±0.1^{a}
Duration of Anaesthesia (minutes)	30.0±5.8^{a}	13.6±4.8^{b}
Time to Standing (minutes)	31.8±6.9^{a}	16.0±6.8^{b}
Onset of Analgesia (minutes)	5.0±2.6	No analgesia
Duration of Analgesia (minutes)	33.6±3.2	No analgesia
Duration of Intubation (minutes)	15.2±7.7^{a}	9.0±6.4^{b}

Values with different superscript within (^{abcd}) a row are significantly different ($p<0.05$)

Table 2: Effect of Acepromazine (0.02mg/kg) - Butorphanol (0.05mg/kg) - Propofol and Propofol (6mg/kg) –Alone TIVA on Physiological variables

Time interval (minute)	Temperature (^{o}C) ABP	PRO	Heart (beats/minute) ABP	PRO	Respiratory rate (breathes/minute) ABP	PRO
Baseline	38.4±0.2^{a}	38.7±0.6	85.2±15.9	84.6±11.2	21.4±6.4^{ab}	26.6±10.9
5	38.2±0.1^{ab}	38.3±0.6	92.4±1.0^{w}	85.8±20.9^{x}	24.8±6.5^{a}	25.8±9.7
10	37.9±0.2^{bc}	38.2±0.5	90.4±17.4^{w}	86.2±21.6^{x}	22.8±8.6^{ab}	21.8±5.4
15	37.7±0.4^{cd}	NR	87.6±16.7	NR	16.4±3.3^{bc}	NR
20	37.5±0.3^{cd}	NR	77.0±15.2	NR	13.6±3.7^{c}	NR
25	37.4±0.5^{d}	NR	79.0±15.3	NR	13.4±5.2^{c}	NR
30	37.5±0.5^{cd}	NR	84.2±5.3	NR	16.8±5.4^{bc}	NR

Values with different superscript (^{abcd}) within columns are significantly different ($p<0.05$) Values within row bearing different superscript (^{wxyz}) are significantly different ($p<0.05$). Key: NR = Not recorded

DISCUSSION

The rapid onset of anaesthesia was recorded in both groups however; it was not significantly different between the two treatments. The rapid onset of action recorded in this study is similar to reports of previous studies that reported onset of anaesthesia with propofol to be between 15 – 30 second irrespective of dose and species of animal (Hall *et al*., 2001; Merik, 2004; Umar *et al*., 2006). The rapid onset of action recorded in this study was faster than the findings of Bolaji-Alabi and Adetunji (2018), who reported 4.3±0.2 minutes to onset.

The longer duration of anaesthesia recorded with ABP-combination is similar to the report of Bufalari *et al*. (1997); Bolaji-Alabi and Adetunji (2018), who reported longer duration of anaesthesia with propofol induction in dogs premedicated with acepromazine and butorphanol. The shorter duration of anaesthesia recorded with Propofol alone is similar with the reports of Umar *et al*., (2006); Bolaji-Alabi and Adetunji (2018) who reported short duration of anaesthesia in horses and dogs respectively. The differences in the duration of anaesthesia between the treatments is attributable to the addition of acepromazine and butorphanol as reported by Umar *et al*., (2006); Bolaji-Alabi and Adetunji (2018), that combining propofol with analgesics or sedative produces an adequate depth and quality of anaesthesia.

The time to standing of the dogs following anaesthesia revealed that dogs in PRO-alone group recovered smoothly, uneventful and much earlier from anaesthesia than dogs from ABP-combination group, which agree with reports of Bolaji-Alabi and Adetunji (2018) who reported that propofol is an ultra-short acting anaesthetic with smooth and fast recovery but when combined with other anaesthetic agents, could delay recovery from the anaesthesia. The longer time to standing recorded is similar to findings of Bufalari *et al*. (1997), who reported a longer time to standing with propofol induction in dogs premedicated with acepromazine and butorphanol. The findings vary with the report of Bolaji-Alabi and Adetunji (2018), who reported 7.8±2.6 minutes following acepromazine-butorphanol and propofol anaesthesia in dogs. Therefore, the long time to standing recorded with ABP-combination in this study could be attributed to the doses of the preanaesthetic medications (acepromazine and butorphanol in the combination), independent of propofol administration which affects recovery characteristics as reported by Radney and Smith, (2018); Emmanuella *et al*., (2020); Salla *et al. (*2013).

The onset of analgesia (5.0±2.6 minutes) obtained in this study can be attributed to presence of butorphanol and acepromazine in the combination as reported by Morton and Hall (2012) who stated that onset of analgesia is between 3 – 5 minutes and 5–7 minutes for acepromazine and butorphanol respectively in dogs following i.v injection. The duration of analgesia of 33.6±3.2 minutes recorded in this study differs with reports of Bolaji-Alabi and Adetunji (2018) who reported 124±1.4 minutes duration of analgesia following the use of acepromazine (0.03mg/kg), butorphanol (0.4mg/kg) and propofol (2mg/kg). The variation in the duration of analgesia with acepromazine and butorphanol premedication is dose dependent, according to Morton and Hall (2012); Stephanie *et al*. (2022); Bolaji-Alabi and Adetunji (2018),

which can last up to 4 hours in dogs. The duration of analgesia recorded is similar to the moderate degree of analgesia reported by Emmanuella *et al*. (2020). The lack of analgesia recorded with PRO-alone agrees with the reports of Tsai *et al*. (2007) and Morton and Hall (2012), who stated that propofol lacks analgesic properties. The differences in duration of intubation recorded between the treatments could be attributed to the presence of premedication in the ABP group as reported by Smith *et al*. (1993); Salla *et al*. (2013); Bolaji-Alabi and Adetunji (2018); Radney and Smith, (2018); Emmanuella *et al*. (2020). Stephanie *et al*. (2022); that the recovery characteristics usually varies with preanaesthetic medication, independent of propofol administration.

Effects on Physiological Variables

The significant ($p<0.05$) decrease from baseline_in rectal temperature in ABP-combination group can be attributed to thermoregulatory activities of acepromazine in the combination (Forney, 2017). The findings of this study is similar to the reports of Bolaji-Alabi and Adetunji (2018), who recorded 37.5±0.3^{o}C following the use of acepromazine-butorphanol-propofol anaesthesia in dogs. The non-changes in the rectal temperature in Propofol group agrees with the reports of Morton and Hall (2012); who stated that effect of propofol on body temperature is dose dependent. Therefore, the non-changes in the rectal temperature could be attributed to dose of propofol used in this study.

The non-variation in heart rate within the groups is similar to the findings of Bufalari *et al*. (1997) who reported no significant decrease in heart rate in dogs. Bolaji-Alabiand Adetunji (2018), reported significant ($p<0.05$) increase in heart rate in dogs following acepromazine-butorphanol-propofol anaesthesia over a period of 120minutes, which is at variance with the findings of this study. The non-decrease in heart rate in Propofol alone group is at variance also with the findings of Cattai, (2018) who reported a significant ($p<0.05$) increase in heart rate in dogs following propofol induction. The non-significant changes in heart recorded in this study can be attributed to the use of appropriate doses for all the drug treatments, as changes in heart rate are often associated to overdose of either acepromazine or propofol (Merik, 2004; Bolaji-Alabi and Adetunji, 2018; Emmanuella *et al*., 2020; Stephanie *et al*., 2022). The significant ($p<0.05$) difference in heart rates between ABP combination and Propofol alone groups is similar with the report of Dzikiti *et al.* (2009) who reported changes in heart rates between propofol and combination of acepromazine – butorphanol on propofol anaesthesia.

The significant ($p<0.05$) decrease in respiratory rate with ABP-combination from baseline after initial increase is similar with findings of Bufalari *et al*. (1997); Stephanie *et al*., (2022) who reported significant decreases in respiratoty rate with apnoea, following propofol induction in dogs premedicated with acepromazine and butorphanol. The fluctuation in respiratory rate with ABP-combination is similar to report of a previous study by Anandmay *et al.* (2012); Emmanuella *et al*. 2020. Stephanie *et al*. 2022), who reported a significant ($p<0.05$) decrease in respiratory rate after propofol, butorphanol and buprenorphine anaesthesia. The non-significant decrease in respiration recorded in Propofol alone group is similar with the report of Dzikiti et al. (2009) who reported no significant decrease in respiratory rate in goats. The significant ($p<0.05$) changes in respiratory rate obtained in ABP combination group is at variance with report of Dzikiti *et al*., (2009) who reported no significant changes in respiratory rate following acepromazine and butorphanol on propofol anaesthesia in goats. The decrease in respiratory rate recorded in this study can be attributed to cardiopulmonary effects of acepromazine and butorphanol on propofol anaesthesia and may also be due to species difference (Umar *et al*., 2006; Dzikiti *et al*., 2009).

Conclusion

This study has shown that ABP-combination TIVA provides balanced anaesthesia with longer duration of anaesthesia that lasted for 30.0±5.8 minutes and analgesia of 33.6±3.2 minutes, whereas, Propofol alone produced a shorter duration of anaesthesia that lasted 13.6±4.8 minutes with no analgesia. Both ABP combination and Propofol alone recorded fast onset of anaesthesia with minimal effects on physiological parameters and the dogs recovered uneventfully from anaesthesia. The ABP combination therefore, can be used for clinical and surgical trials following the quality of anaesthesia it produced.

Acknowledgement

The authors acknowledge the Department of Animal Health and Production Technology, Federal Polytechnic Mubi for Sponsorship of the research and the Department of Veterinary Surgery and Radiology, University of Maiduguri for providing the facilities for the research.

Conflict of Interests

The authors have no conflict of interest to declare.

Authors' Contribution

UMA and MA conceptualized and supervised the work. GRH conducted the laboratory work, analysed the data and wrote the draft manuscript. All authors have read and approved the final manuscript.

REFERENCES

Adetunji, A., Ajadi, R, A., Adewoye, C. O. and Onyemakinde, B. O. (2002). Total intravenous anaesthesia with propofol repeat bolus versus continous propofol infusion technique in xylazine premedicated dogs. *Israel Journal of Veterinary Medicine, 57*(4), pp.139-144.

Anandmay, A. K., Dass, L. L. and Sharma, A. K. (2012). Clinico-anaesthetic changes following administration of propofol alone and in comibnation of buprenorphine in dogs. *Indian Veterinary Journal, 89*(10), pp.77-79.

Bajwa, S. J., Bajwa, S. K. and Kaue, J. (2010). Comparison of two drugs combination in total intravenous anaesthetics: propofol-ketamine and propofol-fentanyl. *Saudi Arabian Journal of Anaesthesia, 4*(2), pp.72-79. DOI**:** 10.4103/1658-354X.65132

Bolaji-Alabi, F.B. and Adetunji A. (2018). Anaesthetic and cardiopulmonary parameters of dogs administered propofol_acepromazine-butorphanol or propofol- acepromazine buprenophine anaesthesia. *Journal of Veterinary Medicine and Animal Health. 10(7). pp.180-184.* https://doi.org/10.5897/JVMAH2018.0682

Branson, K. R. (2007). Injectable and alternative anaesthetic techniques. In W. J. Tranquilli, and L. a. Jones (Ed.), *Veterinary Anaesthesia and Analgesia* (4th ed.,). Blackwell Publishing Limited. pp. 273-299.

Bufalari, A., Miler, S. M., Short, C. E and Gianoni, G. (1997). The use of propofol for induction of anaesthesia in dogs premedicated with acepromazine, butorphanol and acepromazine-butorphanol. *New Zealand Veterinary Journal, 45*(4), pp.129-134. https://doi.org/10.1080/00480169.1997.36012

Cattai, A., Rabozzi, R., Ferasin, H., Isola, M. and Franci, P. (2018). Haemodynamic changes during propofol induction in dogs. new findings and approach of monitoring. *BMC Veterinary Rsearch, 64*(5), pp.590-598.

Cicek, M., Koroglu, A., Demirbilek, S., Teksan, H. and Ersoy, M. O. (2005). Comparison of propofol-alfentanil andpropofol-remifentanil anaesthesia in percutaneous nephrolithotripsy. *European Journal of Anaesthesiology, 22*, pp.683-688. *DOI:* 10.1017/S0265021505001134

Dzikiti, T. B., Stegmann, G. F., Hellenbrekers, L. J., Auer, R. E. and Dzikiti. I. N. (2009). Sedative and cardiopulmonary effects of acepromazine, midazolam and butorphanol, acepromazine-butorphanol on propofol anaesthesia in goats. *Journal of South African Veterinary Association, 80*(1), pp.10-16. https://doi.org/10.4102/jsava.v80i1.162

Emmanuella, A.O.S., Adeniran, A. and Oluwaseun S.A., (2020) Comparison of two neurolept agents on propofol-isoflurane anaesthesized Nigerian indigenous dogs. (2020). *Alexandria Journal of Veterinary Science*, 65(1) pp. 96-101. DOI: 10.5455/ajvs.77317

Elks, J. (2014). *The dictionary of drugs: chemical data, structures and bibliographies.* Springer Science Business Media. Dordrecht: pp.114.

Forney, B. (2017). *www. acepromazine maleate for veterinary use.* Retrieved Sptember 15, 2019, from www.wedgewoodpetrx.com/learning-center/professional-mono.

Hall, L. W., Clarke, K. W. and Trim, C. M. (2001). *Veterinary Anaesthesia* (10th ed.). Edingburg, UK.: WB Sauders. pp.80-97.

IBM - Statistical package for social sciences, 2011 (Version 20.0).

Kajoma K., Nishimura, R., Mutoh, T., Hong, S. H., Mochizuki , M. and Sasaki, N. (2002). Effect of medetomidine-midazolam, acepromazine-butorphanol and midazolam-butorphanol on induction dose of thiopental and propofol and on cardiopulmonary changes in dogs. *American Journal of Veterinary Research, 63*(12), pp.1671-1679. https://doi.org/10.2460/ajvr.2002.63.1671

Matthews N.S. (2007). Inhalant anaesthetics. In Chris Seymour, *BSAVA Manual of Canine and Feline Anaesthesia and Analgesia* 2nd ed., 21(1) pp 47 - 48. Gloucester: British Small Animal Veterinary Association.

Merik. E. P. (2004). Propofol: therapeutic indication and the side effects:. *Current Pharmaceutical design., 10*(29), pp.3639-3649. http://dx.doi.org/10.2174/1381612043382846

Mohammad, N., Zafar, M.A., Mohammad, G., Masood, M. Z., Manzoor, A. and Sarfaraz. I. (2009).Comparative efficacy of propofol, thiopental sodium and combination of propofol with ketamine hydrochloride in dogs. *Pakistani Veterinary Journal, 29*(1), pp.11-15.

Morton. I. K. and Hall, J. M. (2012). *Concise Dictionary of Pharmacological Agents: Properties and Synonyms.* Neitherlands: Springer Science and Business Media. pp.101. https://link.springer.com/book/10.1007/978-94-011-4439-1 Musk, G. C., Pang, D. S., Beths, T. and Flaherty, D. A. (2005). Target-controlled infusion of propofol in dogs: evaluation of four targets for induction of anaesthesia. *The Veterinary Records, 157*, pp.766-770. https://doi.org/10.1136/vr.157.24.766

Radney, D.I. and Smith, L.J. (2018). Comparison of the effects of alfaxalone and propofol with acepromazine, butorphanol and or doxaphram on laryngeal motion and quality of examination in dogs. Veterinary Anaesthesia and Analgesia. 45(3)pp.241-249.https://doi.org/10.1016/j.vaa.2017.08.014

Salla, K. Bennett, R.C., Restitutti, F., Junnila, J., Raekallio, M. and Vainio, O. (2014). A comparison in dogs of meditomidine with or without MK-467 and the combination acepromazine-butorphanol as premedication prior to anaesthesia induced by propofol and maintained with isoflurane. *Veterinary Anaesthesia and Analgesia.* 41(2)pp.163-173. DOI: https//doi.org/10.111/vaa 12094

Smith, J. A., Gaynor, J. S., Bednarski, R. M. and Muir W.W. (1993). Adverse effect of administration of propofol with various preanaesthetic regiments in dogs. *Journal of American Veterinary Medical Association, 202*(7) pp.1111-1115.

Stephanie . C. D., Stephanie, A.K., Christopher, K.S, Sayge, M.S., Xiaojuan, Z and Reza, S. (2022). Effects of intravenous acepromazine and butorphanol on propofol dosage for induction of anaesthesia in healthy Beagle dogs. *Veterinary Anaesthesia and Analgesia,* 49(4):pp. 354-363.https://doi.org/10.1016/j.vaa.2022.03.002

Thurmon, J. C. and Short, C. E. (2007). History and overview of veterinary anaesthesia. In G. K. C., *Lumbs and Jones Veterinary Anaesthesia and Analgesia* (4th ed.,). Oxford: Blackwell Publishing Ltd. pp.3-6.

Tsai, Y. C., Wang, L. Y. and Yeh, L. S. (2007). Clinical comparison of recovery from total intravenous anaesthesia with prpofol and inhalational anaesthesia with isoflurane in dogs. *The Journal of Veterinary Medical Science/ Japanese Society of Veterinary Science., 69*, pp.1179-1182. https://doi.org/10.1292/jvms.69.1179

Umar, M. A., Yamashita, K., Kushiro, T. and Muir, W. W. (2006). Evaluation of total intravenous anaesthesia with propofol or ketamine-meditomidine-propofol combination in horses. *Journal of American*

Veterinary Medical Association., 228(8), pp.1221-1227. https://doi.org/10.2460/javma.228.8.1221

Umar, M. A., Yamashita, K., Kushiro, T. and Muir, W. W. (2007). Evaluation of cardiovascular effects of total intravenous anaesthesia with propofol or a combimation of ketamine-meditomidine-propofol in horses. *Asian Journal of Veterinary Research, 68*(2), pp.121-126. https://doi.org/10.2460/ajvr.68.2.121

Waelbers, Y., Vermoere, P, and Polis, I. (2009). Total intravenous anaesthesia in dogs:. *Diergenees Kundig Tijdschrift Journal, 78*, pp.160-169.

Yamashita, K. Wijayathilaka, T. P., Kushiro, T., Umar, M. A., Taguchi and Muir, W. W. (2007). Anaesthetic and cardiopulmonary effects of total intravenous anaethesia using midazolam, ketamine and meditomidine drug combination in horses. *Journal of Veterinary Medical Science, 69*(1), pp.7-13. https://doi.org/10.1292/jvms.69.7