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The Protocol Verification of Ketamine and Propofol Combination (Ketofol) by Heart Rate Variability in Dogs

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Abstract: In veterinary medicine, an appropriate Procedural Sedation and Analgesia (PSA) protocol is necessary for diagnostic procedures and treatment. To optimize methods for the use of a ketamine and propofol combination (ketofol) for PSA and to provide basic information pertaining to its cardiovascular effects, we investigated the cardiovascular effects of different concentrations of ketofol in beagles. Three dogs per group received either a single bolus of intravenous propofol 8 mg kg^{-1} (group P) or propofol 8 mg kg^{-1} in combination with different doses of ketamine (0.8 mg kg^{-1}, group 10:1; 2 mg kg^{-1}, group 10:2.5; 4 mg kg^{-1}, group 10:5). Heart rate variability was recorded for 3 min prior to anesthesia and at 0, 5, 10 and 30 min after administration of propofol or ketofol. Blood pressure was recorded before anesthesia and at 5, 10 and 15 min during anesthesia. To evaluate anesthesia time, the time from administration of propofol or ketofol to lifting of the head was recorded. Recovery from anesthesia was evaluated by observing the waking condition of the dogs after anesthesia in order to check for behavioral changes. The maximum heart rate during anesthesia was also measured. Ketofol showed a positive synergistic effect that complemented the opposing autonomic nervous system effects of each drug. Our results suggested that 10:2.5 ketofol may be a suitable and relatively safe PSA method for anesthesia in dogs.

Key words: Ketamine, propofol, ketofol, procedural sedation and analgesia, drug interaction, heart rate variability

INTRODUCTION

Procedural Sedation and Analgesia (PSA) is a sedation technique involving the use of sedatives, dissociative agents and analgesics alone or in combination. Analgesics are used to treat pain and sedatives and/or dissociative agents are used to alleviate fear and anxiety (Markovchick *et al*., 2010). PSA, previously referred to as "conscious sedation" is a state of moderate sedation that maintains cardiorespiratory function and retains the subject's ability to respond purposefully to verbal commands and/or light tactile stimulation (Doyle and Colletti, 2006). In humans, PSA is the standard of emergency medical care (Willman and Andolfatto, 2007). The goals of PSA are to relieve fear and anxiety, provide analgesia, sedation and amnesia as needed for an unpleasant procedure in order to minimize adverse effects ofagents, maintain cardiorespiratory functions and control motor behavior. The ideal agents for PSA satisfy all of these goals have a rapid onset and short duration, have the same effect irrespective of the route of administration and are reversible, safe at all ages and simple to administer. Because no such ideal single agent exists, PSA agents must be chosen in combination in order to provide as many of the desired goals as possible (Arora, 2008; Innes *et al*., 1999).

Propofol, a 2, 6-diisopropylphenol was developed in Europe in the 1970s. Its mechanisms of action include inhibitory neurotransmission mediated by Gamma-Aminobutyric Acid (GABA) (Aboeldahab *et al*., 2011). This non-opioid, non-barbiturate intravenous sedative-hypnotic agent has a rapid onset and short

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duration as well as a smooth induction and recovery. Its adverse effects include dose-related apnea and cardiovascular depression such as hypotension, decrease of cardiac output and bradycardia (Da Silva *et al*., 2011). Also, propofol provides little analgesia. Its common uses include the induction and maintenance of general anesthesia, sedation for intubated, mechanically ventilated adults and sedation for procedures such as colonoscopy (Daabiss *et al*., 2009).

Ketamine, a phencyclidine hydrochloride derivative developed in the 1960s (Freese *et al*., 2002) is a non-competitive N-methyl-d-aspartate receptor antagonist. It binds to opioid μ and σ receptors as well (Sarton *et al*., 2001). Ketamineinduces a state referred to as "dissociative anesthesia" which is associated with intense feelings of dissociation from the environment attributable to functional and electrophysiological interruption of connections between the thalamo-neocortical and limbic regions of the brain (Arora, 2008). It provides sedation, amnesia and analgesia and has anticonvulsive and neuroprotective properties (Freese *et al*., 2002; Mion *et al*., 2003; Strayer and Nelson, 2008). Unlike propofol, ketamine causes tachycardia, increased blood pressure and cardiac output and minimal respiratory depression. Its adverse effects are mainly psychomimetic and involve dizziness, hallucinations and frightening dreams (Javery *et al*., 1996). Ketamine is used in trauma and emergency surgical procedures in both humans and animals (Freese *et al*., 2002; Way, 1982).

These two completely different sedatives mitigate each other's deficits due to their opposing physiological effects (Green *et al*., 2011). The advantages of using both ketamine and propofol in combination (ketofol) include analgesia, rapid recovery, preservation of airways and maintenance of spontaneous respiration and haemodynamic stability (Saeed, 2011). It has therefore been suggested that ketofol provides good total intravenous anesthesia. Ketofol has been widely studied and evaluated as a sedative agent with encouraging results, primarily based on use in human emergency departments (Aboeldahab *et al*., 2011; Da Silva *et al*., 2011; Morse *et al*., 2003). However, the evaluation of the effectiveness of different concentrations of ketofol has not been studied in depth (Daabiss *et al*., 2009).

Heart Rate Variability (HRV) is a measure of the variation in the time interval between consecutive heart beats. HRV is influenced by many factors including anesthetics, depth of anesthesia, surgical manipulation and patient body temperature (Eckberg, 1983; Latson *et al*., 1992). It has been suggested that HRV affords a means of evaluating the response to anesthesia.

A sedation protocol like PSA is needed for short, painful diagnostic procedures and treatment in veterinary medicine and the application of an appropriate PSA protocol may provide safety and convenience for clinical veterinarians. Additionally, the evaluation of different concentrations of ketofol may provide useful information pertaining to the effects of different concentrations of ketofol for PSA in human medicine. The aims of the current study were to develop and evaluate practical methods for ketofol administration in veterinary clinical medicine and to provide basic information regarding the cardiovascular effects of ketofol by evaluating HRV.

MATERIALS AND METHODS

Animals: Twelve, 1 year old, 7-10 kg male beagles provided by Orientbio Inc. were housed in an air-conditioned room with a 12 h light-dark cycle under controlled temperature (23±2°C) and humidity (55±10%). The Institutional Animal Care and Use Committee of the Chonnam National University approved the protocols for this animal study (CNU IACUC-YB-R-2014-21) and the animals were cared for in accordance with the Guidelines for Animal Experiments of the Chonnam National University.

Preparation of the ketofol mixture: Propofol (POFOL INJ; Jeil Pharm, Seoul, Korea; 10 mg mL^{-1}) and ketamine (YUHAN KETAMINE 50 Inj.; YUHAN Corporation, Seoul, Korea; 50 mg mL^{-1}) for injection were diluted with water to concentrations of 8 and 25 mg mL^{-1}, respectively. Ketofol was constituted as a 10:1 mixture of propofol 80 mg and ketamine 8 mg, a 10:2.5 mixture of propofol 80 mg and ketamine 20 mg and a 10:5 mixture of propofol 80 mg and ketamine 40 mg.

Experimental procedures: All physiological measurements were performed in a laboratory with standardized experimental conditions including slightly dimmed lighting and thermo-neutral temperature (22-25°C). The animals were fasted for 12 h prior to administration of anesthesia. At the time of the experiment, an intravenous line was introduced into a cephalic vein. Subsequently, a Heart Rate Variability (HRV) transmitter was fitted to the dog's thorax and was allowed to stabilize for 15 min. HRV was then recorded for 5 min prior to the administration of anesthesia and Blood Pressure (BP) was measured. The control group was administered a single bolus of propofol 8 mg kg^{-1} intravenously (group P, n = 3). Experimental groups were administered either a single bolus of 10:1 ketofol 1 mL kg^{-1} (group 10:1, n = 3), 10:2.5 ketofol 1 mL kg^{-1} (group 10:2.5, n = 3) or 10:5 ketofol 1 mL kg^{-1} (group 10:5, n = 3).

HRV evaluation: HRV measurements were taken for 3 min at 0, 5, 10 and 30 min after the administration of propofol or ketofol. Telemetric measurements of heart beat activity (R-R interval) were performed using a Polar S810i device (Polar Electro Co., Kempele, Finland). At the end of each measurement, the stored data were transmitted to a computer via a serial interface. The R-R intervals and information relating to the corresponding autonomic activities were then analyzed using Polar Pro Trainer Software (Polar Electro Co.) which allowed for automatic correction of the recorded tachogram. All files were examined manually for artifacts. Artifact-free HRV signals were analyzed using HRV Analysis Software Version 1.1 (Biomedical Signal Analysis Group, Kuopio, Finland) in the time and frequency domains. Time domain parameters including the mean Heart Rate (HR), the Standard Deviation of NN intervals (SDNN) and the Root Mean Square of Successive Differences of NN intervals (RMSSD) were calculated. In the frequency domain, parameters including Very Low Frequency (VLF), Low Frequency (LF), High Frequency (HF), the LF/HF ratio, and Total Power (TP) were calculated.

Measurements of cardiovascular parameters: BP was measured before anesthesia and at 5, 10 and 15 min after administration of propofol or ketofol. The highest measured HR under anesthesia maximum Heart Rate (max HR) was also recorded.

Recovery time from anesthesia and behavioral changes: To evaluate recovery from anesthesia, the time from administration of propofol or ketofol to Head up Time (HT) and Sternal position Time (ST) were measured. Waking behavior was also observed to assess behavioral changes.

Statistical analysis: All values are expressed as the mean±standard error. Data were analyzed using a one-way repeated analysis of variance followed by the Duncan comparison test. A significant difference was defined as $p<0.05$.

RESULTS

HRV time domain analysis: The time domain results are summarized in Table 1. The HR of group 10:1 was statistically higher than that of group P at 5 min ($p<0.05$). The HR of group 10:2.5 was not statistically different from that of group P while the HR of group 10:5 was statistically higher than that of group P at 0, 5, 10 and 30 min ($p<0.05$). The SDNN for each group did not differ statistically. The RMSSD of group P was significantly higher than that of group 10:1 at 5 min ($p<0.05$).

HRV frequency domain analysis: The frequency domain results are summarized in Table 2. There were no significant differences among the groups for VLF, LF, HF and TP. The LF/HF ratio of group 10:5 was significantly lower than that of group 10:1 at 30 min ($p<0.05$).

Cardiovascular parameters: BP measurement results are summarized in Table 3. Systolic BP (SBP) and Diastolic BP

Table 1: The comparisons of time domain components among the propofol and ketofol administration groups

	HR (beat/min)				SDNN (sec)				RMSSD (msec)			
Time (min)	P	10:1	10:2.5	10:5	P	10:1	10:2.5	10:5	P	10:1	10:2.5	10:5
BA	113.66±12.44^a	114.66±12.41^a	113.66±12.44^a	113.66±12.44^a	47.93±8.49^a	58.20±18.19^a	47.93±8.49^a	47.93±8.49^a	13.26±2.04^a	13.03±1.91^a	13.26±2.04^a	13.26±2.04^a
0	175.33±19.81^a	208.33±6.96^{ab}	205.66±8.19^{ab}	233.33±2.40^b	14.90±7.73^a	5.60±0.92^a	12.20±2.13^a	4.43±2.54^a	4.83±2.24^a	1.53±0.08^a	3.10±0.68^a	1.36±0.49^a
5	113.33±13.56^a	155.66±11.02^b	132.33±10.03^{ab}	158.66±6.88^b	29.90±4.75^a	18.93±3.94^a	27.70±8.98^a	19.03±0.87^a	18.43±4.93^b	6.46±2.78^a	10.73±2.09^{ab}	7.90±2.17^{ab}
10	127.33±10.33^a	174.00±17.00^b	172.00±1.73^b	197.00±23.06^b	43.03±18.01^a	34.26±7.70^a	34.46±5.47^a	22.96±6.93^a	8.66±2.66^a	6.53±2.19^a	5.63±0.27^a	4.36±1.62^a
30	119.00±7.54^a	126.33±14.09^a	143.00±11.84^{ab}	162.33±30.84^b	69.73±13.78^a	70.83±15.41^a	57.70±10.26^a	35.10±5.51^a	11.53±0.46^a	12.73±2.69^a	9.53±2.74^a	8.36±0.98^a

Data are mean±SE. SE: Standard Error, BA: Before Anesthesia; HR: Mean Heart Rate; SDNN: Square root of variance of all R intervals; RMSSD: Root Mean Square of Successive Differences of RR intervals. ^{a,b}Means with different letters were statistically different among groups ($p<0.05$)

Table 2: The comparisons of frequency domain components among the propofol and ketofol administration groups

	VLF				LF			
Time (min)	P	10:1	10:2.5	10:5	P	10:1	10:2.5	10:5
BA	1,965.00±962.41^a	4,185.33±3,152.31^a	1,965.00±962.41^a	1,965.00±962.41^a	795.00±343.80^a	624.66±213.92^a	795.00±373.80^a	795.00±373.80^a
0	136.33±125.92^a	3.66±2.18^a	12.00±8.62^a	2.33±1.20^a	169.33±163.85^a	5.66±2.72^a	78.66±34.16^a	6.00±5.50^a
5	144.00±57.00^a	220.33±101.33^a	196.00±136.18^a	195.33±19.46^a	250.66±148.38^a	50.66±16.12^a	543.66±417.95^a	143.66±28.35^a
10	1,075.33±759.58^a	996.00±424.83^a	866.66±228.36^a	493.33±218.36^a	380.00±245.21^a	284.66±90.80^a	101.66±42.84^a	107.33±72.85^a
30	3,800.66±1,374.00^a	3,921.66±1,653.39^a	2,802.33±631.36^a	498.66±115.50^a	701.00±323.20^a	820.33±219.34^a	494.33±276.54^a	289.33±110.43^a

	HF				LF/HF (ratio)				TP			
Time (min)	P	10:1	10:2.5	10:5	P	10:1	10:2.5	10:5	P	10:1	10:2.5	10:5
Pre	56.33±10.20^a	80.33±30.98^a	56.33±10.20^a	56.33±10.20^a	12.94±4.67^a	7.91±0.65^a	12.94±4.67^a	12.94±4.67^a	2,816.33±1,344.01^a	4,890.33±3,382.52^a	2816.33±1,344.01^a	2816.33±1,344.01^a
0	12.33±8.64^a	1.00±0.57^a	4.33±2.02^a	2.00±2.00^a	9.21±4.53^a	23.66±14.86^a	18.39±2.70^a	9.59±7.53^a	318.33±298.49^a	10.33±2.18^a	95.00±44.19^a	10.33±8.41^a
5	119.00±34.50^a	39.33±24.50^a	150.00±51.29^a	61.66±30.22^a	2.66±1.90^a	2.37±0.99^a	3.76±2.98^a	3.17±0.89^a	513.00±157.01^a	31.066±126.01^a	889.00±558.43^a	400.00±33.48^a
10	30.33±7.88^a	26.00±8.14^a	31.33±12.71^a	21.66±10.34^a	9.99±4.97^a	12.63±4.41^a	3.24±0.21^a	5.43±1.77^a	1,485.33±1,012.69^a	1,307.66±509.86^a	1,000.00±174.66^a	622.66±287.86^a
30	58.33±9.95^a	61.33±15.34^a	79.00±34.53^a	63.33±11.86^a	11.22±3.47^{ab}	13.16±2.05^b	5.66±1.72^{ab}	4.27±0.89^a	4,560.00±1,693.52^a	4,803.33±1,752.08^a	3,375.66±937.77^a	851.00±183.44^a

Data are mean±SE. SE: Standard Error; BA: Before Anesthesia; VLF: Very Low Frequence; LF: Low Frequence; HF: High Frequence; TP: Total Power. ^{a,b}Means with different letters were statistically different among groups ($p<0.05$)

Table 3: The comparisons of blood pressure among the propofol and ketofol administration groups

	SBP (mmHg)				DBP (mmHg)				MBP (mmHg)			
Time (min)	P	10:1	10:2.5	10:5	P	10:1	10:2.5	10:5	P	10:1	10:2.5	10:5
BA	181.00±22.60^a	191.33±15.70^a	172.00±27.22^a	169.67±23.21^a	117.33±8.95^a	119.00±9.00^a	137.00±28.04^a	104.67±19.23^a	125.37±4.70^a	143.00±0.57^a	132.33±21.40^a	129.67±20.91^a
5	136.33±4.97^a	148.00±7.31^a	146.33±9.93^a	138.33±3.33^a	60.67±7.86^a	68.67±2.96^a	72.33±8.66^a	69.00±1.52^a	86.33±5.78^a	94.33±4.97^a	97.33±2.60^a	96.67±2.60^a
10	139.00±3.05^a	151.67±6.88^a	150.67±14.31^a	160.00±3.46^a	79.67±8.51^a	84.67±12.54^a	98.00±12.50^a	100.67±6.36^a	100.00±3.21^a	108.33±8.09^{ab}	119.00±8.38^{ab}	123.33±4.91^b
15	175.67±14.94^a	166.67±14.90^a	154.67±25.39^a	163.33±25.98^a	107.33±9.24^a	105.33±7.68^a	125.33±17.70^a	100.33±20.51^a	131.67±9.17^a	129.33±10.20^a	135.67±20.85^a	123.00±21.07^a

Data are mean±SE. SE: Standard Error, BA: Before Anesthesia; SBP: Systolic Blood Pressure; DBP: Dystolic Blood Pressure, MBP: Mean Blood Pressure. ^{a,b}Means with different letters were statistically different among groups ($p<0.05$)

Table 4: The comparisons of the head up time, sternal position time and maximum heart rate among the propofol and ketofol administration groups

Groups	HT (min)	ST (min)	Max HR (beat)
P	12:23±0:50^a	12:48±0:50^a	187±15^a
10:1	10:57±1:24^a	11:48±1:45^a	219±10^{ab}
10:2.5	11:47±0:20^a	12:13±0:20^a	219±10^{ab}
10:5	11:09±0:41^a	13:00±0:19^a	239±0^b

Data are mean±SE. SE: Standard Error; HT: Head up Time; ST: Sternal Position Time; max HR: the maximum Heart Rate. ^{a,b}Means with different letters were statistically different among groups ($p<0.05$)

(DBP) were not statistically different between the groups. The Mean BP (MBP) of group 10:5 was statistically higher than that of group P at 10 min ($p<0.05$). The max HR and HT results are summarized in Table 4. The max HR of group 10:5 was significantly higher than that of group P ($p<0.05$).

Recovery time from anesthesia and behavioral changes: HT and ST were not statistically different among the groups (Table 4). As the effect of the anesthesia dissipated, no behavioral changes were observed in groups P or 10:1. In group 10:2.5, however, abnormal behaviors such as howling or shivering were observed in one dog and abnormal behaviors were observed in all dogs in group 10:5.

DISCUSSION

In the current study, we compared HRV components and cardiovascular parameters of propofol and different concentrations of ketofol in beagles. HRV originates from the dynamic interaction between the multiple physiologic mechanisms that regulate the instantaneous HR. Short-term regulation of HR has been associated with the sinoatrial node which is influenced by both the Sympathetic Nervous System (SNS) and the Parasympathetic Nervous System (PNS) that branch from the Autonomic Nervous Systems (ANS). Increased SNS or decreased PNS activity promotes myocardium contraction and causes cardio acceleration. Conversely, decreased SNS activity or increased PNS activity results in cardio deceleration. Thus, HRV can be used as a quantitative marker of the ANS. Acharya *et al.* (2006), Bilchick and Berger (2006) and Niskanen *et al.* (2004). The individual response to anesthetic induction may be affected by autonomic dysfunction and changes in the sympathovagal balance (Fleisher, 1996). HRV analysis is based on two core components. The time domain analysis components are easy to calculate directly from the raw RR interval time series and can be assessed through observation of ANS activity (Sztajzel, 2004).

In the time domain components, HR is assessed as the mean heart rate which is calculated during the recording period. SDNN is the square root of the variance. A variance is mathematically equal to the total power of the frequency analysis, therefore, SDNN reflects the long-term components and circadian rhythms responsible for variability in the recording period. Furthermore, SDNN primarily indicates a reduction in dynamic complexity and thus, low SDNN signifies low HRV. RMSSD reflects an estimate of the parasympathetic regulation of the heart. Collectively, SDNN and RMSSD reflect the complexity and safety of the heart (Malik *et al.*, 1996). The assessment of the frequency domain of HRV takes the form of a Power Spectral Density (PSD) analysis. The frequency domain analysis provides information regarding the frequency distribution of the components of HRV and the amount of their power, thereby assessing the balance between SNS and PNS activity. Additionally, it assists in the identification of relationships between BP and HR and can be calculated based on a relatively short period of observation (DeBoer *et al.*, 1987; Malik *et al.*, 1996; Sztajzel, 2004). In the frequency parameters, the frequency range of VLF ranges between 0.0033 and 0.04 Hz. Generally, it reflects varying, slow modulation of the mean heart rate including sympathetic function, thermo-regulation processes and humoral influences of the renin-angiotensin-aldosterone system. LF which relates to the power spectrum range between 0.04 and 0.25 Hz, reflects both sympathetic and parasympathetic activity and is generally considered to be a strong indicator of sympathetic activity (Fleisher, 1996; Malik *et al.*, 1996). HF is represented by a band of power spectrum ranging between 0.15 and 0.4 Hz. It is generally considered to indicate parasympathetic (vagal) activity and also reflects respiratory function as it represents the NN variations which are caused by respiration. The LF/HF ratio reflects the global balance between the sympathetic and parasympathetic systems. Higher values represent domination of the sympathetic system while lower values reflect domination of the parasympathetic system (Fleisher, 1996; Wu *et al.*, 2012). TP is a short-term

estimate of the total power of PSD in the entire range of frequencies. TP indicates overall autonomic activity where sympathetic activity is a primary contributor (Arlt *et al*., 2003).

In the time domain analysis results from the current study, the HR of each group was increased at 0 min, decreased at 5 min and increased again at 10 min. Subsequently, the HR of each group showed a downward tendency. These changes in HR reflected the response to changes of the stages and depths of anesthesia. At 0 min, HR was significantly increased in group 10:5 compared with group P. At 5 min, HRs in groups 10:5 and 10:1 were higher than the HR of group P. HR was significantly increased in group 10:5 compared with group P at 10 min. The study conducted by Komatsu *et al.* (1995) showed the sympathetic activation expected from the use of ketamine. In the current study, this rapid increase in HR in group 10:5 was caused by a cardiovascular stimulation effect of ketamine in a brief space of time. SDNN was not significantly different between the groups. The RMSSD measurements from each group, except group 10:1, were not significantly different. The RMSSD of group 10:1 was significantly decreased compared to that of group P at 5 min. Administration of ketamine is known to increase sympathetic activation, however, the RMSSD was lowest in the 10:1 ketofol group which included the lowest ketamine concentration in the current study. Although, further study is required to elucidate the mechanism underlying this result, it suggests that 10:1 ketofol may not be suitable for PSA in dogs. In the frequency domain components, VLF, LF, HF and TP were not significantly different between the groups in the current study. The LF/HF ratio of group 10:5 was statistically lower than that of group 10:1 at 30 min. These unexpected results were likely due to large individual differences among the test animals. The using of the 10:5 ketofol which included highest ketamine concentration resulted in higher MBP and max HR than when profofol was used. These results were similar to those observed for the time domain HR of group 10:5. Therefore, the 10:5 ketofol group showed the highest potential for the induction of ketamine side effects. HT and ST were not statistically different among the groups, suggesting that increased concentrations of ketamine did not affect the anesthesia time. As the effect of the anesthesia dissipated, behavioral changes were observed in all dogs in the 10:5 ketofol group. It suggests that 10:5 ketofol may not be suitable for PSA in dogs.

CONCLUSION

Our results suggested that the 10:2.5 ketofol concentration was comparatively suitable for prevention of the cardiovascular depression commonly associated with propofol and may be an appropriate and safe PSA Method for anesthesia in dogs. However, further research pertaining to the using of ketofol for PSA is required.

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