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Physiological Response of Bali Cattle on Anesthetic of Ketamine and Propofol

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Abstract. General anesthesia in Bali cattle using ketamine and propofol has not been reported. Therefore, research is needed to determine the dosage, time of anesthesia and physiological response of ketamine, propofol, and combinations of both (ketafol). Twelve male calves, weighing 25-45 kg with age of 2-4 months were used in this research. Physiological changes in the cardiovascular and respiratory system, also body temperature was monitored using a physiograph tool. All calves were premedicated with xylazine (0.1 mg/kg BW) intramuscularly, and induced with ketamine (2 mg/kg BW), propofol (2 mg/kg BW) and ketafol (1 mg/kg BW ketamine and 1 mg/kg BW propofol) intravenously after 10 minutes. Ketamine induced calves showed results of induction time after 4.75 ± 1.73 minutes, duration of anesthesia is 13.03 ± 1.15 minutes, and recovery time is 12.01 ± 5.05 minutes. The induction time using propofol is 2.50 ± 0.58 minutes, duration of anesthesia is 15.50 ± 1.91 minutes and recovery time is 2.75 ± 0.96 minutes. Calves induced with ketafol produced5.00 ± 1.41 minutes for induction time, duration of anesthesia was 14.00 ± 1.83 minutes, and recovery time was 4.50 ± 0.58 minutes. The calves that were induced with ketamine, propofol, and ketafol show that the induction time and duration of anesthesia are not significantly different, but for propofol's recovery time was significantly lower compared with ketamine, but not significantly different from ketafol. Anesthesia using propofol or ketafol can be used in Bali cattle because the physiological changes in the cardiovascular and respiratory system are more stable and no extreme changes was found.

Key words: anesthesia, ketamine, propofol, physiological response, Bali cattle.

I. INTRODUCTION

Surgery cannot be performed when anesthesia not implemented, makinganesthesia a strategically very important stage in surgery. History has shown thatknowledge in surgery undergoes a rapid revolution after ether was discovered as anesthesia by William Thomas Green Morton in 1846 [1] [2]. General anesthesia has greater risk than surgical procedure because the life of an anesthetized patient could be threatened. A selection for an ideal anesthetic agent is needed in order to produce analgesia, sedation, relaxation, safety and comfort for the body's vital systems, economical, and easy to apply. Until now,there is

noanesthesia that passedthe ideal requirements[3].

General anesthesia is often used and declared safe in animals, especially inhalation anesthesia that is used in small animals. But the anesthetic inhalation requires a complicated and expensive machine, the induction time (onset) was relatively slow, and also impractical for surgery cases outside clinic. Inhalation anesthetics such as halothane can lead to organ toxicity and causes pollution of the individuals who were in the operating room. Individuals that were exposed to subclinical halothane may result in livermalfunction [4]. In addition, the inhalation anesthetics such as nitrous oxide and anesthetic gas that vaporized by halogen can result in environmental pollution and depletion of the ozone layer [5].

The use of general anesthesia throughinjection or inhalation in Bali cattle has not been reported. According to [6], anesthesia in cattle has some disadvantages such as the occurrence of hypersalivation, limited peripheral blood vessels making it difficult to do intravenous anesthesia, anatomical shape of the larynx making the intubation more complicated and often caused laryngospasm. Restraining Bali cattle is difficult, making it hard to do an intravenous injection. With these difficulties, the combination of intramuscular and intravenous anesthesia methods is the only solution available to do anesthesia [7]. Therefore, components in intramuscular anesthesia used in cattle should have a rapid onset and a small amount of volume so the drugs canbe administered quickly. A fast onset of the drugs also must have a wide margin of safety, immediately give effect of hypnosis, as well as a strong analgesia [6].

Parenteral anesthetics that can be given intravenously is propofol [8]. Propofol is a parenteral substance and an induction agentin general anesthesia, especially inhalational anesthetic [9] [10]. Propofol has a short recovery time, but it can lead to bradycardia and a high dosage of propofolcan risk the patient's life. Ketamine can be combined with propofol to lower propofol's dosage and reducing the influence of cardiovascular depressiondue to propofol [11]. Dosage of propofol in small ruminants such as goat is 2-6 mg/kg BW [12].

Propofol was a parenteral anesthetic agent that was introduced in veterinary medicine practice in the 1990s. Propofol, if administered intravenously and at high dosage can cause cardiovascular depression characterized by a decrease in blood pressure due to a decrease in cardiac output [10]. Propofol's anesthetic influence works at GABA receptor [13]. Propofol will increase the effect of GABA receptor

which has the function to inhibit central nervous system and increasing Cl conduction that causes hyperpolarization that will decrease excitability of the cells, making the muscles more relaxed [14] [13]. Propofol's effectwill eliminatethe sense awareness and a good muscle relaxant, causing arterial hypotension, bradycardia, cardiovascular and respiratory depression, especially if given quickly with a high dose [15]. Propofol is very safe for animals with liver and kidney dysfunction sincemetabolism on propofol is very fast [16] [17].

Ketamine is from phencyclidine group with 2-(0-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride formula [18] and is a type of general anesthetic injection thatoften chosen for pet such as dogs that can be administered intramuscularly and intravenously. Ketamine belongs to a dissociative anesthesia from a non-barbiturate groupwitha strong pain relief and does not cause drowsiness [19] [20]. Ketamine produces anesthetic effect through a mechanism that acts on N-methyl-D-aspartate (NMDA) receptors. Inhibition on NMDA receptors with a low dosage of ketamine will produce a good analgesic effect [13]. Ketamine also prolongs the action of GABA (Gamma Amino Butyric Acid), an inhibitory neurotransmitter in brain that works with blocking the binding at the end of the nerve [21]. The usage of ketamine alone will cause poor muscle relaxation and will cause muscle spasms in the dog with a short duration of the anesthesia. An anesthesia dosage for ketamine in calves is 2-5 mg/kg BW when administered intravenously or 10 mg/kg BW when administered intramuscularly with xylazine as the premedication [12].

To overcome these side effects, ketamine is often combined with a hypnotic sedative premedication from α2-adrenoceptor group like xylazine or benzodiazepine. Xylazine is one of the alpha2-adrenoceptor stimulant group that produces sedation effect, muscle relaxation, and analgesia. Xylazine works through a mechanism that inhibits parasympathetic tone, for it activates post-synaptic-α_2-adrenoseptor that caused mydriasis, muscle relaxation, decreased heart rate and peristaltic movement, relaxation of the gastrointestinal tract, and sedation. Xylazine's activity in the central nervous system works through activation or stimulation of α_2-adrenoseptor, causing a decrease in the sympathetic discharge and reducesnor-epinephrine and dopamine excretion that makes relaxation in muscles by inhibiting the impulses in intraneural transmission at the central nervous system and can cause vomiting. Xylazine'srecommended dosage in cattle is

0.11 to 0.22 mg/kg BW intramuscularly [12].

The combinations of ketamine and propofol in pets, especially dogs have been reported and can be used as an alternative general anesthetic inhalation when giventhrough an intravenous drip (gravimetric method) [22]. In Bali cattle, ketamine and propofol usage for anesthesia have not been reported, therefore, a data quality of anesthesia is neededin order to understand if the anestheticcan be used for a long-term anesthesia in Bali cattle. Until now, propofol dosage in cattle has not been reported; but in dogs, cats, monkeys, and small ruminants such as goat has been widely reported. Given the usage of the anesthetic ketamine and propofol on Bali cattle have never been reported, it is necessary to do a research with the purpose of knowing how the physiological responses on Bali cattle, especially calvestowards ketamine, propofol, and combinations of both for anesthesia usage. The other goal is to determine the dosage, induction time, duration, and recovery time of ketamine, propofol, and combinations of both.

II.MATERIALS AND METHODS

Twelve male calves weighing 25-45 kg and aged 2-4 months were used in this research. The calves were adapted for 14 days before given treatment. During the adaptation process, all the animals were released from internal parasitic worms by giving the drug orally [16].

Physiograph BSM-800 model (Nihon Kohden®) were used to monitor changes in physiological parameters during anesthesia. The entire physiological parameters can be measured simultaneously during anesthesia. The parameters observed in this study are induction time, duration of actions, recovery time, respiratory rate, oxygen saturation, heart rate, CRT (Capillary Refill Time) value, and rectal temperature.

Before anesthetized (minute 0) measurement on all parameters was carried out, continued by parameter measurement every 10 minutes (calculated from the time of anesthesia). Before treatment, the animals were fasted for 18 hours and were not given any water to drink three hours before treatment [13].

Research carried out using three types of treatments and four calves as replicates for each treatment.**P1(XK)**: Xylazine (0.1 mg / kg BW) were injected IM in the gluteus muscle and a 10 minute IV inducement was carried out in the jugular vein using ketamine (2 mg / kg BW); **P2(XP):** Xylazine (0.1 mg / kg BW) were injected IM in the gluteus muscle and a 10 minute IV inducement was carried out in the jugular vein using propofol (2 mg / kg

BW); **P3 (X-KP):** xylazine (0.1 mg / kg BW) were injected IM in the gluteus muscle and a 10 minute IV inducement was carried out in the jugular vein using a combination of ketamine and propofol (1 and 1 mg / kg BW)

Anesthesia Measurement

Induction timeis the time measured from the beginning of injection until the onset of anesthesia, namely the disappearance of pain (clamped on the ears, tail, and interdigit), loss of reflexes (reflex eyelid, pupil, and pedals), and eyeballs towards ventrocantus. ***Duration of action***is the time measured from the starting point of the anesthesia to start workingmarked by disappearance of pain to the animal began to gain consciousness(movement of the tail, legs, ears or head), pain response (clamped with tweezers on the ears, tail, and interdigit), presence of animal sound, presence of reflexes (eyelid, pupil, and pedals).***The recovery time/ period***is the time measured from the animals began to gain consciousness until the animal be able to stand.

Respiration Frequency Measurement

Bottom panel slot of ECG / RESP of physiographic tool is connected with the slot that connects patients with the code AC-800PJ with three electrodes. Place the red electrode (R) and green electrode (F) so that the lungs are between the two electrodes. Installation of the electrode made in the same way by electrocardiogram (ECG).

Heart Rate Measurement

Bottom panel slot of NIBP (non-invasive blood pressure) is connected with a slot that connects patients with AP-860PA code slot. At the end of the slot, the small size cuff (Model YS-025P4, diameter of 18-26 cm) was installed. The cuff was installed on one third the proximal radius of the area to measure the brachial artery blood pressure [23]. Monitoring of heart rate, respiratory rate, rectal temperature, oxygen saturation, and CRT value automatically readable on physiograph monitor.

Research Design and Statistical Analysis

The study design is using Complete Randomized Design (CRD) and the data were analyzed by analysis of variance (Anova). If there is any real difference between treatments, Duncan's Multiple Regional Test will be carried out with a confidence interval of 95% and 99% [24].

III.RESULTS AND DISCUSSION

Anesthesia time

The average values of the induction, duration of anesthesia, and recovery time of anesthetic ketamine and propofol on Bali cattle, are presented in Table 1.

Table 1. The average value ± standard deviation (minutes) induction time, duration of anesthesia, and recovery time of anesthetic ketamine, propofol, and combinations of ketamine-propofolon Bali cattle.

Treatment Anesthesia	**Time (min)**		
	Induction	**Duration**	**Recovery**
P1 (XK)	4.75±1,73a	13.03±1,15a	12.01±5,05aα
P2 (XP)	2.50±0,58a	15.50±1,91a	2.75±0,96b β
P3 (X-KP)	5.00±1,41a	14.00±1,83a	4.50±0,58b β

Information : Xylazine sedation dose of 0.1 mg / kg bw intramuscularly, then P1 (XK): 10 minutes later induced intravenously with ketamine (2 mg / kg) .; P2 (XP): 10 minutes later induced intravenously with propofol (2 mg / kg); P3 (X-KP): 10 minutes later induced intravenously with propofol ketamin- mixture (Ketapol) (1 and 1 mg / kg); In the column (anesthesia time) letters (a, b, c, d) different show significantly different (P <0.05), letter (α, B,δ) Different show significantly different (P <0.01).

The calves that were premedicated withxylazine and induced with ketamine (P1),the time needed for induction is 4.75±1.73 minutes and the duration of anesthesia is 13.03±1.15 minutes while the longest recovery time is about 12.01±5.05 minutes. Premedication of xylazine and induced with propofol (P2) had the most rapid induction time of 2.50±0.58 minutes, where the longest duration of anesthesia were 15.50±1.91 minutes and the shortest recovery time wassignificantly faster than P1 treatment, but not significantly different from P3 treatment. Thecalves with xylazine premedication and ketafol induced (P3) showed the induction time for about 5.00±1.41 minutes, 14.00±1.83 minutes duration of anesthesia, and the recovery time was 4.50 ± 0.58 faster thanP1 but not significantly different withP2.P1, P2, and P3 treatment results in induction time and duration of anesthesia that were not significantly different. Anesthesia using xylazine and propofol (P2) significantly showed that recovery time was shorter than xylazine and ketamine (P1) but not significantly different with combinations of xylazine, ketamine, and propofol (P3).

All treatments showed that the time of induction were not significantly different because the same premedication is used in this research, which isxylazine HCl. As well as thedurationstime shown by alltreatments were also not having a significant differences, which means that the anesthetized status using ketamine-propofol combinations showed no significant difference with ketamine or propofol induced. The combinations of xylazine-propofol, nor combinationsof xylazine-ketamine-propofol has a good potential as an anesthesiafor Bali cattle. Treatment with xylazine-propofol anesthesia producedsignificantly shorter revovery time compared to ketamine induced which caused by a quick metabolism of propofol [16] [17].

Physiological Responses

Physiological responses during anesthesiawith ketamine, propofol and combinations of ketamine-propofol on Bali cattle, are presented in Table 2.

Table 2. Physiological response of anesthetic ketamine, propofol, and combination of ketamine-propofolon Bali cattle

Treatment of Anesthesia	Physiological responses (minutes)		
	hypersalivation	Bloat	Devication
P1 (XK)	9.00±0.35	10.00±0.40	-,
P2 (XP)	9.00±0.50	10.00±0.50	-,
P3 (X-KP)	11.00±0.38	11.00±0.42	-, -

Information :Xylazine sedation dose of 0.1 mg / kg BW intramuscularly, then P1 (XK): 10 minutes later, induced intravenously with ketamine (2 mg / kg) .; P2 (XP): 10 minutes later induced intravenously with propofol (2 mg / kg); P3 (X-KP): 10 minutes later induced intravenously with ketamine-propofol (1 mg / kg ketamine and 1 mg / kg BW propofol).

All treatments showthat physiological responses of hypersalivation started at 9th minute after treatment and shows a flatulence or bloat responsethat began at the 10th minute after treatment. There are no defecations found in cattle during anesthesia and recovery periode. As reported before by [6] that said anesthesia in cattle has some disadvantages such as the occurrence of hypersalivation and flatulence. The presence of bloat itself wascaused by the cattle that didn't undergo fasting well considering themaintenance system for the cattleis free-range and there is no isolation cage at the research place.

Heart rate

The average value of Bali cattle heart rate before treatment (at minute0) and during anesthesiausing ketamine, propofol, and combinations of ketamine-propofol, can be seen in Figure 1.

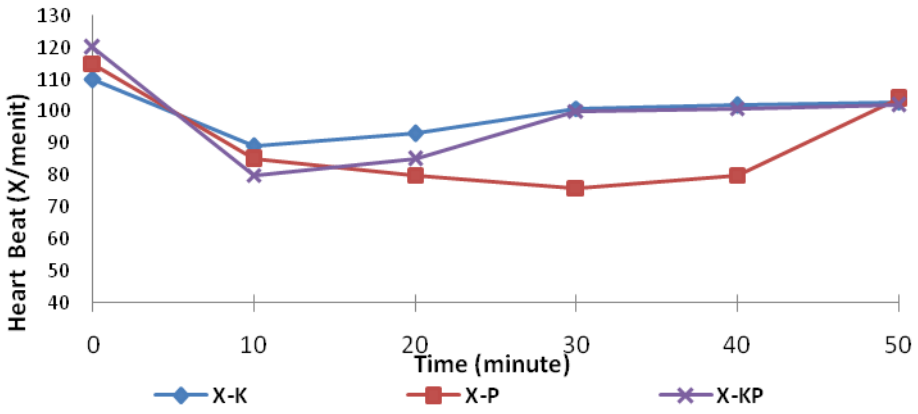

Figure 1. Changes in the average value of heart rate before anesthesia (0 minute) and during anesthetized ketamine and propofol on Bali cattle.
X = xylazine, K = ketamine, P = propofol

The treatment of anesthesia with combinations of xylazine-ketamine, xylazine-propofol,and xylazine-ketamine-propofol show the change in heart rate pattern which is almost the same, but the anesthesiatreatment with combinations of xylazine-propofol shows that the pattern of heart rate decreased more sharply up to the minute 30th. During anesthesia, all treatments showed that the average value of the heart rate dropped before anesthesia was done (minute 0). The treatment of xylazine-ketamine and xylazine-ketamine-propofol showed that there are decreased heart rate patterns until 10th minute, then it goes upand keeps stable until the end of the anesthetic treatment. The treatment with xylazine-propofolshowed a decreased heart rate pattern thatcontinued until 30th minute and increased until the end of the anesthetic treatment. This shows that propofol can cause a depression in cardiovascular system that caused heart rate and blood pressure drop due to cardiac output decrease [10].

Respiration

The average value of respiration frequencyon Bali cattle before treatment (minute 0) and during anesthesia using ketamine, propofol, and combinations of ketamine-propofol, can be seen in Figure 2.

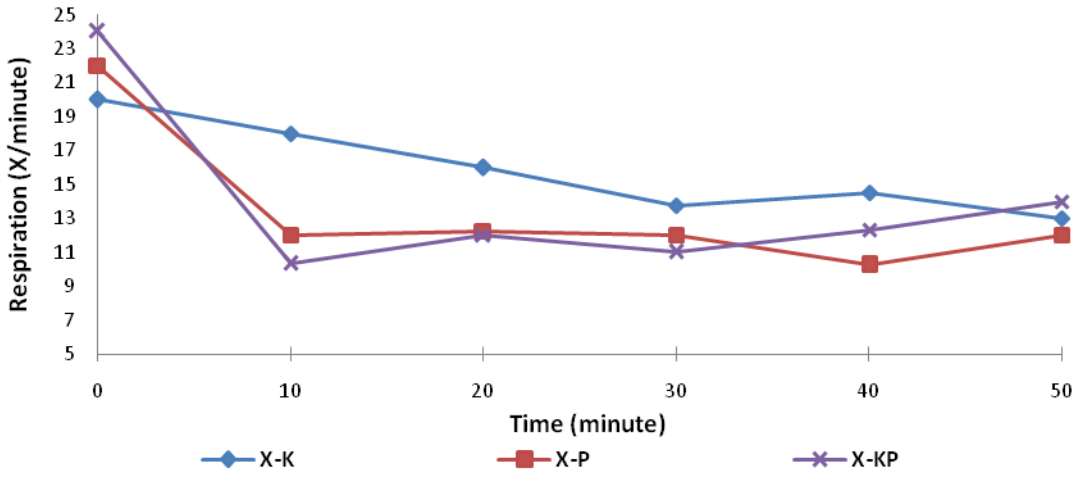

Figure 2. Changes in the average value of respiration before anesthesia (minute 0) and during anesthesia with yilazine, ketamine and propofol on Bali cattle.
X = xylazine, K = ketamine, P = propofol

All of the anesthesia treatments show that there are same drop pattern inthe respiratory score. During the duration of anesthesia, there was a decline in average value of respiration before it was done (minute 0). A sharp drop in respiration value which occured in xylazine-propofol and xylazine-ketamine-propofol

treatmentsat minute tenth to minute thirty, then increased back towards normal values until the end of anesthesia treatment, whereas xylazine-ketamine treatment showed a more stable decreaseuntil the minute 30th and increased back towards normal values. A sharp drop in respiration that happenedwith propofol treatmentwas caused by propofol can eliminate consciousness and makes relaxation on muscles, especially on abdominal muscles that can cause respiration depression [15].

Rectal Temperature

The average value of a rectal temperature on Bali cattle before treatment (minute 0) and during anesthesia with ketamine, propofol, combinations of ketamine-propofol, can be seen in Figure 3.

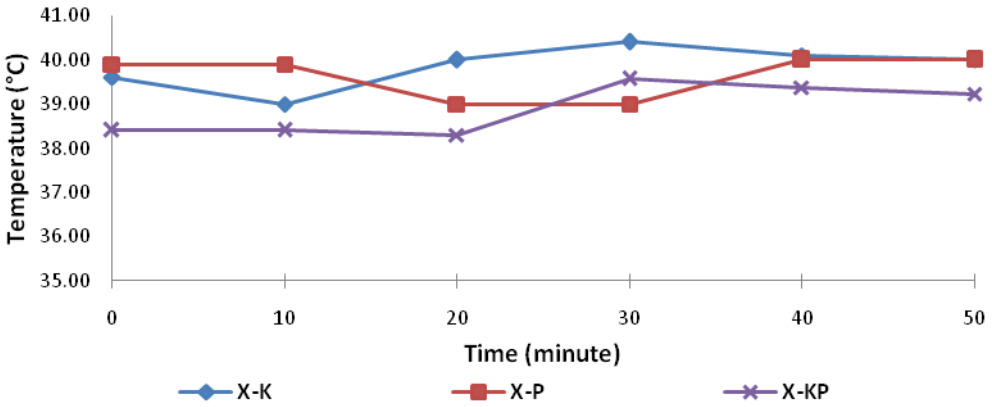

Figure 3. Changes in the average value of the rectal temperature before anesthesia (minute 0) and during anesthesia with ketamine and propofol on Bali cattle.X = xylazine, K = ketamine, P = propofol

Rectal temperature dropson anesthesia treatment with ketamine or propofol. The temperature keeps dropping until minute 10-20thfor anesthesia with propofol,meanwhilethe temperature with ketamine treatment drops until 10th minute and increased back to normal. The temperature drop because of the low metabolism rate that also lowers the body heat. Xylazine can cause sedation, decreased metabolism, muscle relaxation. and suppression of the central nervous system and caused thermoregulatory suppression resulting in a decrease in body temperature [23].

Oxygen saturation

The average value of the oxygen saturation on Bali cattle before treatment (minute 0) and during anesthesia with ketamine, propofol, and combinations of ketamine-propofol, can be seen in Figure 4.

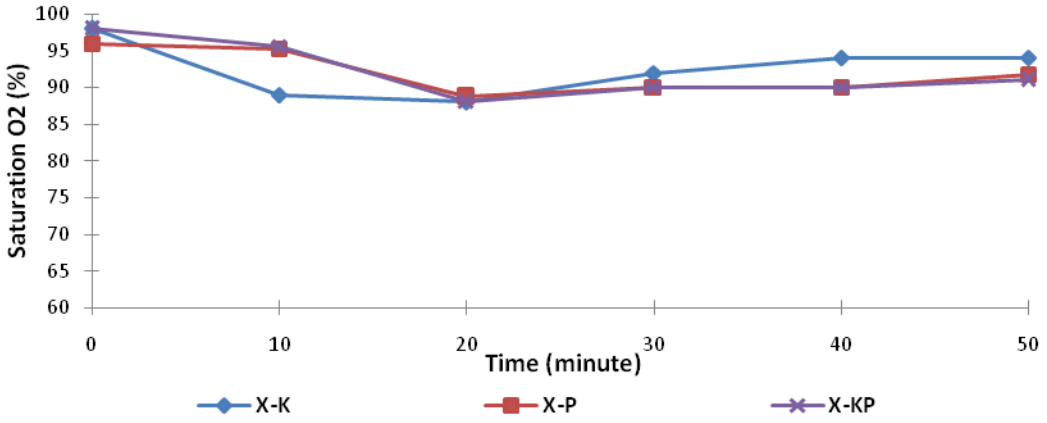

Figure 4. Changes in the average value of saturation before anesthesia (minute 0) and during anesthesia withxylazine, ketamine and propofol on Bali cattle. X = xylazine, K = ketamine, P = propofol

The change of pattern during respiration on anesthetized calves didn't show a significant change, as well the type of treatment didn't show any significant difference. The reason is anesthesia treatment of ketamine, propofol, and combinations of both haven't cause any changes towards tidal volume and oxygen value in respiration.

Capillary Refill Time (CRT)

The average value of CRT (capillary refill time) on Bali cattle beforetreatment (minute 0) and during anesthesia with ketamine, propofol, and combinations of ketamine-propofol, can be seen in Figure 5

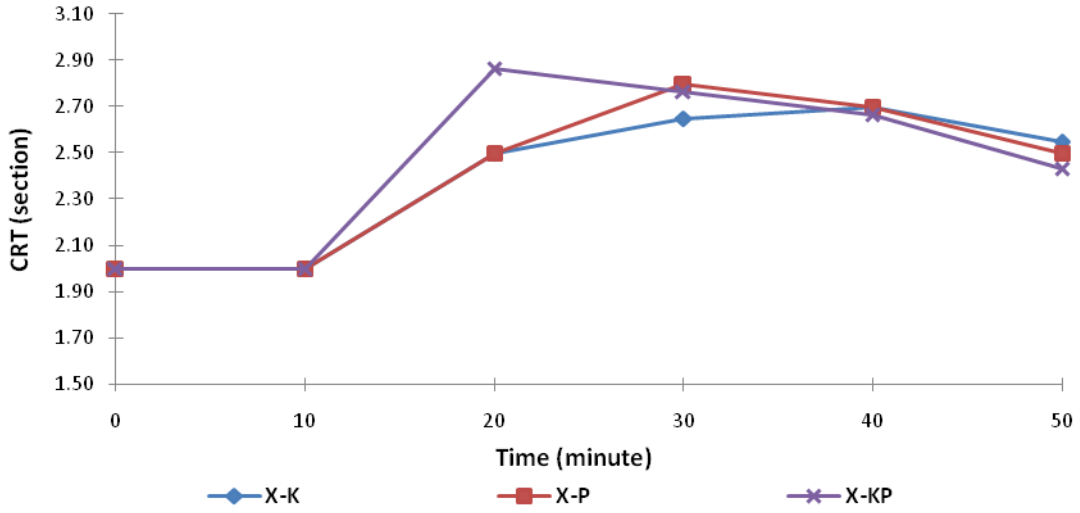

Figure 5. Changes in the average value of CRT (Capillary Refill Time) before anesthesia (minute 0) and during anesthetized xylazine, ketamine and propofol on Bali cattle.
X = xilazin, K = ketamine, P = propofo

The CRT graphic during anesthesia with ketamine, propofol and combinationsof both were shown to have the same changes in pattern. During

anesthetizedcondition, there was an increase in the CRT's value that starts at the minute 10th up to 30th, after that the CRTdropped back to normal. Changes in the average value of CRT along with an increased heart rate begins at minute 20 to 40 and back to in a stable line until the end of the treatment the anesthesia.

Anesthesia with xylazine as a premedication and induced with ketamine-propofol (ketafol) shows changes in heart rate, respiration, oxygen saturation, body temperature, and CRT pattern in Bali cattle that are more stable compared

stomach more relaxed and will inflate and deflate the chest cavity during respiration [18]. Xylazine belonged toα2-adrenergic agonist group, if combined with ketamine will cause sedation and respiratory distress [23].

V. CONCLUSION

Anesthesia with combinations ketamine and propofol (ketafol) can be used as an anesthesia for Bali cattle, especially in calves since the induction of anesthesia isfast, fairly long duration,a shortertime to recover, and more stable changes in physiological responses in the cardiovascular, respiration system,and body temperature and does not cause extreme changes in the body.It is necessary to do an examination of hematology, withthe treatment of anesthesia with only ketamine or propofol. The reason is a low-dose propofol (1 mg / kg BW) will cause no significant effect on heart rate [25]. [26] states that propofol can cause blood pressure to drop but did not cause any changes in heart rate. Cardiovascular depression occurs when propofol was immediately administered with a high dosage [11]. Heart rate, respiration and oxygen saturation decrease was due to pre-anesthetized xylazine. Xylazinewas classified as a "muscle relaxant", which will make the muscles between the ribs and kidney and liver function parameter post-anesthesia and a further research about the influence onphysiological response of the body when given ketamine-propofol combinations using gravimetric methods (drip infusion) as an alternative for general anesthetic inhalation in Bali cattle.

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