

Bispectral index assessment in calves subjected to the continuous infusion of propofol combined with fentanyl administration

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ABSTRACT: *The aim of this study was to evaluate the bispectral index (BIS) effects in calves through continuous infusion of propofol with or without fentanyl. Eight Holstein male calves (ages from six to twelve months old) with an average weight of 123±18kg were used. All animals participated in both groups, always keeping a minimum interval of one week between the anesthetic procedures; the calves were randomly distributed between groups. Anesthesia was induced with an intravenous (IV) dose of propofol of 5mg kg⁻¹ in control group (G_p) or with propofol (4mg kg⁻¹) associated with IV fentanyl 0.001mg kg⁻¹ (G_f). All the calves were positioned in right lateral recumbency and were allowed to spontaneously breathe room air. Subsequently, the anesthesia was maintained by continuous infusion of propofol at the rate of 0.6mg kg⁻¹ min⁻¹ IV in G_p and associated with the infusion of fentanyl 0.001mg kg⁻¹ hour⁻¹ in G_f. Measurements of BIS, signal quality index (SQI) and electromyography (EMG) were evaluated before anesthesia induction (T_b), and at 15, 30, 45 and 60 minutes after the beginning of continuous drugs infusion (T₁₅, T₃₀, T₄₅ and T₆₀, respectively). The heart rate (HR), respiratory rate (f), end-tidal carbon dioxide tension (ETCO₂) and recovery times were evaluated as well. No significant differences were observed between the groups in the BIS variables and the recovery time was longer in G_f. Co-administration of propofol and fentanyl infusions, at the doses reported here, did not change the values of BIS in cattle, but delayed the recovery time.*

Key words: calves, ruminants, balanced anesthesia, anesthetic monitoring.

Índice bispectral em bezerros submetidos à infusão contínua de propofol associado ao fentanil

RESUMO: *O estudo teve por objetivo avaliar o índice bispectral (BIS) durante a infusão contínua de propofol associado ou não ao fentanil em bezerros. Foram utilizados oito animais machos entre seis e doze meses de idade, holandeses, com massa corporal média de 123±18kg. Todos os animais participaram de ambos os grupos, respeitando-se sempre um intervalo mínimo de uma semana entre uma anestesia e outra, sendo aleatoriamente distribuídos entre os grupos. A anestesia nos bezerros foi induzida com propofol na dose de 5mg kg⁻¹; intravenoso (IV), grupo controle (G_p) ou propofol 4mg kg⁻¹ associado ao fentanil 0,001mg kg⁻¹; IV, grupo fentanil (G_f) e posicionados em decúbito lateral direito, onde permaneceram respirando espontaneamente ar ambiente. Ato contínuo, a manutenção anestésica foi realizada pela infusão contínua de propofol na taxa de 0,6mg kg⁻¹ min⁻¹; IV G_p, associado ou não à infusão de fentanil 0.001mg kg⁻¹ hora⁻¹ G_f. A mensuração das variáveis do BIS, índice de qualidade de sinal (IQS) eletromiografia (EMG), frequência cardíaca (FC), frequência respiratória (f) e dióxido de carbono ao final da expiração (ETCO₂) foram avaliadas antes da indução anestésica no momento basal (M_b), e 15, 30, 45 e 60 minutos após o início da infusão contínua dos fármacos (M₁₅, M₃₀, M₄₅ e M₆₀, respectivamente); o tempo de recuperação também foi avaliado. Não foram observadas diferenças significativas entre os grupos nas variáveis do BIS e o tempo de recuperação foi maior no G_f. A co-administração das infusões de propofol e fentanil, nas doses utilizadas nesse estudo, não alterou os valores do BIS em bezerros, porém, prolongou o tempo de recuperação.*

Palavras-chave: bezerros, ruminantes, anestesia balanceada, monitoração anestésica.

INTRODUCTION

The use of different intravenous (IV) anesthetic drugs for induction and maintenance of general anesthesia, also known as total intravenous anesthesia (TIVA), facilitates patient anesthesia and analgesia owing to the depression of the central

nervous system (CNS), which causes a loss of awareness and a lack of response to noxious stimuli (MUSK et al., 2005).

Propofol is considered a key alternative among the various drugs that are used in IV anesthesia protocols SELMI et al. (2005), because of its pharmacokinetic characteristics, including rapid

clearance and high volume of distribution, despite its lack of analgesic properties. Propofol is an effective IV agent for maintaining anesthesia by constant rate infusion (CRI) in several species, including llamas DUKE et al. (1997), horses OKU et al. (2006); UMAR et al. (2015), pigs XIAO et al. (2014), dogs LOPES et al. (2008a), and cattle DESCHK et al. (2015), in addition to its extensive use as an inducing agent.

Similarly, fentanyl, which is a μ -opioid receptor agonist, is used in many species via administration of CRI to provide analgesia during anesthesia with propofol (SMITH et al., 1994). Fentanyl has already been used as an anesthetic and as a pre-anesthetic in buffalos, in combination with different alpha-2 receptor agonists SINGH et al. (2013). However, its use in cattle has only been reported as an adjunctive analgesic, administered as a bolus WILSON et al. (2000), and not as an agent for continuous infusion in these species.

When using these drugs to maintain anaesthesia, the assessment of anaesthetic depth is mandatory. In addition to ocular reflex testing, further methods for assessing CNS depression may also be useful, including electroencephalogram (EEG), which may be effectively correlated with changes in the level of consciousness, and is a continuous and noninvasive measurement. Nonetheless, the routine use of EEG was impractical because of the complexity of its parameters and operator-dependent nature for the interpretation of results DUARTE, (2006); CAMPAGNOL et al. (2007). Since then, the bispectral index (BIS) monitor was developed through extensive research to numerically assess the degree of anesthetic depth of patients.

The interpretation of BIS monitor values is relatively simple, with values ranging from zero to 100. In humans, zero corresponds to an isoelectric EEG, with the total suppression of cortical electrical activity, and 100 corresponds to a normal state of consciousness (HAJAT et al., 2017). In dogs, values ranging from 40 to 60 represent an adequate anesthetic plan, without occurring intraoperative awareness (GUERRERO & NUNES, 2003).

Another key issue during an anesthetic procedure is the assessment of patients anesthetic depth. An inadequate anesthetic plane may be harmful for the large-sized animal and surgical team. Its use has been reported in horses (HAGA & DOLVIK, 2002) and in calves (ARAUJO et al., 2015; DESCHK et al., 2016).

This study aimed to assess the use of BIS monitoring during CRI of propofol alone, or combined with fentanyl in cattle. Moreover, to

evaluate its effects over the following variables: heart rate (HR), respiratory rate (f), end-tidal CO_2 concentration (ETCO_2) and recovery times.

MATERIALS AND METHODS

This prospective, randomized, non-blinded, crossover study. Eight Holstein bull calves, with ages ranging from six to twelve months (mean weight: $123 \pm 18 \text{kg}$) were enrolled in this study. Based on a completed blood count performed two days prior induction of anaesthesia and a physical examination (HR and f , rectal temperature and the inspection of the color of the visible mucosae) on the day of the experiment, they were considered healthy and classified as ASA I (American Society of Anesthesiologists).

Calves were randomly distributed between the groups, via simple, random sampling. All animals were anesthetized twice and participated in both groups, with at least a one-week interval between each induction of anesthesia.

After selection and weighing, the animals were subjected to water and feed fasting for 24 and 12 hours, respectively. On the day before the experiment, each animal was restrained in a standing position in order to perform trichotomy on the area of the left jugular and cephalic veins and on the frontal, cephalic, and zygomatic areas to place the BIS electrodes. On the day of the experiment, the animal was placed on the surgical table and restrained in a right lateral decubitus position; an introducer^a was placed in the left jugular vein using the Seldinger technique, through which a Swan-Ganz catheter was introduced for CRI of propofol^b, allowing for maintenance fluid therapy with the administration of Ringer's solution with lactate^c, at an infusion rate of $5 \text{mL kg}^{-1} \text{hour}^{-1}$. Another catheter^d (20G) was placed in the left cephalic vein for IV administration of fentanyl.

After preparation and instrumentation, the animal remained restrained in right, lateral decubitus for a 10-minutes period to minimize the effect of animal handling stress on the baseline values of the study variables. Baseline parameters were assessed immediately before anesthetic induction (T_B) and included BIS, SQI, EMG, HR, f and ETCO_2 . Immediately after baseline parameters recording, anesthesia was induced with propofol at an IV dose of 5mg kg^{-1} , in the group that was anesthetized with propofol infusion only (G_p). In the group G_{fp} , the propofol dose was 4mg kg^{-1} mixed with 0.001mg kg^{-1} fentanyl, in the same syringe,

for two minutes, in the group that was anesthetized with propofol infusion combined with fentanyl (G_F). Immediately after, the animals were intubated, using a long, blade laryngoscope with tracheal probes of compatible size, while maintaining the cuff inflated throughout the anesthetic procedure.

The calves were hoisted, transferred onto a surgical table, placed in right lateral recumbency and were allowed to breathe room air ($FiO_2=0.21$) throughout the experiment. Immediately thereafter, anesthesia was maintained with a CRI of propofol, administered using an infusion pump^e at an IV rate of $0.6\text{mg kg}^{-1}\text{ min}^{-1}$, combined with or without the CRI of fentanyl at a $0.001\text{mg kg}^{-1}\text{ hour}^{-1}$ infusion rate, for 60 minutes. The use of these infusion rates was described by DESCHK et al. (2015), TRANQUILLI et al. (2007) and pilot studies performed at our institution.

Selected variables were assessed at T_B and at 15, 30, 45 and 60 minutes after the beginning of the CRI of propofol with or without fentanyl. The assessment of anesthetic recovery began as soon as the drug infusion was completed.

Heart rate was assessed using an electrocardiograph set to read in DII derivation. Respiratory rate was assessed via a direct read of the monitor^f using a suction sensor placed in front of the nostrils on the face mask outlet. This set-up was connected to the end portion of the orotracheal tube. End-tidal carbon dioxide tension values were assessed from a direct read of a capnograph^g using the placement of the suction sensor in a similar manner to its placement during f assessment.

Direct monitoring of BIS was used by means of a specific device^h, involving the placement of its electrodesⁱ in the frontotemporal position adapted from CAMPAGNOL et al. (2007). Electrode impedance was automatically checked using the monitor, and the electrodes were discarded if the impedance was higher than $7.5\text{k}\Omega$, as recommended by the manufacturer. The signal quality index (SQI) was also assessed and the BIS discarded when the SQI was lower than 50. Bispectral index values were recorded, and had their mean values calculated, at all time points for one minute. In addition to BIS, the electromyography (EMG) and SQI values were also assessed.

After 60 minutes of anesthesia, the infusions were stopped. Anesthetic recovery involved the observation of the animal in the recovery room of a surgical center with a rubber floor and padded walls. Animal contact was avoided, and the animal was engaged only if it

showed intense movements so as to prevent it from hitting its head on the floor. The times between the cessation of the CRI of propofol and the positioning of the animal in sternal recumbency (SR) and the standing position (SP), were recorded.

Data were tested for normality using the Shapiro-Wilk test and subjected to analysis of variance for repeated measures using the MIXED procedure of the Statistical Analysis System (SAS) and multiple mean comparisons with the Least Squares Means (LSMEANS), adjusted for the Tukey's test at a 5% significance level. Statistical analysis of variables without normal distribution was performed using the Friedman test for comparison between the times points and the Wilcoxon signed-rank test for comparison between groups. Data were analyzed using the software SAS 9.3 (SAS, 2011).

RESULTS

No additional boluses were required to induce general anaesthesia, in any calve. Endotracheal intubation was successfully and smoothly performed in most of the calves. Only one animal from the group G_F showed a small quantity of ruminal liquid reflux during intubation, albeit without any repercussions regarding the tracheal aspiration of such contents.

After anaesthetic induction, HR was higher for both groups at all time points compared to baseline, with the exception of G_F at T_{30} . Between treatments, differences in HR were only seen at T_{15} . Compared to baseline, f was significantly lower at all time points compared with T_B in both treatments, with no differences between them. With regard to $ETCO_2$, the values were significantly lower at baseline compared with all the other time points. No differences between treatments were observed within this parameter.

The BIS and EMG values were significantly lower throughout all the period compared to baseline, with no differences between treatments. No significant differences in sternal recumbency times occurred between groups (Table 1). However, animals receiving in group G_F required longer periods of time to adopt the standing position than those in group G_p (Table 2).

DISCUSSION

It is worth highlighting that the methodology that was used in the present study

Table 1 - Mean \pm standard deviation of the variables of heart rate (HR), respiratory rate (f) end-tidal CO₂ concentration (ETCO₂), bispectral index (BIS), signal quality index (SQI) and electromyography (EMG) assessed in calves (n=8) anesthetized by continuous infusion of propofol at a rate of 0.6mg kg⁻¹ min⁻¹; intravenous (IV), combined with or without fentanyl infusion at 0.001mg kg⁻¹ hour⁻¹.

Variable	Treatment	T _B	T ₁₅	T ₃₀	T ₄₅	T ₆₀
HR (beats minute ⁻¹)	G _P	74±24 ^{a*}	104±20 ^{b*}	98±15 ^{a*}	106±12 ^{a*}	110±10 ^{a*}
	G _F	72±13 ^{a*}	122±33 ^{a*}	113±28 ^{a*}	112±23 ^{a*}	116±23 ^{a*}
f_R (breaths minute ⁻¹)	G _P	42±12 ^{a*}	17±2 ^{a*}	18±3 ^{a*}	19±2 ^{a*}	20±3 ^{a*}
	G _F	38±18 ^{a*}	20±6 ^{a*}	18±1 ^{a*}	18±1 ^{a*}	18±1 ^{a*}
ETCO ₂ (mmHg)	G _P	17±5 ^{a*}	54±4 ^{a*}	56±4 ^{a*}	55±5 ^{a*}	54±5 ^{a*}
	G _F	19±7 ^{a*}	55±4 ^{a*}	55±5 ^{a*}	56±6 ^{a*}	53±8 ^{a*}
BIS	G _P	93±5 ^{a*}	52±10 ^{a*}	51±8 ^{a*}	51±8 ^{a*}	51±8 ^{a*}
	G _F	89±9 ^{a*}	56±11 ^{a*}	53±8 ^{a*}	52±11 ^{a*}	54±12 ^{a*}
SQI (%)	G _P	87±8 ^{a*}	97±3 ^{a*}	93±6 ^{a*}	90±15 ^{a*}	96±4 ^{a*}
	G _F	86±12 ^{a*}	89±14 ^{a*}	89±11 ^{a*}	93±9 ^{a*}	91±14 ^{a*}
EMG	G _P	51±3 ^{a*}	35±4 ^{a*}	33±4 ^{a*}	35±4 ^{a*}	32±5 ^{a*}
	G _F	51±4 ^{a*}	33±5 ^{a*}	34±6 ^{a*}	33±2 ^{a*}	32±5 ^{a*}

Different superscript letters for values within a treatment are significantly different (P<0.05). *GF significantly different from GP at the same time point (P<0.05).

was performed adequately and smoothly. To our knowledge, this is the first report of the administration of a CRI of propofol combined with fentanyl in calves, based on the literature review performed. The propofol dose which was used was retrieved from DESCHK et al. (2015), who assessed two different propofol infusion rates in calves (0.6mg kg⁻¹ min⁻¹ and 0.8mg kg⁻¹ min⁻¹), whereby the best results were assessed using the 0.6mg kg⁻¹ min⁻¹ infusion rate in this study.

The necessity of adding an analgesic to this protocol as an adjunct method for TIVA was identified in the present study. Thus, the drug chosen was fentanyl, using an infusion rate of 0.001mg kg⁻¹ hour⁻¹ as indicated by TRANQUILLI et al. (2007).

After beginning the infusion, the HR increased significantly in both groups, remaining

high throughout the infusion period, which was in contrast to the findings by DZIKITI et al. (2010), who observed no increase in HR when using propofol and fentanyl or midazolam infusion in goats. A possibility accounting for such a difference might be related to the higher infusion rate (12mg kg⁻¹ hour⁻¹ and 0.02mg kg⁻¹ hour⁻¹) of drugs (propofol and fentanyl, respectively) used in the aforementioned study, which mediated a decrease in HR during the infusion, albeit without statistically significant differences.

At T_B, the values of f and ETCO₂ were the highest and the lowest, respectively, significantly differing from the other time points. These results can be explained by the fact that all animals were restrained at baseline. DZIKITI et al. (2010) also observed significant differences between T_B and the other time points, which were assessed when infusing propofol combined with fentanyl in goats. However, that difference was much steeper, with f values of approximately 7 respiratory movements per minute, without requiring the use of mechanical ventilation. An adverse effect of fentanyl is respiratory depression, according to TRANQUILLI et al. (2007). However, the results from our study were similar across both groups G_P and G_F; thereby, suggesting that the infusion rate that was used was insufficient to cause the expected, adverse effects.

With regard to ETCO₂, both groups showed a considerable increase in their values, confirming that the respiratory changes that were

Table 2 - Mean \pm standard deviation of the sternal recumbency (SR) time, in minutes, and the standing position (SP) time, in minutes, according to groups.

Variable	SP e SR ($\bar{X} \pm s$)	
	G _P	G _F
Sternal Recumbency	26±6A	31±18A
Standing Position	35±8B	46±17A

Means followed by the same letter, in rows, are not different from each other according to the Tukey's test (P>0.05).

observed were propofol-mediated and were not attributable to the synergistic effects of fentanyl infusion. Such a significant increase in ETCO_2 may also be associated with the position of the animals because of the abdominal compression of the diaphragm, compromising a correct ventilation by reducing the residual lung capacity, even when remaining in lateral decubitus throughout the experimental period.

Bispectral index is still seldom used in cattle anesthesia, mainly due to the cost benefit of the device and the fact that few studies have been conducted in cattle. This has precluded the validation of BIS values because the development of this index for humans, as well as for use in animals, especially in cattle, has only recently begun. Using the BIS, APREA et al. (2014) clearly showed in a case report of the cardiopulmonary resuscitation of a propofol-anesthetized calf that the BIS values that were assessed had varied with cardiovascular function and that BIS was indicative of cerebral perfusion in cattle.

ARAÚJO et al. (2014) and ARAÚJO et al. (2015) reported mean BIS values of approximately 40 when conducting studies in calves using inhalation anesthesia with isoflurane combined with butorphanol infusion, and assessing BIS in isoflurane-anesthetized calves with or without CRI of lidocaine, respectively. Such values were slightly lower than those reported in this study, which is most likely related to the protocol that was used and to the difference in anesthetic plan. Similarly, DESCHK et al. (2015) reported mean BIS values of 50 in calves anesthetized with propofol at two infusion rates and reported no significant differences in the variable between groups, which showed that the increase in infusion rate was insufficient to change BIS values proportionally. This demonstrated that the results from the BIS assessment was directly dependent upon the anesthetic protocol which was used for cattle. Conversely, the study by DESCHK et al. (2015), who also used the same protocol and assessed values that were very similar to those of the present study, suggested that the low infusion rate of fentanyl was insufficient to further depress the CNS of the animals. This resulted in a decrease in the BIS values, and/or a BIS value of approximately 50 in calves anesthetized with CI of propofol.

Considering the method that was used, the BIS values reported herein are presumably reliable because the SQI, which is the parameter assessing signal intensity and quality, did not differ between the time points or the groups. Similarly, EMG did not

differ between groups either and had only differed at the baseline values when compared against the other time points in both groups. Additionally, as muscle contraction directly affects the EMG values, the difference between the baseline values and that of the other time points can be explained by the fact that the calves were resisting restraint, and that the subsequent muscle activity would have accounted for the changes in those values. Conversely, the values reported during the infusion period corroborated with those of GUERRERO & NUNES, (2003), who used SQI values higher than 90 and EMG values lower than 30; LOPES et al. (2008a), who assessed EMG values lower than 43 and SQI values higher than 92; and LOPES et al. (2008b), who assessed mean SQI values higher than 84 and EMG values lower than 40; thereby, confirming that the difference in the baseline values was directly related to muscle contraction.

The G_F prolonged recovery times when the animal was positioned in both sternal recumbency and in a standing position, revealing significant differences between the groups only during the SP time. These results go against the findings reported by DZIKITI et al. (2010), who observed no significant differences in the recovery time when combining propofol infusion with the adjunctive administration of midazolam or fentanyl in goats. Those authors also reported that goats from the fentanyl group showed signs of disparate behavior at the time of recovery, displaying unrest, which was also observed in the present study in the animals in group G_F . However, the severity of these effects were less intense and were restricted to chewing movements. Nonetheless, we believed that the incidence of adverse effects during recovery could be similar to those observed by DZIKITI et al. (2010) in goats if the infusion rate of fentanyl was increased.

However, our study is not free of limitations. Another way to assess anesthetic depth involves subjective evaluation, which was not performed in this study, such as the use of Guedel's classification combined with BIS values. Therefore, further studies aims to perform a subjective evaluation of anesthetic depth correlated with BIS values, which should be conducted, in order to define a more reliable range of BIS values for cattle. Moreover, the absence of a painful stimulus to test analgesia against the BIS values could be considered as a limitation, primarily in group G_F . Nonetheless, for ethical reasons, the animals in group G_p could not receive a noxious stimulus because no analgesia

is provided by propofol. Thus, further studies should be performed using other fentanyl infusion rates until the adequate dose that provides anesthesia and analgesia to patients is determined.

CONCLUSION

In conclusion, propofol infusion combined with or without fentanyl, induced significant respiratory depression without changing the BIS values and prolonged the total recovery time of the group anesthetized with the CRI of fentanyl.

VERBAL REPORT

^aIntroducer Percutaneous Intro-Flex.5F - Edwards Lifesciences - São Paulo, SP.

^bPropovan 10mg / ml Laboratory Cristália - Pharmaceutical Chemicals Ltda, Itapira, SP.

^cRinger Lactate, Equiplex pharmaceutical industry Ltda., Aparecida de Goiânia, GO.

^dCatheter BD Intracath 16G - Becton, Dickinson Ind Surgical. Ltda. - Juiz de Fora, MG.

^eLinear Volumetric Infusion Pump ST1000-Samtronic-São Paulo, SP. (Proc. FAPESP 2010 / 19568-9)

^fDixtal - mod. DX-2020, Manaus, AM. (Proc. FAPESP 2009/08879-6)

^gDixtal, mod. DX-2020 - Module gas analyzer. Manaus, AM. (Proc. FAPESP 2009 / 08879-6)

^hDixtal, mod. DX-2020 - bispectral index module. Manaus, AM, Brazil. (Proc. FAPESP 2009 / 08879-6)

ⁱBis Four Sensor, Aspect Medical Systems, Norwood, MA, USA.

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BIOETHICS AND BIOSSECURITY COMMITTEE APPROVAL

The study was approved by Ethics Committee on Animal Use (CEUA; Process FOA-0107-2013).

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