Title: Use of the combination of xylazine, Ketamine and butorphanol as premedication to enhance sedation and decrease thiobarbital requirements in female dogs undergoing ovariohysterectomy.

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USE OF THE COMBINATION OF XYLAZINE, KETAMINE AND BUTORPHANOL AS PREMEDICATION TO ENHANCE SEDATION AND DECREASE THIOBARBITAL REQUIREMENTS IN FEMALE DOGS UNDERGOING OVARIOHYSTERECTOMY.

ABSTRACT

Ovariohysterectomy is a very common surgery in hospitals and veterinary clinics and is also the most common procedure in shelters, like other surgeries, it requires an adequate anesthetic protocol, which includes a correct premedication avoiding the adverse effects derived from the use of these drugs.

- **Objective:** The aim of this study is to compare the effects of butorphanol in combination with xylazine and ketamine to enhance sedation and reduced the thiobarbital requirement. This study was designed to assess anesthetic and analgesic effects during pre-anaesthesia and to analyze cardiopulmonary and analgesic effects as well as anesthesia depth.

- **Materials and Methods:** This study was carried out using 24 females dog from the Insular of Gran Canaria Shelter. All the animals were selected without distinction of race, age, size, or weight and randomly assigned in 2 groups, each group used two alpha 2 adrenergic drugs in combination with or without butorphanol, group A (ketamine-xylazine), group B (ketamine-xylazine-butorphanol). Sedation scales and systematic recording of vital signs were recorded in all groups. Anesthetic induction was performed with thiopental, maintenance with isoflurane, and local anesthetic (bupivacaine). Was also included in the anesthesia protocol for both groups.

- **Results:** All the animals of study were surgically managed without complications and recovered properly. The results obtained were analyzed in a comparative study between both groups, using for some variables a mixed linear model and the Wilcoxon method for others.
In general, group GB showed better results in sedation level, thiobarbital requirement, recovery and Glasgow scale.

- **Conclusion:** The use of butorphanol combined with Xylazine, Ketamine and bupivacaine (Group B) showed a better quality of sedation and recovery and values for the Glasgow scale although this difference was not statistically significant compared with the group GA. The addition of Butorphanol to the standard protocol GB showed the lowest thiobarbital requirement being this difference statistically significant compared to the Group A where Butorphanol was not included.

INTRODUCTION

OVARIOHYSTERECTOMY (OVH), the most common surgical procedure performed in veterinary practice (Bloomberg, 1996), prevents or lessens the risk of development of mammary cancer and pyometra, and the inconvenience of vaginal discharge and male attraction during estrus. OVH is the method of choice for sterilization in the dog (Bloomberg, 1996), (Olson & Johnston, 1993).

Ovariohysterectomy is a surgical procedure that may cause moderate to severe pain after surgery (Slingsby et al., 2011). Pain relief is required during the perioperative period to ensure the comfort and rapid healing of the patient. Pain increases the likelihood of immune suppression by activation of the neuroendocrine system and the rise in serum cortisol and catecholamine levels. Postoperative pain may be accompanied by secondary illness or loss of appetite and can negatively affect the recovery time (Mathews, 2000). Besides, it has been reported that alterations in animal behavior might occur due to pain (Bufalari et al., 2007), (Buhari et al., 2012).

However, postoperative pain can be controlled using analgesics. It is important to determine whether the analgesics used to prevent these undesirable effects have a long duration of action (Mathews, 2000). It is essential to identify safer drug delivery routes for effective control of pain in small animals (Buhari et al., (2012). An ideal anesthetic agent should provide good muscle relaxation, adequate analgesia and sedation along with smooth induction and safer recovery (Sharma et al., 2014). Balanced anesthesia consists of the administration of more than one anesthetic drug, which allows administering lower doses of the individual drugs in order to achieve an appropriate plane of anesthesia, while minimizing the adverse effects associated with each drug. Balanced anesthetic techniques using intravenous (IV) anesthetics produce rapid onset, redistribution and clearance (Jena et al., 2014).

Ketamine increases heart rate and mean arterial pressure, stimulates cardiovascular functions and when used alone. It can induce undesired effects such as muscular hypertonicity, myoclonus, and convulsions. To minimize these unwanted and

restricting effects, ketamine is administered in combination with other drug groups such as benzodiazepines, and alpha-2 agonists (Özkan et al., 2010), (Dzikiti et al., 2007). It is referred to as a “dissociative anesthetic” because it makes patients feel detached from their pain and environment. Ketamine can induce a state of sedation (feeling calm and relaxed), immobility, relief from pain, and amnesia (no memory of events while under the influence of the drug) (Drug Enforcement Administration; 2020).

Xylazine, an alpha-2 agonist used in animal experiments, stimulates alpha-2 adrenergic receptor in cerebral presynaptic nerve ends, inhibits release of catecholamines and dopamine resulting in analgesic and sedative effects, and hinders nerve conduction in the central nervous system leading to relaxation of striated muscles. Xylazine is usually used in combination with ketamine during anesthetic applications (Özkan et al., 2010). Produce pronounced cardiovascular side effects including vasoconstriction associated hypertension, which is followed by hypotension (primarily with xylazine) secondary to a decrease in norepinephrine release and sympathetic outflow centrally, with pronounced decreases in heart rate and cardiac output. They may cause respiratory depression, emesis, and increased urine production (Perkowski S. Z., 2006).

Opioids are frequently used for acute pain control in veterinary medicine and are the mainstay of therapy in the perioperative period. Not only are opioids highly effective analgesics for moderate to severe pain, but they may also be given pre-operatively to provide sedation and aid restraint. Opioids tend to be relatively sparing of the cardiovascular system and their use as a premedication allows for a decrease in the amount of other, more cardiovascularly depressant agents needed to provide anesthesia (Perkowski S. Z., 2006).

Butorphanol is a synthetic opioid derivative analgesic that exerts its effect on kappa receptors. Though it binds to mu-receptors, its effect on these receptors is minimal. Therefore, it is also used as a mu-receptor antagonist (Caulkett et al. 2003). This last effect explains its low potential to produce respiratory depression. It has been reported to provide sedation and limited, short-term analgesia for various diagnostic or therapeutic procedures (Caulkett et al. 2003).

Thiobarbital induces anesthesia of longer duration than pentobarbital. Stable anesthesia for 3 hours has been documented in rats. Administration of additional anesthetic boluses, typically given by the IP route, may be necessary for anesthesia of longer duration. This agent is most useful when a long anesthetic period is needed; however, redosing using higher than published doses may be needed to maintain the absence of pedal withdrawal reflexes (Brammer et al., 1993). Thiobarbital, like pentobarbital, has variable analgesic activity (Brammer et al., 1993), (Flecknell, 1996).

Non-steroidal anti-inflammatory drugs (NSAIDs) may provide post-operative analgesia for up to 24 hours after a single dose (Mathews, 2002). At therapeutic doses, carprofen appears to be a poor inhibitor of prostaglandin and COX-2 enzymes (Frölich et al. 1984), but has good anti-inflammatory (Maeda et al., 1977) and analgesic properties (Al-Gizawiy & Rude, 2004).

Carprofen is used for the control of post-operative pain in dogs (Pfizer Animal Health), and is not subject to the strict record-keeping of opioids. New information and the availability of new drugs are changing the way that non-steroidal anti-inflammatory agents (NSAIDs) are being viewed as part of the multimodal approach to treating pain in the perioperative period (Perkowski S. Z., 2006)

Intraperitoneal (IP) administration of bupivacaine in dogs undergoing ovariohysterectomy (OVH) has been described as an effective technique for management of postoperative pain, with dogs receiving IP bupivacaine requiring less rescue analgesia compared to placebo treated dogs (Carpenter et al., 2004),(Campagnol et al., 2012).

Volatile anesthetics, including isoflurane, have been proven to provide cardioprotective effects against reversible or irreversible myocardial ischemia/reperfusion injury by limiting infarct size and ameliorating contractile and diastolic function (Hanley et al., 2002) (Symons and Myles, 2006) (Tanaka et al., 2002, 2004).

Therefore, the aim of this study is to compare the effects of butorphanol in combination with xylazine and ketamine to enhance sedation and reduced the thiobarbital requirement. This study was designed to assess anesthetic and analgesic effects during pre-anaesthesia and to analyze cardiopulmonary and analgesic effects as well as anesthesia depth throughout surgery and during the post-surgical recovery period.

MATERIAL AND METHODS

A blind study was carried out in this study and 24 female dogs aged 6 months to 8 years, body weight range 2,8 kg to 30,4 kg were randomly scheduled for routine ovariohysterectomy from the Shelter of Bañaderos. After a physical exam all the animals were classified as ASA 1 according to the American Society of Anesthesiologists (ASA) classification (American Society of Anesthesiologists Status Scale). All the animals were tested for filarial blood test and positive cases were excluded of this trial.

Procedure

Premedication was given according to 2 different drug combination groups: Group A, ketamine (10 mg/kg)-xylazine (0,3 mg/kg); group B, ketamine (10 mg/kg)-xylazine (0,3 mg/kg/kg)- butorphanol (0,2 mg/kg). All drugs used to provide sedation were combined into a single syringe and administered subcutaneously.

After 15 minutes, the sedation score was recorded using the Grint sedation scale (Grint et. al., 2009). The scale included seven items: spontaneous posture, palpebral reflex, eye position, jaw & tongue relaxation, response to noise, resistance when laid into lateral recumbency, and general appearance/attitude (Annex 1). Each item was assigned a score and scores summed to give a sedation score (range 0 to 21), with higher scores indicating a greater level of sedation (Wagner, 2017). The different

levels of sedation according to the scores assigned by (Wagner, 2017), little or no sedation: score 0–2; moderate sedation: score 4–11; Intense sedation: score >13.

This study was performed by the same evaluator which was blinded to the anesthetic protocol at time of surgery.

When the sedation was set up an IV catheter was placed in the cephalic vein and all the animals received thiobarbital as the induction agent (10 mg/kg). An extra 1 ml dose was always loaded into the syringe and marked in case it was necessary, if with that dose intubation were not possible more doses were necessary. The dose and the time of induction were registered.

After induction, endotracheal intubation and was accomplished and the the surgical area was clipped and antiseptic scrubbed was carried out properly, with chlorhexidine and alcohol

Anesthesia was maintained by the administration of isoflurane in 100% Oxygen. Blood pressure (both systolic and diastolic), heart rate, respiratory rate, O2 saturation, CO2 saturation and the percentage of inhalation anesthesia used was monitored every 5 minutes.Similarly, the number of tracheal tubes used, bupivacaine dose, start time, end time, time of extubating and quality of awakening were also recorded.

The surgery started with an incision at the level of the post umbilical midline at a distance of 1 cm from the umbilicus. All the surgical procedures were performed following the standard technique described by Fossum T. et al., 2019. The subcutaneous tissue is then carefully sectioned until the white line (white fibrous band) is reached, where the muscles that make up the abdominal wall converge. Then with the help of tweezers we raise the white line and with the help of a scalpel we make a small opening at this level.

Then we introduce the finger through this buttonhole and check that there are no adhesions at this level. In some cases, when the bitch is pregnant, has pyometra or is in heat, a larger incision is required.

Using dissection forceps, we elevate the left abdominal wall, and with the help of an Ovariohysterectomy hook, we locate the left uterine horn. The suspensory ligament is then stretched or broken with the help of the fingers. When the ovarian bag is located, it should be clamped caudally with two hemostatic forceps while we hold the entire ovary with our fingers. When the forceps are removed, a groove is left where it is sutured with absorbable monofilament. Before making the cut, a dose of bupivacaine is administered. The same process is then repeated in the other uterine horn.

Then an opening is made in the broad ligament and a suture of the uterine arteries and veins is performed. Finally, the uterine body is exteriorized until the cervix is located and two hemostats are placed, with which some grooves will be created that we will use to make two Miller sutures. Finally, bupivacaine was administered into the abdominal cavity and closed in layers with absorbable monofilament suture.

Once the operation was finished, Carprofen was administered via SC.

The recovery quality was determined using a semi-objective method in which different parameters were determined, such as time to awakening, postoperative pain, if it was nervous, anxious, scared, depressed, whether he was stiff, aggressive, or if it was crying or whimpering.

Depending on how they were found, it was classified on a 5-point scale. 1 (very poor quality), 2 (poor quality), 3 (good quality), 4 (very good quality), 5 (excellent quality).

Once the surgery was finished, the recovery of the animal was evaluated by means of the pain scale of the modified Glasgow scale (Testa et. al., 2021) (Annex 2), was used to obtain semiquantitative data of the degree of postoperative pain. This numerical figure was obtained by adding different scores depending on how the animal is, if has pain in the incision, if it shows signs of pain on palpation, if it is able to move without pain after surgery, if it is relaxed or on the contrary, he is nervous, anxious or in pain, etc.

Those animals that exceeded 6 points indicate that they are showing some sign of pain and that is why, in the case of these animals, a rescue microdose of xylazine was needed. Although the ideal would be its assessment at half an hour, at one hour and at two hours, it was only possible to carry out the assessments at an hour after each surgery.

Statistical Analysis

For the statistical analysis, means and their respective standard deviations were made, for some of the variables studied (sedation scale, awakening and Glasgow scale) the data have been analyzed using the Wilcoxon method, which is a non-parametric test that allows to check if the mean values of two dependent groups differ significantly from each other. The analysis was carried out using the R program version 4.05. For the variables that were measured at all times (Pre, time 5 - 85 min, post, 1h), which are the variables isoflurane, heart rate, respiratory rate, systolic and diastolic blood pressure, the data have been analyzed using a mixed linear model. This model allows comparing the evolution of each of these variables between anesthetic protocols and / or between times.

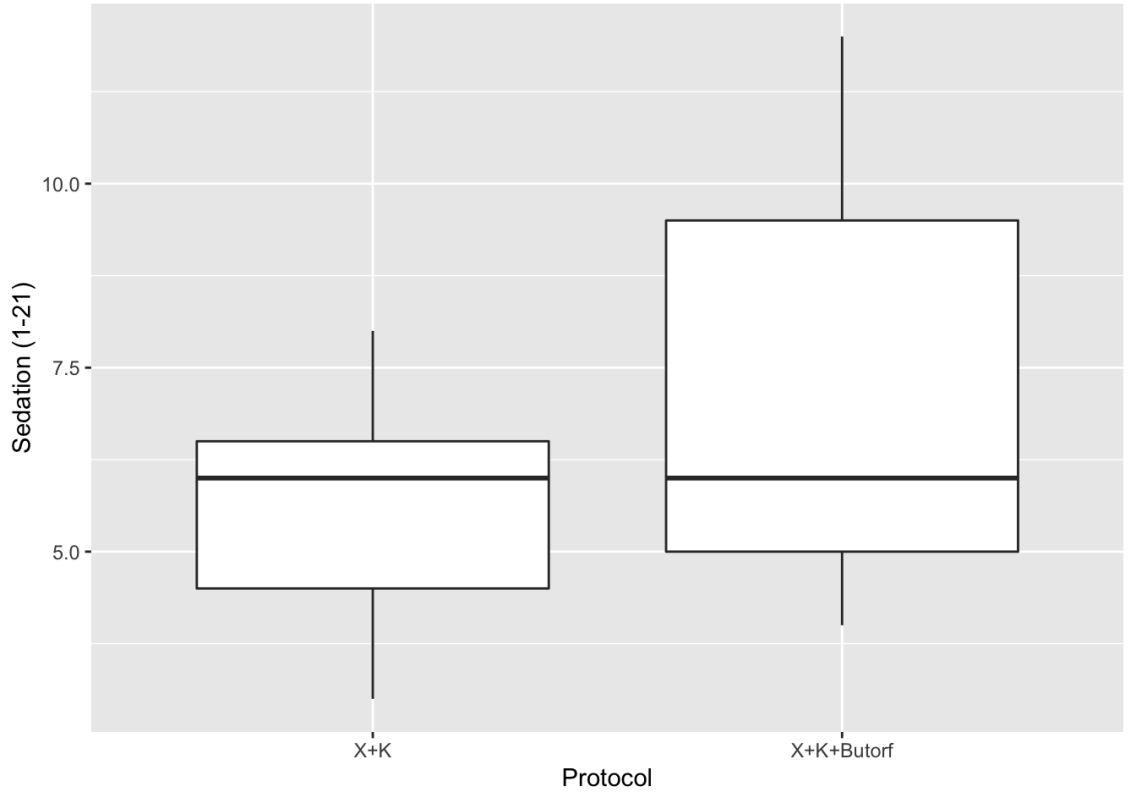
RESULTS

All dogs successfully completed the trial and no complications were observed. Two patients had to be removed from the study, for positive filarial test, for being classified as ASA 2 and to maintain 11 dogs per group, respectively.

Sedation

The means of the preanesthetic values were different, the preanesthetic mean of group A was (5,55±1,75), compared to that of group B, which was (7,09±2,84).

This difference is not statistically significant between the two control groups, since the value of p > 0,05 (0,333). But we see that the GB group has a tendency to deeper sedation, than that of the GA group, which has less sedation.



X+K	X+K+Butorf
5.55 (1.75)	7.09 (2.84)

##

Wilcoxon rank sum test with continuity correction

##

data: Sedation (1-21) by Protocol

W = 45.5, p-value = 0.333

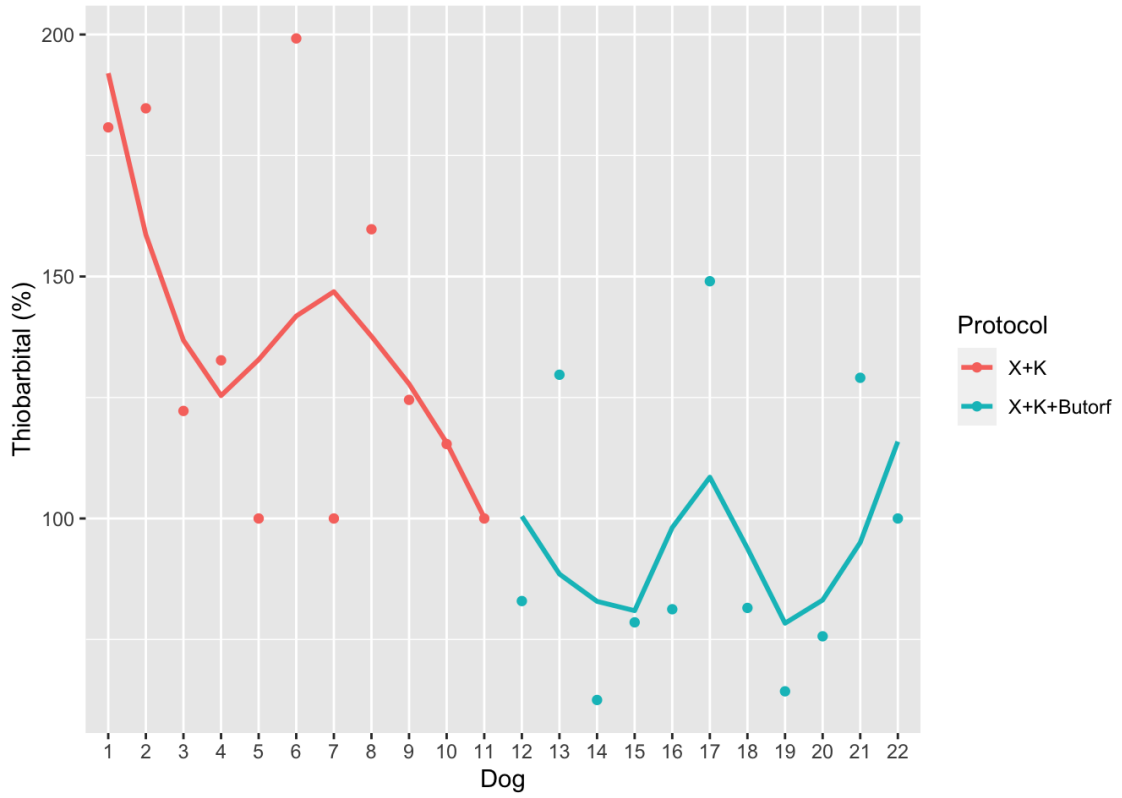
alternative hypothesis: true location shift is not equal to 0

In this graph, although the median are equal, and there are no statistical differences, we see that there is a greater tendency in group B to have deeper sedation than that of group A.

Induction

The thiobarbital dose varied depending on grade of sedation of each animal, to determine the statistical variability and see if there were significant differences, the average of the two protocols was made. The thiobarbital mean of group GA (Xylazine + Ketamine) was 138,12 ± 36,80, compared to that of group GB (Xylazine + Ketamine + Butorphanol), which was 94,04 ± 29,08.

There were statistically significant differences between the two groups, with a p value < 0,05 (0,00781), with a confidence level of 95%.



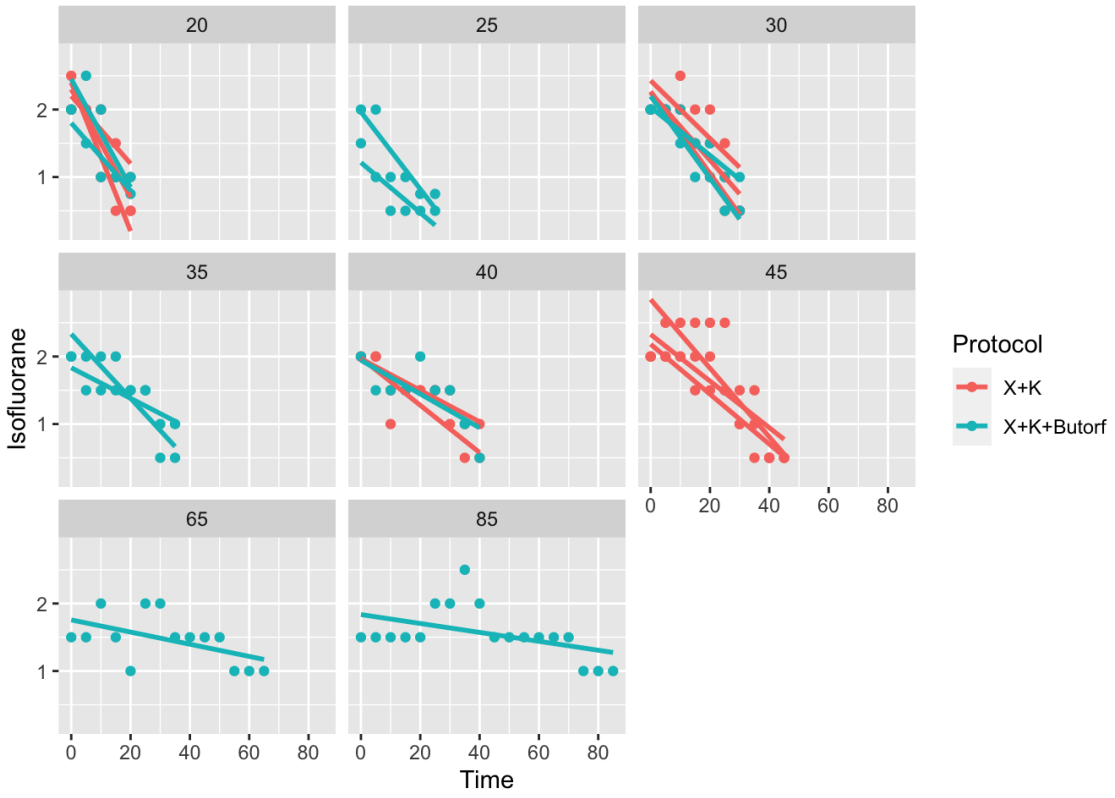
X+K	X+K+Butorf
138.12 (36.80)	94.04 (29.08)

```
##
 ##  Wilcoxon rank sum test with continuity correction
 ##
 ## data:  Thiobarbital (%) by Protocol
 ## W = 101.5, p-value = 0.00781
 ## alternative hypothesis: true location shift is not equal to 0
```

This graph indicates that GA required a higher dose of thiobarbital than GB. GA required its standard dose and an extra dose of thiobarbital (in most cases), while GB required a lower dose than the standard dose. This informs us that the animals in the GB group are more sedated than those in the GA group.

Maintenance

In these graphs we see that there are no significant differences in terms of the decrease in isofluorane requirements between one protocol and another, since p > 0,005 (0,61054). But if we see a statistically significant difference in terms of time, since as shown in graph 2 dogs in group B, had a longer surgery, compared to the other animals, that the longest surgery was 45 minutes, p < 0,005 (< 2e-16).

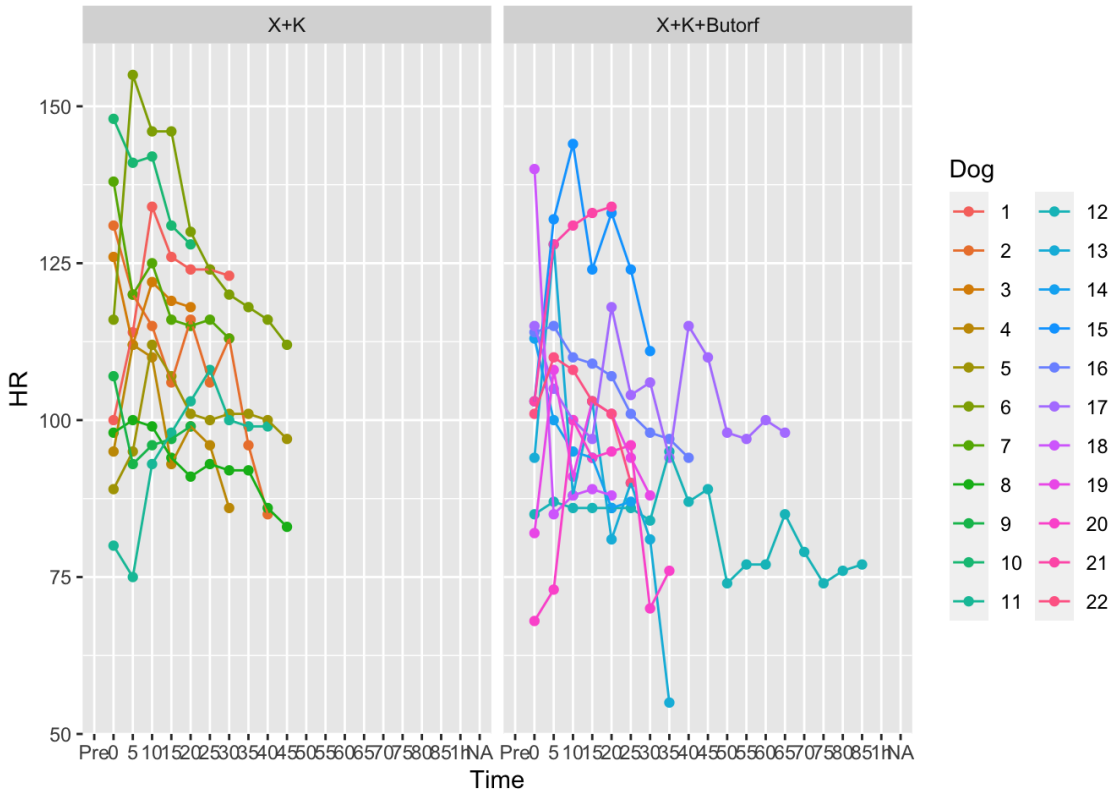



```
## Type III Analysis of Variance Table with Satterthwaite's method
##               Sum Sq Mean Sq NumDF   DenDF  F value  Pr(>F)
## Time         25.2075 25.2075      1 146.639 237.6549 < 2e-16 ***
## duration      1.5297  0.2185      7  31.016   2.0603 0.07854 .
## Protocol      0.0289  0.0289      1  13.152   0.2722 0.61054
## Time:duration 12.9610  1.8516     7 146.639  17.4565 < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Heart rate

In these graphs we see that there are no significant differences in heart rate between one protocol and another, since p > 0,005 (0,1058). But if we see a statistically significant difference in terms of time, since as shown in graph 2 the dogs of group B, had a longer surgery, compared to the other animals, that the longest surgery was 45 minutes, p < 0,005 (2,272e-5).

Although there is no statistically significant difference, in the graph we see a tendency for group B to have a lower heart rate than group A.

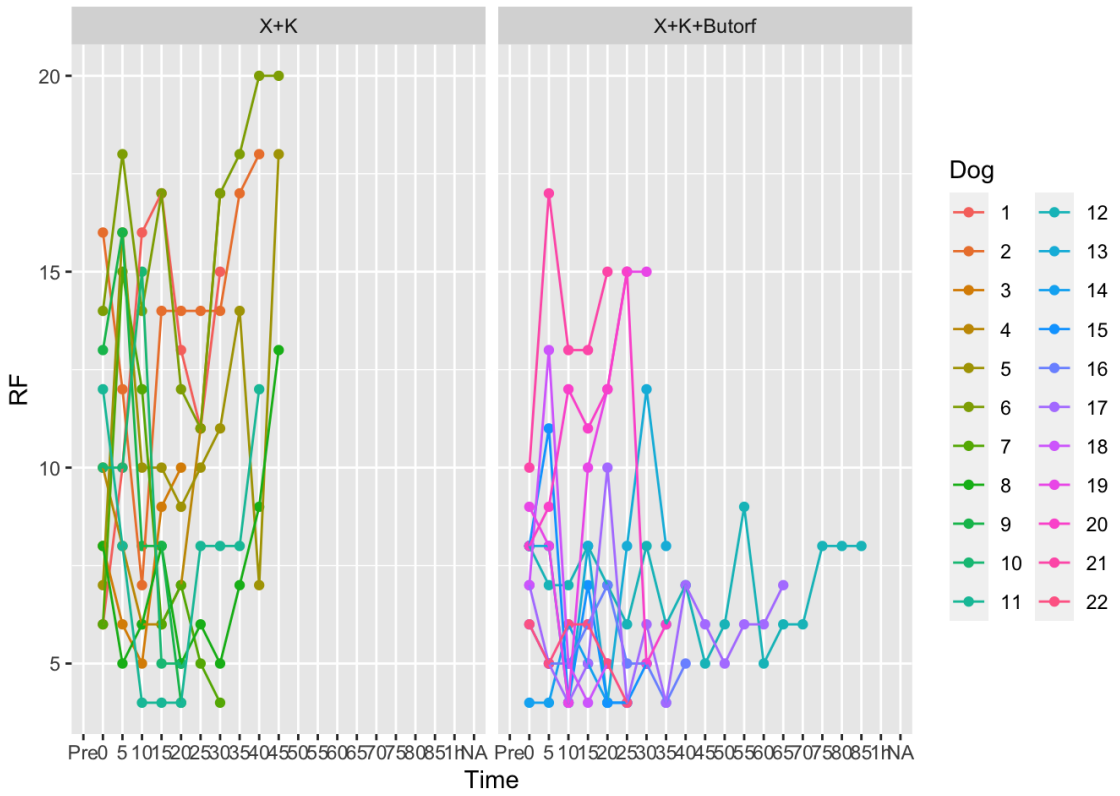



```
## Type III Analysis of Variance Table with Satterthwaite's method
##              Sum Sq Mean Sq NumDF   DenDF F value Pr(>F)
## Time         2075.65 2075.65      1 157.590 19.0715 2.272e-05 ***
## Protocol      306.86  306.86      1  24.491  2.8195    0.1058
## Time:Protocol  11.89   11.89      1 157.590  0.1092    0.7415
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Respiratory rate

In these graphs we see that there are no significant differences in respiratory rate between one protocol and another, since p > 0,005 (0,20739). But if we see a statistically significant difference in terms of time, since as shown in graph 2 the dogs of group B, had a longer surgery, compared to the other animals, that the longest surgery was 45 minutes, p < 0,005 (0,04947).

Although there is no statistically significant difference, in the graph we see a tendency for group B to have a lower respiratory rate than group A.



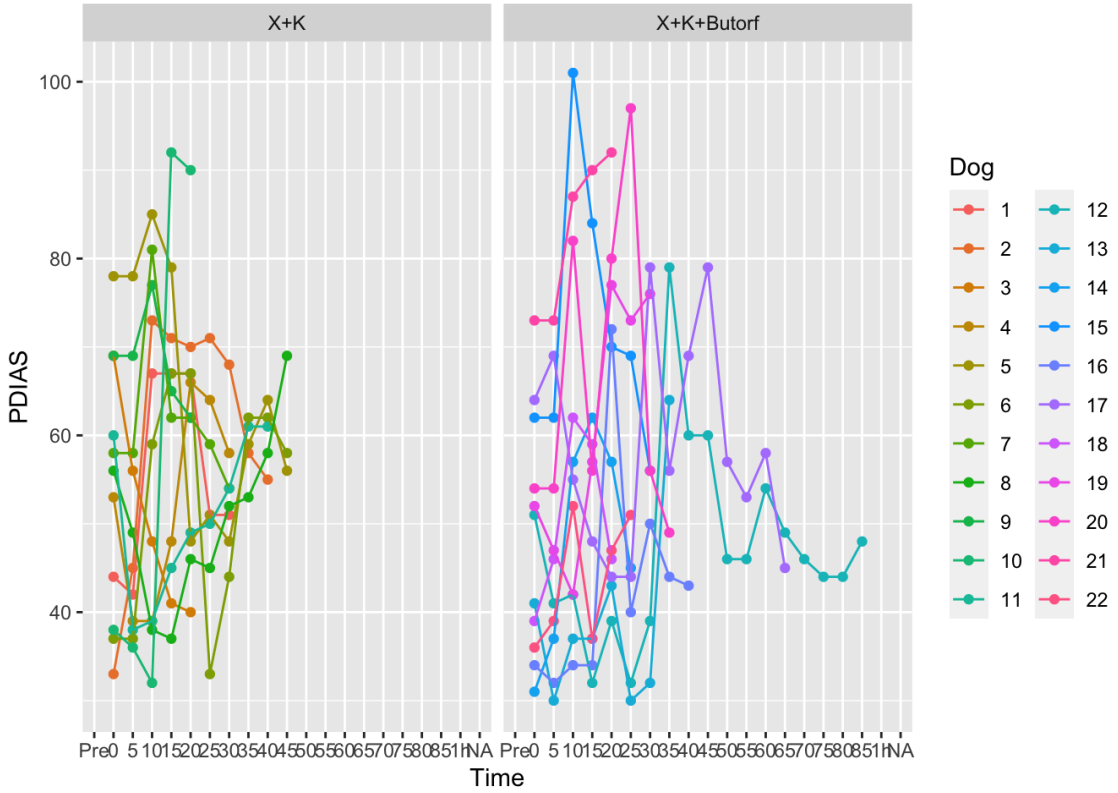
Type III Analysis of Variance Table with Satterthwaite's method

	Sum Sq	Mean Sq	NumDF	DenDF	F value	Pr(>F)	
Time	32.042	32.042	1	161.592	3.9180	0.04947	*
Protocol	13.597	13.597	1	29.179	1.6625	0.20739	
Time:Protocol	36.386	36.386	1	161.592	4.4491	0.03646	*

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Diastolic pressure

In these graphs we see that there are no significant differences in diastolic pressure between one protocol and another since p > 0,005 (0,88308). But if we see a statistically significant difference in terms of time, since as shown in graph 2 the dogs of group B, had a longer surgery, compared to the other animals, that the longest surgery was 45 minutes, p < 0,005 (0,02591).



Type III Analysis of Variance Table with Satterthwaite's method
Sum Sq Mean Sq NumDF DenDF F value Pr(>F)
Time 3372.7 374.74 9 126.002 2.2032 0.02591 *
Protocol 3.8 3.76 1 22.122 0.0221 0.88308
Time:Protocol 585.6 65.06 9 126.002 0.3825 0.94168

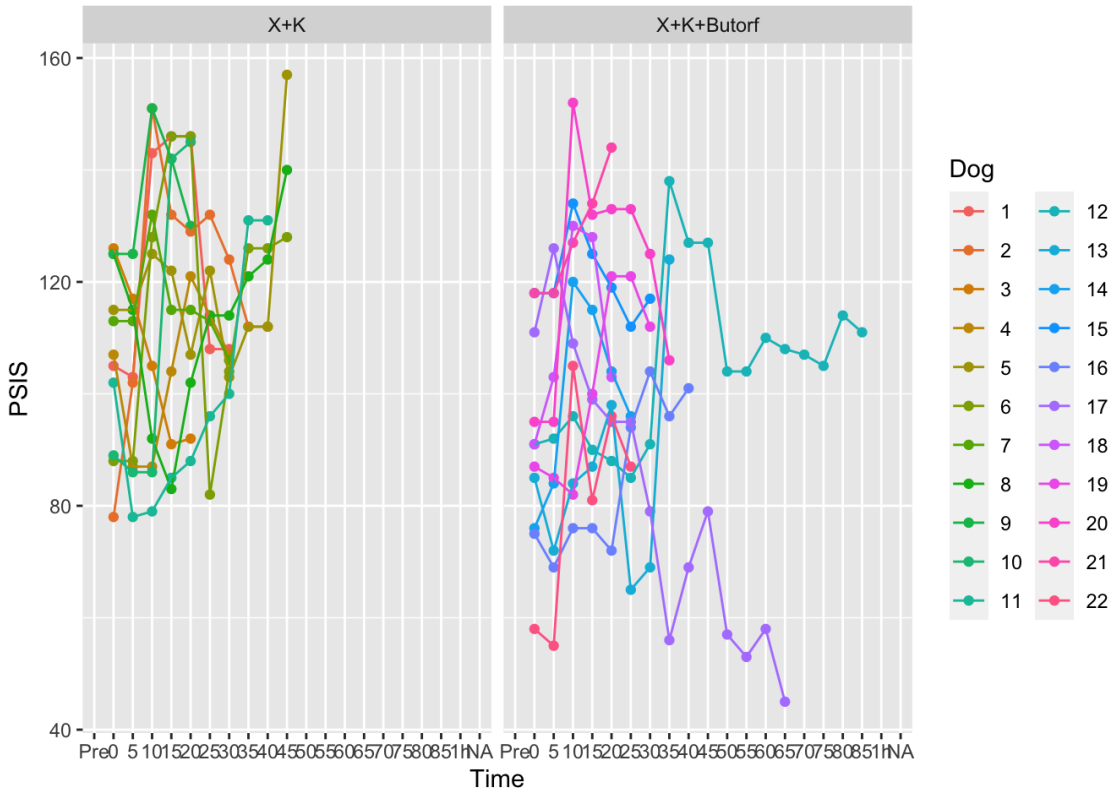
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Systolic pressure

In these graphs we see that there are significant differences in systolic pressure between one protocol and another since p > 0,005 (0,028100). Also, we see a statistically significant difference in terms of time, since as shown in graph 2 the dogs of group B, had a longer surgery, compared to the other animals, that the longest surgery was 45 minutes, p < 0,005 (0,002576).

The mean systolic pressure of GA was 141,67 ± 14,57, compared to that of GB, which was 103,0 ± 33,94, at minute 45.

This indicates that systolic pressure was lower in group B than in group A, which is indicative of greater sedation and therefore a lower level of pain.



Type III Analysis of Variance Table with Satterthwaite's method

##	Sum Sq	Mean Sq	NumDF	DenDF	F value	Pr(>F)
## Time	8236.9	915.22	9	126.194	3.0333	0.002576 **
## Protocol	1663.9	1663.85	1	22.355	5.5145	0.028100 *
## Time:Protocol	980.3	108.92	9	126.194	0.3610	0.951391

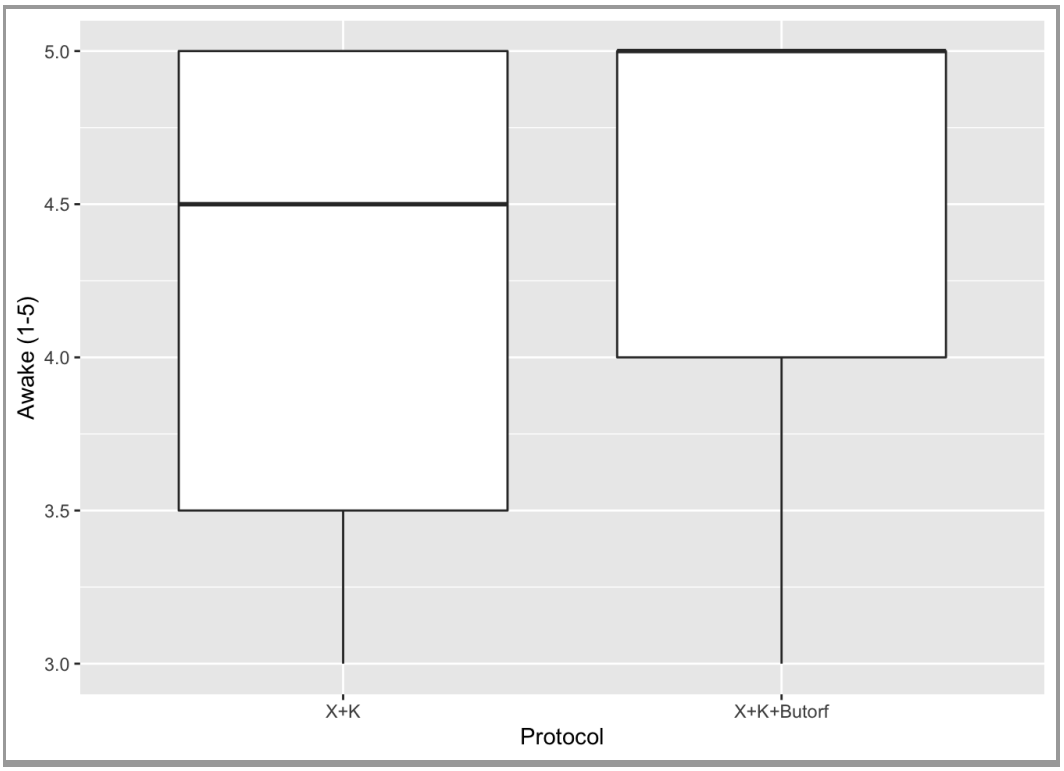
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Protocol	0	5	10	15	20	25	30	35	40	45
X+K	106.64 (16.32)	102.64 (15.69)	116.27 (27.32)	118.91 (24.84)	120.09 (21.18)	110.12 (15.37)	108.25 (7.57)	120.40 (8.44)	121.00 (8.60)	141.67 (14.57)
X+K+Butorf	91.36 (18.69)	92.45 (22.46)	110.45 (24.42)	106.09 (21.48)	106.64 (20.83)	98.67 (20.48)	99.57 (20.64)	104.00 (31.34)	99.00 (29.05)	103.00 (33.94)

Recovery quality

The means of the Recovery Quality were different, the mean of group A was (4,23±0,88), compared to that of group B, which was (4,55±0,69).

This difference is not statistically significant between the two control groups, since the value of p > 0.05 (0,3847). But we see that the GB group has a tendency to a better awakening level than the GA group, which has a lower/worse awakening level.



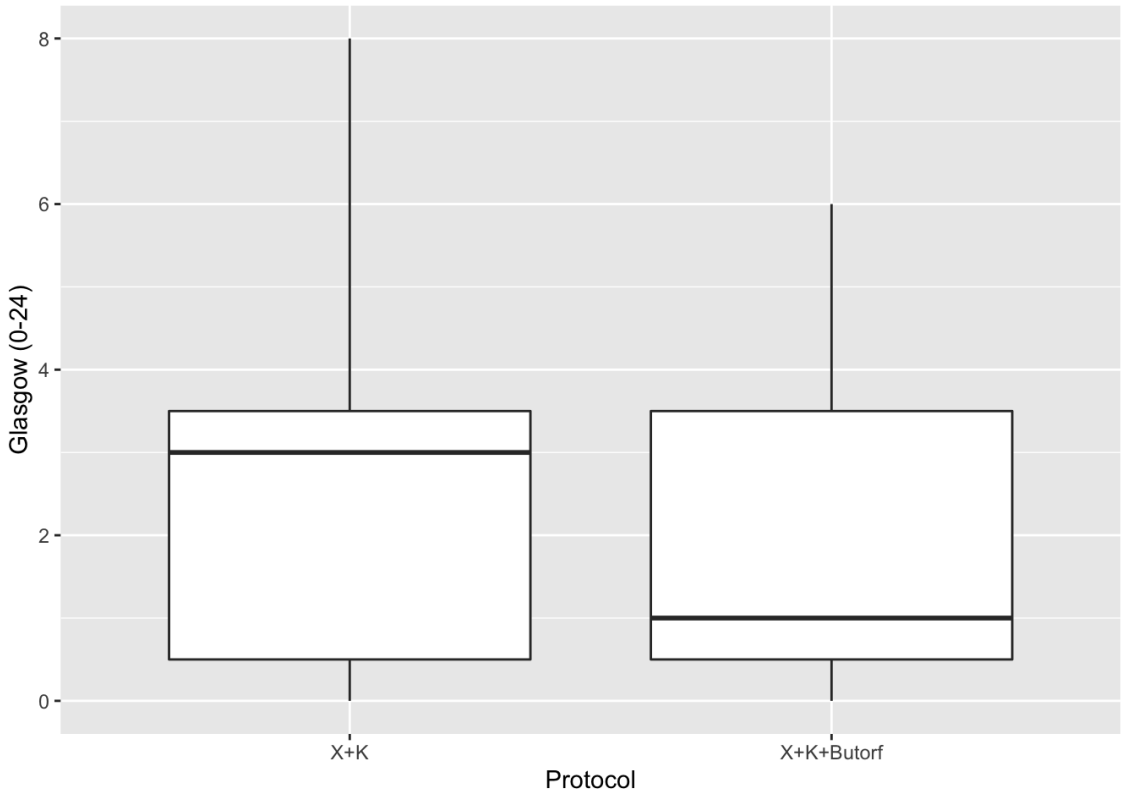
X+K	X+K+Butorf
4.23 (0.88)	4.55 (0.69)

##
Wilcoxon rank sum test with continuity correction
##
data: Awake (1-5) by Protocol
W = 48, p-value = 0.3847
alternative hypothesis: true location shift is not equal to 0

Glasgow

The means of the Glasgow scale were different, the Glasgow mean of group A was (2,64±2,62), compared to that of group B, which was (1,91±2,02).

This difference is not statistically significant between the two control groups, since the value of p > 0.05 (0,6618). But we see that the GB group has a tendency to a lower pain level than the GA group, which has a higher pain level. This indicates that the GB has a better analgesia than the GA group.



##

Wilcoxon rank sum test with continuity correction

##

data: Glasgow (0-24) by Protocol

W = 67.5, p-value = 0.6618

alternative hypothesis: true location shift is not equal to 0

X+K	X+K+Butorf
2.64 (2.62)	1.91 (2.02)

DISCUSSION

Ovariohysterectomy is a very common surgery in hospitals and veterinary clinics and, like other surgeries, requires an adequate anesthetic protocol, which includes a correct premedication avoiding the adverse effects derived from the use of these drugs.

The selection of appropriate pre-anaesthetic drugs prior to general anesthesia will provide a smoother induction and maintenance phase of anesthesia. Catecholamine release will be reduced, subsequently reducing anxiety and problems associated with catecholamine release such as cardiac arrhythmias. Intravenous catheter placement and pre-oxygenation can prove less challenging (Waring, 2017). Unfortunately, no single drug has all these properties, therefore a multi-modal approach is required to fulfill a patient's needs (Waring, 2017).

Pre-anesthetic medicines are generally given to avoid the adverse events associated with general anesthesia, facilitate surgery, and reduce the risk of postoperative complications (Kulkarni & Patil, 2017). Preanesthesia varies depending on which protocol was applied, group GA (Ketamine and Xylazine), group GB (Ketamine, Xylazine and Butorphanol).

In our work Butorphanol was included in our study based on its analgesic properties and our lack of opioids.

Ketamine, in contrast to most of the anesthetic drugs, it has been shown to possess incremental effects on the heart rate, blood pressure and respiratory rate due to increase in sympathetic activation (von Ungern-Sternberg et al., 2007). Although ketamine does not have a specific antagonist, at clinically used dosages in dogs, ketamine has a relatively short anesthetic action with minimal cardiovascular adverse effects(Haskins et al., 1985). Ketamine is frequently used in combination with other sedatives and tranquilizers that have muscle relaxation properties to attenuate muscle hypertonic effects (Haskins et al., 1985).

Ketamine has been used to produce isoflurane-sparing effects and postoperative analgesia. Ketamine continuous rate infusion reduced the minimum alveolar concentration of isoflurane in a dose-dependent fashion (Muir et al., 2003).

Alfa-2 Agonists have a versatile dosing profile. That allows low and even micro doses in combination with opioids to be clinically useful and minimizes the cardiovascular effects. (Epstein et al., 2015).

This is because alfa-2 adrenergic agonists (Xylazine), are synergistic with opioids allowing them to be used in low-dose combinations, either with or without ketamine, to great effect for both sedation and analgesia (Epstein et al., 2015). The results obtained suggest that the second protocol in which butorphanol (opioid) is included, gives better results in combination with ketamine and xylazine, corroborating the Perkowski´s hypothesis.

Butorphanol is a synthetic opioid derivative analgesic that exerts its effect on kappa receptors. Though it binds to mu-receptors, its effect on these receptors is minimal. Therefore, it is also used as a mu-receptor antagonist (Caulkett et al. 2003). This last effect explains its low potential to produce respiratory depression. It has been reported to provide sedation and limited, short-term analgesia for various diagnostic or therapeutic procedures (Caulkett et al. 2003).

In my study with the combination of ketamine, xylazine and butorphanol have been observed to decrease the amount of thiobarbital as an inducing agent. Other studies such as the study of Dr. Campbell., observed a decrease in thiobarbital requirements, but using acepromazine as a premedication (Campbell et. al., 2003).

Combination of drugs with different pharmacological mechanisms provides greater analgesia than each drug given alone, with further inhalation sparing effect (Muir et al., 2003; Aguado et al., 2011; Gutierrez-Blanco et al., 2013). Butorphanol is a short acting opioid analgesic and decreases the concentration of isoflurane needed for anesthesia (Camargo et al., 2011).

Anesthetic maintenance forms an important part of surgery, in this case both isoflurane and sevoflurane have rapid onset and offset of action which allows for quick onset of sedation and awakening. Volatile anesthetics primarily act on the cerebral cortex, depressing the sensorium even at low concentrations, and leave autonomic functions relatively undisturbed (Misra & Koshy, 2012).

The Isoflurane requirement is an easily quantifiable pattern that provides us with important data, which is the state of sedation of the animal and therefore the analgesic requirement. In our case, it was found that there were no statistically significant differences between both groups, however there was a small trend that show better results. Further studies with a larger sample probably it would show data statistically significant in terms of butorphanol usefulness in practice.

It should be noted that during anesthetic maintenance there are a series of adjuvants that help maintain better control of intraoperative and postoperative pain, like local anesthetics and NSAIDs

Local anesthetic (LAs) is the only class of drug that renders complete analgesia. The totality of evidence in humans and animal studies reveal the predictable analgesic and anesthetic drug-sparing effects of LAs. LAs are reported that can diminish postoperative maladaptive pain states. They do not appear to delay tissue healing. LAs can be administered either directly at a simple incision site or at a specific nerve to provide analgesia to a large region (or area) (Epstein et al., 2015).

Local anesthetics are frequently given in combination with an opioid (e.g., bupivacaine with butorphanol) to produce effective analgesia while decreasing the overall dose of local anesthetic given (Perkowski S. Z., 2006) Local anesthetic, bupivacaine has been included in our study in both groups (GA and GB) as a part of multimodal anesthetic and provides its sinergetic effect in order to improve depth anesthetic and a better quality of pain control. These results are also showed by other authors (Campagnol et. al., 2012).

During the study carried out, all the patients that were approved for the ovariohysterectomy, they were administered ketamine in combination with xylazine

during the premedication, furthermore a local anesthetic block with Bupivacaine intraoperative (blockage suspensory ligament and intraperitoneal instillation) was performed during the surgery and finally after the surgery they were administered NSAIDs (carprofen), obtaining in all cases good results, without statistical significance. Al-Gizawiy et al. stated that preoperative carprofen provided better pain control compared with postoperative butorphanol in the 24 h following ovariohysterectomy in cats (Al-Gizawiy & Rudé, 2004).

The evaluation of vital signs is one of the important tasks of the anesthesiologist during maintenance control. It provides a great deal of information about the patient's condition during anesthesia. The stress response is a physiological response to trauma or surgery and is generally considered to be proportional to the degree of surgical trauma (Höglund et al., 2016).

Physiological parameters such as heart rate and blood pressure can be used as surrogate measures of the stress response and there are studies of the perioperative surgical stress response in healthy female dogs subjected to neutering (Höglund et al., 2016).

The heart beats because of a tiny electrical current that originates in the heart’s pacemaker called the sinoatrial node. Rhythmic electrical impulses or discharges cause the contraction of muscle fibers in the heart. While an animal is at rest, the sinoatrial node discharges many times each minute 60 to 120 times per minute in the dog. In general, the larger the species, the slower the rate of sinoatrial node discharge and the slower the heart rate (M. Cunningham, 2020). Although there is a trend of a higher values for heart rate group GA, this is not statistically significant.

A respiratory rate is how many times a dog takes a breath in a minute. This is usually done through a dog's nose but can also occur through the mouth when they are panting. The normal respiratory rate of a dog is 10-30 BPM (Kruzer Adrienne, 2022) There are some factors that could interfere in that range, like pain, exciting, exercise...

The values of respiratory rate were higher in GA, this is because butorphanol can cause respiratory depression, although it is also common to observe panting (Caulkett et al. 2003), however the differences were not statistically significant.

Blood pressure measurement is expressed as diastolic, systolic or as a mean arterial blood pressure. Normotension was considered to be 130 to 180 mm of Hg, systolic, and 60 to 95 mm of Hg, diastolic. (Weiser et al., 1977). In diastolic pressure there were no statistically significant differences between the two groups. On the other hand, in systolic pressure there were statistically significant differences, so that GB had values lower than those of the GA. Butorphanol causes hypotension, this would explain why it has lower diastolic values than those of group A. In addition, this would indicate that the animal has a deeper level of sedation than those of group A

These physiological parameters indicate that the GB group has better levels of sedation and analgesia than those of the GA group. Butorphanol produces hypotension, and decreases heart and respiratory rate, due to its effect on analgesics and sedatives.

Quality of recovery is a high-quality tool to assess patient perception for recovery after anesthesia and surgery (Surender et al., 2018). The presence of severe or uncontrolled pain after surgery has a negative impact not only on the quality of postoperative recovery but also on the occurrence of persistent or chronic pain. (P. Cata & Girish P., 2018).

Morton, define pain in animals is “an aversive sensory and emotional experience which elicits protective motor actions, results in learned avoidance and may modify species specific traits of behaviour including social behaviour” (Morton et al., 2005).

Despite evidence for physiological similarity across dog breeds, that the human perception of pain sensitivity in dogs is heavily influenced by group psychology (Gruen et al., 2020). This leads to the prediction that salient features that distinguish breed groups, like body size, age, body condition, breed will be related to ratings of pain sensitivity. However, these differences between races and ages occur because in their studies the assessments were based on subjective aspects of how each

person perceived the animals' pain and not through more objective pain determinations such as the modified Glasgow scale. Therefore, pain is quantifiable and measurable in dogs regardless of the subjective interpretation that each individual may have

Group GB, in which butorphanol was included, obtained better results, but these differences were not statistically significant in the quality of sedation, recovery and analgesia.

Is the use of opioids necessary or significantly advantageous, compared to their increasing abuse?

The “black box” warnings opioids carry on their prescription labels point out the dangers and risks of dependency for humans. Although veterinarians prescribe opioids for animals, they should be mindful of the potential for drug diversion abuse or illegal distribution on the part of the pet owner. These medications are potentially dangerous because they can cause profound sedation, respiratory depression and death, particularly when combined with other CNS depressants like benzodiazepines and alcohol (Yamamoto et. al., 2019).

The UN’s 2017 report on narcotic use reveal that the US, currently facing a crisis of opioid overuse, is an extreme outlier. US opioid use is the highest of any country in the world, in contraposition of so many poor countries that cannot access to this drug. Yet in India and other poor countries, many people are not being prescribed opioids when strong pain relief is necessary. In many of these countries, there is still an unfortunate taboo around the use of these drugs (Kopf, 2018).

This makes us ask if the use of opioids is necessary for pain management or if, on the contrary, there are other pharmacological alternatives for pain control.

Due to the low sample number and the differences between the times and ignorance on the part of the student in anesthesia, it is recommended to do new studies with a larger sample number and with greater knowledge on the subject, to provide more reliable results.

CONCLUSSION

The use of butorphanol combined with Xylazine, Ketamine and bupivacaine Group B showed a better quality of sedation. This difference was not statistically significant compared with the group GA although a clear tendency of a deeper sedation was showed in the Group B comparing with the Group A.

The presence of butorphanol in our standard protocol, Group A of the study demonstrated that thiobarbital requirement was reduced in this group. This difference was statistically significant compared with the Group A.

Physiologycal parameters HR, RF and Blood pressure did not demonstrate differecences statistically significant between both groups although the systolic pressure values were in general significantly lower in the Group B comparing with the Group A.

The standard combination Xylazine, Ketamine and bupivacaine blockage currently applied in the Insular Shelter of Gran Canaria provides a great level of sedation and analgesia and it can be taken into consideration especially when the access to the opioids is restricted.

Further studies are recommended in order to obtain a higher number of cases to consolidate the results obtained in this study.

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ANNEX 1. Sedation scale from Grint et al. 2009

1. Spontaneous posture

- standing =0
- tired but standing =1
- lying but able to rise =2
- lying but difficulty rising =3
- unable to rise =4

2. Palpebral reflex

- brisk =0
- slow but with full corneal sweep =1
- slow but with only partial corneal sweep =2
- absent =3

3. Eye position

- central =0
- rotated forwards/downwards but not obscured by third eyelid =1
- rotated forwards/downwards and obscured by third eyelid =2

4. Jaw & tongue relaxation

- normal jaw tone, strong gag reflex) = 0
- reduced tone, but still moderate gag reflex =1
- much reduced tone, slight gag reflex =2
- loss of jaw tone and no gag reflex =3

5. Response to noise (handclap)

- normal startle reaction (head turn towards noise/ cringe) =
- reduced startle reaction (reduced head turn/ minimal cringe) = 1
- minimal startle reaction =2
- absent reaction =3

6. Resistance when laid into lateral recumbenc

- much struggling, perhaps not allowing this position =0
- some struggling, but allowing this position =1
- minimal struggling/ permissive =2
- no struggling = 3b

7. General appearance/attitude

- excitable =0
- awake and normal =1
- tranquil =2
- stuporous =3

ANNEX 2. GLASGOW SCALE

SHORT FORM OF THE GLASGOW COMPOSITE PAIN SCALE

Dog's name _____

Hospital Number _____ **Date** / / **Time**

Surgery Yes/No (delete as appropriate)

Procedure or Condition_____

_____

In the sections below please circle the appropriate score in each list and sum these to give the total score.

A. Look at dog in Kennel

Is the dog?

(i)		(ii)	
Quiet	0	Ignoring any wound or painful area	0
Crying or whimpering	1	Looking at wound or painful area	1
Groaning	2	Licking wound or painful area	2
Screaming	3	Rubbing wound or painful area	3
		Chewing wound or painful area	4

In the case of spinal, pelvic or multiple limb fractures, or where assistance is required to aid locomotion do not carry out section **B** and proceed to **C**
Please tick if this is the case ☐ then proceed to C.

B. Put lead on dog and lead out of the kennel.

When the dog rises/walks is it?

(iii)	
Normal	0
Lame	1
Slow or reluctant	2
Stiff	3
It refuses to move	4

C. If it has a wound or painful area including abdomen, apply gentle pressure 2 inches round the site.

Does it?

(iv)	
Do nothing	0
Look round	1
Flinch	2
Growl or guard area	3
Snap	4
Cry	5

D. Overall

Is the dog? *(v)*		*Is the dog?* *(vi)*	
Happy and content or happy and bouncy	0	Comfortable	0
Quiet	1	Unsettled	1
Indifferent or non-responsive to surroundings	2	Restless	2
Nervous or anxious or fearful	3	Hunched or tense	3
Depressed or non-responsive to stimulation	4	Rigid	4

Total Score (i+ii+iii+iv+v+vi) = _____