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DIPARTIMENTO DI SCIENZE VETERINARIE

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Comparative study of premedication with Dexmedetomidine or Medetomidine combination with Methadone in cats.

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Abstract

Objective: This study evaluated and compared the haemodynamic and respiratory effects of two sedative premedication protocols based on alpha-2 adrenergic receptor agonists, Dexmedetomidine and Medetomidine, each combined with Methadone, in a homogeneous sample of clinically healthy feline subjects.

Materials and Methods: 19 cats were allocated into two groups (Dexmedetomidine Group and Medetomidine Group) and received intramuscular administration of either Dexmedetomidine or Medetomidine, both in combination with Methadone. The physiological parameters monitored included body temperature, heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure and peripheral oxygen saturation. Measurements were taken at regular intervals of 5 minutes over a twenty-minute period following injection.

Results: Both protocols produced effective sedation, although the group treated with Medetomidine exhibited statistically significant changes in several monitored parameters at 15 minutes post-administration. These included a more pronounced reduction in heart rate, systolic blood pressure, diastolic blood pressure, and peripheral oxygen saturation compared to the group treated with Dexmedetomidine, in which only systolic blood pressure showed a significant variation. While the combination with Methadone enhanced the sedative effects in both groups, notable physiological differences were observed between the two alpha-2 adrenergic agonists.

Conclusions: Medetomidine induced deeper sedation but was associated with greater cardiovascular and respiratory depression compared to Dexmedetomidine. These differences suggest that the choice of sedative protocol should be guided by an individualised clinical assessment, taking into account the patient's overall condition. The introduction of novel formulations, such as the combination of Vatinoxan and Medetomidine, may represent a promising alternative by offering effective sedation with an improved haemodynamic safety profile.

Chapter III

Materials and Methods

3.1 Study Population

This experimental study was carried out at the University Veterinary Teaching Hospital of the University of Messina, within the Department of Veterinary Sciences, located in Messina, Sicily (Italy).

The research involved a population of domestic cats (*Felis catus*), comprising 19 individuals: 10 males and 9 females ranging in age from 6 months to 2 years. The animals were sourced from both private households and animal shelters. Prior to inclusion, each cat underwent a thorough clinical examination to assess general health status and confirm suitability for participation in the trial.

Informed consent was obtained from either the owners or the responsible personnel at the care facilities, ensuring compliance with ethical standards and the welfare of the animals involved, in accordance with European Directive 2010/63/EU and the principles outlined by the Federation of Veterinarians of Europe (European Parliament and Council, 2010).

3.2 Sample Selection Criteria

The selection of subjects for inclusion in the study was based on clearly defined clinical criteria, with the aim of ensuring a homogeneous sample and minimising the influence of potential confounding variables. Domestic cats of both sexes were enrolled, with no restrictions regarding breed or body weight, provided they were classified as ASA I indicative of healthy individuals with no underlying systemic conditions (Grimm et al., 2015).

Cats presenting with systemic diseases, clinically significant abnormalities identified during the preoperative assessment, or a history of adverse reactions to sedatives or anaesthetic agents were excluded from participation.

All experimental procedures were carried out in full compliance with current ethical regulations concerning animal welfare and adhered to standards of Good Veterinary Clinical Practice (OIE, 2023).

3.3 Equipment, Materials Used and monitoring device

During the premedication phase, key physiological parameters were continuously monitored using a dedicated veterinary multiparameter monitor (Mindray, ePM 12MVet), calibrated in accordance with the manufacturer's specifications. The parameters assessed included:

- Body temperature (T), measured using a digital rectal probe connected to the monitoring unit;
- Heart rate (HR), recorded via a standard three-lead electrocardiogram (ECG), with electrodes positioned according to conventional anatomical landmarks;
- Respiratory rate (RR), evaluated non-invasively through visual inspection of thoracic movements and confirmed using a thoracic motion sensor integrated with the monitor;
- Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP), obtained via oscillometric technique using an appropriately sized cuff placed either on the forelimb or at the base of the tail, with the sensor aligned over a palpable artery (Hall et al., 2014);
- Peripheral oxygen saturation (SpO₂), measured using a digital pulse oximeter probe applied to the tongue or pinna, depending on peripheral perfusion quality.

All medications were administered using sterile single-use needles (22G–25G). All equipment employed during the procedures including syringes, needles, butterfly needles, intravenous catheters, ECG gel, sensors, and pressure cuffs was sterile and disposable.

3.4 Drugs Used in the Protocol

During the study, the feline subjects received intramuscular premedication consisting of either DEX (Dexdomitor, Zoetis) or MED (Sedator, Dechra) in combination with Methadone (Semfortan, Dechra), depending on their assigned experimental group.

3.5 Cat Preparation

Prior to the commencement of the study, each animal underwent a comprehensive clinical evaluation, including medical history, a general physical examination, and an assessment of vital parameters such as HR, RR, body temperature, and, depending on the animal's temperament, SBP, DBP and MBP.

All cats were fasted for at least 8 hours prior to pharmacological treatment, with unrestricted access to water maintained until 2 hours before the procedure, consistent with recommendations found in the American Animal Hospital Association (AAHA) guidelines for anesthesia [American Animal Hospital Association (AAHA) (2020)].

The injection site was prepared using 2% chlorhexidine digluconate applied with sterile gauze in a circular motion, to ensure local aseptic conditions. Throughout both the preparation and treatment phases, the animals were closely monitored for any signs of discomfort or adverse reactions.

3.6 Pre-anesthetic Pharmacological Treatment

The cats were randomly allocated into two groups, each receiving a different pharmacological premedication protocol:

- Dexmedetomidine Group (DG);
- Medetomidine Group (MG).

Throughout the study, relevant clinical and physiological variables were carefully monitored and recorded in order to assess the efficacy and safety of the two premedication protocols. All procedures were conducted in accordance with the protocols approved by the relevant institutional ethics committee.

3.6.1 Dexmedetomidine Group (DG)

The DG group received a premedication protocol based on the administration of DEX. The drug was administered intramuscularly at a dosage of 20 µg/kg prior to the initiation of the experimental procedures.

3.6.2 Medetomidine Group (MG)

The MG group underwent premedication with MED, administered intramuscularly at a dose of 40 µg/kg prior to the commencement of the experimental procedures.

3.7 Analgesic Treatment with Methadone

Methadone was chosen as the analgesic agent within the premedication protocols for both the Dexmedetomidine (DG) and Medetomidine (MG) groups due to its comprehensive pharmacological profile. This compound acts as a selective agonist of the μ -opioid receptors, which mediate central analgesia, and as an antagonist of N-methyl-D-aspartate (NMDA) receptors, thereby contributing to the prevention of central sensitisation and modulation of persistent pain (Kissin, 2000; Davis & Glare, 2003).

This dual mechanism of action makes Methadone particularly suitable for managing perioperative pain in veterinary patients, where profound and sustained analgesia is required with minimal disruption to physiological homeostasis. Furthermore, its combination with α 2-adrenergic agonists enhances both sedative and analgesic effects, improving the overall efficacy of premedication. (Robertson & Taylor, 2004). The synergy between methadone and α 2-agonists has been documented in veterinary anaesthesia studies, showing improved analgesia and reduced anaesthetic requirements (Slingsby et al., 2011; Posner et al., 2013). Such a protocol facilitates a balanced anaesthetic state, reduces surgical stress, and eases animal handling during the pre- and intraoperative phases.

3.7.1 Dosage and Administration

In both experimental groups, Methadone was administered intramuscularly at a dose of 0.2 mg/kg. The administration was timed to coincide with the corresponding α 2-agonist DEX in the DG and MED in the MG either simultaneously or within a short interval, to ensure optimal pharmacodynamic synergy (Reid et al., 2001). Injection sites were selected based on available muscle mass and strict aseptic conditions were maintained throughout the procedure.

3.7.2 Role of Methadone in Premedication

Methadone played a crucial role in the pre-emptive management and control of intraoperative pain, enhancing the overall analgesic profile of the premedication protocol. Its administration prior to anaesthetic induction allowed early intervention on nociceptive pathways, thereby reducing the requirement for additional analgesics during the procedure (Wagner et al., 2002). This pre-emptive effect proved beneficial in limiting pain transmission and contributed to a smoother and less stressful postoperative recovery for the patients (Woolf & Chong, 1993; Slingsby et al., 2011).

3.7.3 Possible Effects on Sedation

The combination of Methadone with α 2-agonists demonstrated positive effects on sedation quality. Treated subjects exhibited a deeper and more consistent level of sedation, accompanied by effective suppression of nociceptive reflexes and increased tolerance to clinical manipulations (Granholm et al., 2006a; Pascoe, 2000). From a haemodynamic perspective, this association helped minimise the risk of sudden fluctuations or instability. Furthermore, administering methadone in both groups allowed exclusion of its potential interference in the comparative evaluation of DEX and MED.

3.8 Evaluation of sedation parameters

Vital parameters were recorded at regular intervals of every 5 minutes throughout the 20-minute premedication phase to assess the pharmacodynamic effects and any physiological alterations induced by the different protocols. Monitoring began with an initial evaluation at time zero, that is, before the administration of the drugs. The variables measured during this period included body temperature, heart rate [HR (beats per minute, bpm)], respiratory rate [RR (respirations per minute, rpm)], systolic blood pressure [SBP (mmHg)], diastolic blood pressure [DBP (mmHg)], mean blood pressure [MBP (mmHg)], and peripheral oxygen saturation [SpO₂ (%)]. Clinical assessment of anaesthetic depth was based on observation of eye position, response to nociceptive stimuli, palpebral reflex, and mandibular muscle tone.

3.9 Statistical Analysis

All variables are reported as frequencies and percentages for categorical data, and as mean $\pm$ standard deviation (SD) for continuous variables. Student's t-test was performed for continuous clinical data to assess differences between groups. The Chi-squared test was used for categorical variables. To evaluate the variation of individual continuous variables over time within each treatment group, the paired Student's t-test was employed. In light of the findings presented in Table 6 namely, the presence of statistically significant changes in some of the variables analysed (HR, SBP, DBP and MBP, and SpO₂) at 15 minutes following administration of the drug assigned to each group further analyses were conducted.

Specifically, we assessed whether these significant changes were also maintained within each individual treatment group, using the paired Student's t-test. Differences were assumed to be significant for $p < 0.05$. All analyses were carried out with the statistical package R

(version 4.2.3) and RStudio Version 2025.05.1+513 for Windows (Posit Software, PBC, Boston, Massachusetts, USA).

Chapter IV

Results

4.1 Study Population

The entire study population ($n = 19$) was divided into two treatment groups: DG ($n = 9$) and MG ($n = 10$). Of the 19 enrolled subjects, 52.6% were male, and the mean age was 8.8 ± 3.2 months. Within the DG, the mean age was 8.0 ± 1.1 months, with males accounting for 55.5% of the subjects. In the MG, the mean age was 10.2 ± 5.2 months, and 50% of the subjects were male.

Table 5 presents the baseline clinical characteristics of the entire population divided into the two groups. No statistically significant differences were observed between the groups with regard to sex, weight, BCS, or any of the variables assessed at baseline, indicating excellent homogeneity between the two cohorts.

Table 6 presents the trends of the monitored variables across the entire population, divided into two groups, at 5, 10, 15, and 20 minutes following the administration of the study drugs, according to the treatment protocols applied to each group. Statistically significant differences were observed for the following variables: Heart rate at 5 minutes (HR5, $p = 0.008$), 10 minutes (HR10, $p = 0.005$), and 15 minutes (HR15, $p = 0.025$); Respiratory rate at 5 minutes (RR5, $p = 0.037$); Systolic blood pressure at 5 minutes (SBP5, $p = 0.0001$), 10 minutes (SBP10, $p < 0.0001$), 15 minutes (SBP15, $p < 0.0001$), and 20 minutes (SBP20, $p < 0.0001$); Diastolic blood pressure at 10 minutes (DBP10, $p = 0.018$), 15 minutes (DBP15, $p = 0.011$), and 20 minutes (DBP20, $p = 0.023$); Mean blood pressure at 15 minutes (MBP15, $p = 0.008$); Peripheral oxygen saturation at 5 minutes (SpO_2 5, $p = 0.020$), 15 minutes (SpO_2 15, $p = 0.010$), and 20 minutes (SpO_2 20, $p = 0.010$). Conversely, no statistically significant differences were observed for the following variables: T5, T10, T15, T20; HR20; RR10, RR15, RR20; DBP5; MBP5, MBP10, MBP20; SpO_2 10 ($p \geq 0.05$).

Table 5 – Demographics and clinical characteristics of whole population according to treatment group

Variable	All (19)	MED (10)	DEX (9)	P
Male, <i>n/%</i>	10/52.6	5/50	5/55.5	0.16*
Age, <i>months</i>	8.8±3.2	10.2±5.2	8±1.1	0.22^
Weight, <i>Kg</i>	4.3±1.0	4.2±0.9	4.6±1.1	0.33^
BCS	5.2±1.3	5.1±1.4	5.5±1.0	0.45^
T0, °C	38.6±0.3	38.7±0.3	38.5±0.3	0.29^
HR0, <i>bpm</i>	113.6±10.6	113.8±10.1	113.7±1.8	0.97^
RR0, <i>rpm</i>	37.7±4.9	37.5±5.1	37.9±4.9	0.83^
SBP0, <i>mmHg</i>	164.5±22.7	149.5±10.8	139.9±31.7	0.72^
DBP0, <i>mmHg</i>	113.5±13.4	118±13.4	108.8±12.1	0.13^
MBP0, <i>mmHg</i>	124.4±12.5	126±10.4	122.5±15.1	0.58^
SpO ₂ , %	99.2±0.8	98.9±1.0	99.8±0.3	0.1^

*: χ^2 ^: Student's t-test. **Abbreviations:** **MED:** Medetomidine; **DEX:** Dexmedetomidine; **BCS:** Body condition score; **T:** Temperature; **HR:** Heart rate; **RR:** Respiratory rate; **SBP:** Systolic blood pressure; **DBP:** Diastolic blood pressure; **MBP:** Mean blood pressure; **SpO₂:** Peripheral oxygen saturation.