Research in Veterinary Science 177 (2024) 105355

Contents lists available at ScienceDirect

Research in Veterinary Science

journal homepage: www.elsevier.com/locate/rvsc

Clinical effects of perineural dexmedetomidine or magnesium sulphate as adjuvants to ropivacaine in dogs undergoing tibial plateau leveling osteotomy

Federica Alessandra Brioschi [a,*], Vanessa Rabbogliatti [a], Luigi Auletta [a], Giuliano Ravasio [a], Martina Amari [a], Luigi Elia [a], Ilaria Gritti [b], Francesco Ferrari [a]

[a] Department of Veterinary Medicine and Animal Sciences, University of Milan, Milan, Italy
[b] Free Practitioner, Bergamo, Italy

ARTICLE INFO

Keywords:
Dexmedetomidine
Dog
Magnesium sulphate
Peripheral nerve block
Ropivacaine

ABSTRACT

The study aimed to compare the quality of perioperative analgesia, the motor block duration, and the effects on main cardiovascular parameters of dexmedetomidine (1 μg/kg/nerve block) or magnesium sulphate (2 mg/kg/nerve block) as adjuvants to 0.3% ropivacaine for sciatic and saphenous nerves block in dogs undergoing tibial plateau leveling osteotomy (TPLO). Dogs randomly received perineural dexmedetomidine-ropivacaine (D group), magnesium sulphate-ropivacaine (M group), or ropivacaine (C group). Fentanyl was administered in case of intraoperative nociception. Postoperative pain was assessed using the Short Form-Glasgow Composite Measure Pain Scale (SF-GCMPS) and VAS scale. The duration of motor blockade and intra- and postoperative cardiovascular parameters were also recorded. Group M required significantly more fentanyl than D group ($p = 0.04$). Group M had a significantly higher SF-GCMPS score than group C at 4 ($p = 0.002$) and 5 h after extubation ($p = 0.01$), and a significantly higher VAS score than group D at 3 h after extubation ($p = 0.03$), and at 4 h if compared to group C ($p = 0.009$). No significant differences regarding the duration of motor blockade were detected between groups ($p = 0.07$). The heart rate was significantly lower in group D than in M and C groups intraoperatively and during the first 1.5 h post extubation. The addition of dexmedetomidine or magnesium sulphate as adjuvants to perineural ropivacaine did not improve the quality of perioperative analgesia and did not prolong the motor blockade in dogs undergoing sciatic and saphenous nerves block for TPLO surgery.

1. Introduction

Tibial plateau leveling osteotomy (TPLO) is an invasive and painful surgery of the stifle, that requires an effective perioperative analgesic approach (Hoelzler et al., 2005). In dogs undergoing TPLO, peripheral nerve blocks (PNBs) provide better perioperative pain relief and comfort than systemic analgesics (Boscan and Wennogle, 2016; Palomba et al., 2020). In particular, the ultrasound-guided block of the sciatic nerve, combined with the block of the saphenous nerve, has been successfully used for the analgesic management of this type of surgery (Kalamaras et al., 2021; Marolf et al., 2021). Unfortunately, most of the PNBs' advantages are short-lived. Combinations between local anesthetics and adjuvant drugs have gained popularity in human medicine because they prolong sensory nerve block, enhance patients' satisfaction, and reduce postoperative opioid requirements (Edinoff et al., 2021). However, a limited number of studies have investigated the effects of adjuvant drugs combined with local anesthetics for PNBs in dogs (Acquafredda et al., 2021; Di Bella et al., 2023; Marolf et al., 2021; Marolf et al., 2022; Trein et al., 2017).

Dexmedetomidine is a potent α2-adrenoceptor agonist, with sedative and analgesic properties (Murrell and Hellebrekers, 2005). In humans, perineural dexmedetomidine, combined with a long-lasting local anesthetic agent, significantly prolongs sensory and motor nerve block durations, and limits the perioperative consumption of systemic analgesics, compared with local anesthetic alone (Vorobeichik et al., 2017); it is also reported that perineural administration of dexmedetomidine has the potential to induce bradycardia and hypotension in a dose-dependent manner (Rancourt et al., 2012). In dogs, perineural

* Corresponding author.
E-mail addresses: federica.brioschi@unimi.it (F.A. Brioschi), vanessa.rabbogliatti@unimi.it (V. Rabbogliatti), luigi.auletta@unimi.it (L. Auletta), giuliano.ravasio@unimi.i (G. Ravasio), martina.amari@unimi.it (M. Amari), luigi.elia@guest.unimi.it (L. Elia), francesco.ferrari@unimi.it (F. Ferrari).

https://doi.org/10.1016/j.rvsc.2024.105355
Received 21 April 2024; Received in revised form 20 June 2024; Accepted 9 July 2024
Available online 10 July 2024

dexmedetomidine, administered in combination with lidocaine (Acquafredda et al., 2021) and bupivacaine (Di Bella et al., 2023) for sciatic and femoral nerve blockage, prolonged the sensory block duration of the local anesthetics. However, veterinary studies disagree about dexmedetomidine's effectiveness in prolonging the sensory block duration of perineural ropivacaine (Marolf et al., 2021; Trein et al., 2017), and it seems not to reduce perioperative rescue analgesics requirement in dogs undergoing TPLO (Marolf et al., 2022).

Magnesium sulphate has antinociceptive effects by blocking the *N*-methyl-D-aspartate (NMDA) receptors and associated calcium channels, thus preventing central sensitization caused by peripheral nociceptive stimulation (Soave et al., 2009). In humans, the addition of magnesium sulphate to local anesthetics for PNBs prolongs sensory and motor blockage (Elyazed and Mogahed, 2018; Gunduz et al., 2006). To date, the effects on perioperative analgesia and motor block duration of perineural magnesium sulphate combined with local anesthetics for PNBs have not been investigated in dogs. Adding magnesium sulphate to spinal ropivacaine increased the duration of analgesia and the motor block provided by ropivacaine alone in dogs undergoing TPLO (Adami et al., 2016). In contrast, no analgesic benefits were reported when magnesium sulphate was combined with epidural ropivacaine in dogs undergoing hip arthroplasty (Lardone et al., 2017).

The present study aimed to evaluate and compare the quality of perioperative analgesia, the motor block duration, and the effects on main cardiovascular parameters in dogs undergoing TPLO, when the preoperative sciatic and saphenous PNBs were performed with a combination of 1 μg/kg dexmedetomidine and ropivacaine, 2 mg/kg magnesium sulphate and ropivacaine or ropivacaine alone. It has been hypothesized that 1) perineural dexmedetomidine or magnesium sulphate combined with ropivacaine would similarly improve perioperative analgesia, if compared to ropivacaine alone; 2) both perineural dexmedetomidine and magnesium sulphate combined with ropivacaine would prolong the motor blockage when compared with ropivacaine alone; 3) 1 μg/kg per nerve block dexmedetomidine would influence perioperative heart rate (HR) and arterial blood pressure.

2. Materials and methods

2.1. Animals

The study protocol was approved by the Institutional Ethical Committee for Animal Care at the University of Milan (OPBA_52_2023); the owner's written informed consent was obtained for all the dogs included in the present study. It enrolled client-owned dogs, presented to the Veterinary Teaching Hospital of the University of Milan (Lodi, Italy) for unilateral cranial cruciate ligament injury, that underwent elective TPLO surgery between May 2023 and December 2023. To be included in the study, all dogs were required to be 6 months-12 years old and to weigh 5–60 kg; they were also considered eligible for study participation if they were classified as American Society of Anesthesiologist physical status I or II, if they had a body condition score ranging between 4 and 6 out of 9 (Freeman et al., 2011) and if they could be hospitalized for 24 h after the end of surgery. The health status of dogs was confirmed by physical examination, complete blood cell count, serum biochemical analysis, electrocardiography, and echocardiography. Aggressive dogs, those that were affected by concurrent clinically significant orthopedic and/or neurologic diseases, that were administered analgesics and/or anti-inflammatory drugs within 15 days before surgery or that required other stifle surgeries in addition to TPLO, were excluded from the study; other exclusion criteria were: the presence of skin infection at the injection site for the sciatic or saphenous nerve block and the occurrence of persistent hypotension that required treatment with vasopressors during general anesthesia.

Forty-two client-owned dogs were initially recruited and four of them did not match the inclusion criteria; two dogs were excluded from the study because they experienced intraoperative hypotension requiring dopamine treatment due to the laceration of the popliteal artery, one dog underwent TPLO and simultaneous trochlear block recession and tibial tuberosity transposition to address medial patellar luxation, while one dog did not complete the 24-h postoperative assessment. Seven patients underwent bilateral TPLO surgery in two separate surgical sessions with a minimum of 8 weeks between interventions. Therefore, 38 dogs and 45 hindlimbs (25 right and 20 left hindlimbs) were finally enrolled in the study, the latter evenly distributed in the three groups of treatment (15 hindlimbs/group). The study sample included 32 female and 13 male dogs, ageing 86 ± 36 months, and weighting 27.9 ± 12.3 kg.

2.2. Study design

This clinical study was conceived as prospective, randomized, and blinded. All dogs were submitted to a temperament evaluation, using a score ranging from 1 (calm and friendly) to 4 (very excitable and nervous) (Maddern et al., 2010). Preoperative pain (T0, baseline) was assessed using the Short Form-Glasgow Composite Measure Pain Scale (SF-GCMPS) scoring from 0 (no pain) to 24 (20 if mobility is impossible to assess) (severe pain) (Reid et al., 2007) and with a 10 cm visual analogue scale (VAS) with endpoints labeled as “no pain” (0) and “worst imaginable pain” (10) (Adami et al., 2016).

Food was withheld 8 h before premedication and access to water was allowed up to 2 h before sedative drugs administration. Each dog was premedicated intramuscularly with acepromazine (0.02 mg/kg; Prequillan, FATRO, Italy) and methadone (0.2 mg/kg; Dechra Veterinary Products, Italy). After 30 min, a catheter was aseptically placed in the cephalic vein, and general anesthesia was induced with intravenous propofol (Proposure, Merial Italia S.p.A., Italy), titrated to effect, to achieve endotracheal intubation. Anesthesia was maintained with isoflurane (Isoflo, Esteve S.p.A., Italy) in oxygen. The end-tidal isoflurane concentration (FE'Iso) was initially set at 1.3% and adjusted by ±0.1% every 2 min, by the assessment of the anesthesiologist, to reach an anesthetic plane that maintained the absence of palpebral reflex, a ventral eye position, and relaxed jaw tone. Dogs were mechanically ventilated (Wato EX-35Vet, Mindray Animal Medical, USA), and the respiratory rate was set to maintain the end-tidal carbon dioxide concentration within the range of 35–45 mmHg (4.7–6.0 kPa). Lactated Ringer's solution (Ringer Lattato, Fresenius Kabi, Italy) was given intravenously at the rate of 3 mL/kg/h until extubation. Intravenous cefazolin (Cefazolina, Teva, Italy) 30 mg/kg was administered immediately before PNBs execution and subsequently repeated every 90 min.

In all dogs the pelvic limb requiring TPLO surgery was clipped and aseptically prepared for ultrasound-guided PNBs of the sciatic and saphenous nerves. The sciatic nerve block was achieved with the mid-femoral approach (Campoy et al., 2010) and the saphenous nerve block was performed using the technique described by Costa-Farré et al. (2011). Dogs were randomly (Microsoft Office Excel 2023, Microsoft Corp, USA) assigned to three different groups (15 dogs in each group) according to the composition of the perineural solutions. The three groups were administered a total volume of 0.1 mL/kg for each nerve block. The 30% of the total volume was 1% ropivacaine (Naropina 1%, Astra-Zeneca, Italy), while the remaining 70% was composed of adjuvants and sterile saline, to reach a final ropivacaine concentration of 0.3%. In the D group, the perineural solutions contained 0.3% ropivacaine and 1 μg/kg dexmedetomidine (Dexdomitor 0.5%, Vetoquinol S.p.A., Italy); in M group PNBs were performed with a solution containing 0.3% ropivacaine and 2 mg/kg magnesium sulphate (Magnesio Solfato Salf 20%, Salf S.p.A., Italy), whereas in C group 0.3% ropivacaine was given. The solutions were prepared by an operator not involved in the study. An anesthesiologist, unaware of the treatment allocation, performed the ultrasound-guided PNBs and all the intraoperative and postoperative evaluations.

Relevant variables, including HR, systolic, mean, and diastolic oscillometric noninvasive arterial pressure (SAP, MAP, DAP) measured

at 2-min intervals with the cuff placed around the right or left antebrachium, FE'Iso, end-tidal carbon dioxide concentration, body temperature and peripheral oxygen saturation were continuously monitored with a multiparameter monitor (S5 Compact Anesthesia Monitor, Datex-Ohmeda, USA). Furthermore, a lead II electrocardiogram was applied to identify the occurrence of any arrhythmias. In case of hypotension, defined as MAP lower than 60 mmHg, an intravenous crystalloid bolus (10 mL/kg lactated Ringer's solution, over 10 min) was given. Data regarding HR, SAP, MAP, DAP, and FE'Iso were recorded 5 min before PNBs execution (Tpre-PNB), immediately before surgical incision (Tpre-inc), at surgical skin incision (Tinc), and every 10 min thereafter. One orthopedic surgeon performed all the procedures, with the same surgical technique. In the event of a nociceptive response to surgery, defined as a sudden 20% increase in HR and/or MAP compared with the pre-stimulation values (defined as the values immediately preceding the sudden increase), an intravenous bolus of fentanyl (Fentadon, Eurovet Animal Health B.V., The Netherlands) at the dose of 1 μg/kg was immediately administered; the number of intraoperative fentanyl boluses given to each dog was recorded. Surgery time and time from induction of general anesthesia to extubation (anesthesia time) were also recorded.

Thirty minutes after extubation all dogs received a subcutaneous administration of 0.2 mg/kg meloxicam (Meloxidyl, Ceva, Italy); it was continued once a day for the next week. At 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12,18, and 24 h after extubation, HR, SAP, MAP, and DAP were recorded, and sedation, postoperative pain, and motor function were evaluated. The sedation level was assessed with a numerical scoring system ranging from 0 (no sedation) to 3 (profound sedation). Postoperative pain was evaluated using the SF-GCMPS (Reid et al., 2007) and the VAS (Adami et al., 2016) scoring systems. Rescue methadone (0.2 mg kg-1) was administered if an SF-GCMPS score $\geq$ 5/20 or $\geq$ 6/24 and/or a VAS score $>$ 4 were registered. The degree of motor blockade of the pelvic limb was assessed with a dedicated scale, developed by the Authors of the present study (Table 1). The duration of motor blockade, defined as the time elapsed from extubation to the return of normal movements of the pelvic limb (score 4) was also recorded. A small amount of food was offered 1.5 h after extubation and at any consecutive postoperative time points; time elapsed from extubation to first food intake was recorded. A follow-up period of 60 days was planned to evaluate any adverse effects.

2.3. Statistical analysis

An *a priori* sample size calculation (G*Power 3.1, Germany) was performed to identify the number of dogs required in each group. A minimum of 15 dogs per group was necessary to have a power of 80% with an alpha level of 0.05 and an effect size of $f = 0.49$ regarding the number of intraoperative fentanyl boluses (anticipated mean 3.5, 1.5, 1.5 for C, D, and M group respectively, with 1.9 standard deviation, SD). Mean number of fentanyl boluses and standard deviation were estimated from a previous pilot study. In addition, a *post hoc* sample size calculation (G*Power 3.1, Germany) was performed for F tests analysis of variance (ANOVA), with an effect size $f = 0.57$ (based on the mean and SD of the SF-GCMPS at 4 h after extubation within each study group), an alpha level of 0.05, and a total number of 45 patients and 3 groups. The achieved power resulted in 80%.

Table 1
Scale used for the assessment of the degree of motor blockade of the pelvic limb.

Grade	Description
Grade 0	No movements of the pelvic limb, the dog is unable to stand and walk
Grade 1	No movements of the pelvic limb, the dog can stand and walk
Grade 2	Minor movements of the pelvic limb and altered limb orientation while walking
Grade 3	Moderate movements of the pelvic limb and altered limb orientation while walking
Grade 4	Normal movements of the pelvic limb

Prism 8.2.0 (GraphPad Software, Inc., USA) was used for statistical analysis. The normality of data distribution was tested by Shapiro-Wilk's *W* test. Parametric data were reported as mean ± SD, and non-parametric data as median (range). Differences in basal values between groups were tested with ANOVA or by Kruskal-Wallis, according to distribution. *Post hoc*, Tukey's HSD or Dunn's test was applied, accordingly. Categorical variables were compared between groups with a chi-square test. Scored variables were compared between groups by the median test. Intra- and postoperative variables measured over time were compared between groups with a two-way repeated-measures mixed effect ANOVA with Geisser-Greenhouse correction. *Post hoc*, a Fisher's LSD test was applied to explore differences between groups and within groups over time. Values for $p < 0.05$ were considered significant.

3. Results

No statistical differences in sex distribution ($p = 0.64$), age ($p = 0.99$), body weight ($p = 0.81$), and temperament ($p = 0.13$) were detected between groups. The side of the hindlimb undergoing TPLO did not significantly differ between groups ($p = 0.31$). No statistical differences could be detected for the basal SF-GCMPS score ($p = 0.87$) nor the VAS ($p = 0.73$).

The intraoperative HR was significantly influenced by the treatment ($p < 0.0001$), by the time ($p = 0.002$), and by their interaction ($p < 0.0001$). Heart rate was significantly lower in the D group than in the M and C groups from Tpre-inc to T130 and from Tpre-inc to T110, respectively (Fig. 1-A). No dogs experienced atrioventricular block or other cardiac arrhythmias. Systolic arterial pressure, MAP, and DAP were significantly influenced by the time ($p = 0.002$, $p < 0.0001$, and $p < 0.0001$, respectively) and by interaction with the treatment ($p = 0.02$), but not by the treatment ($p = 0.06$, $p = 0.07$ and $p = 0.09$, respectively). In the D group, SAP was significantly higher at Tpre-inc, Tinc, T10, from T50 to T70 and T90 compared to values obtained in group M, and it was significantly lower at Tpre-PNB and higher at T100 compared to group C (Fig. 1-B). In the D group, MAP was significantly higher at Tpre-inc, Tinc, T20, T40, T60, T70, and T90 compared to group M, and it was significantly lower at Tpre-PNB and higher at T100 compared to group C (Fig. 1-C). In the D group, DAP was significantly higher at Tpre-inc, Tinc, T10, T20, T60, T70, and T90 compared to group M, and at Tpre-inc, T70, and T100 compared to group C (Fig. 1-D). Differences between and within groups on intraoperative HR, SAP, MAP, and DAP are summarized in Supplementary Table 1.

The FE'Iso was significantly influenced by the treatment ($p = 0.02$) and by the time ($p < 0.0001$), but not by their interaction ($p = 0.69$). Differences between and within groups on FE'Iso are summarized in Supplementary Table 1. The number of intraoperative fentanyl boluses ($n = 7$, $n = 25$, $n = 10$, in D, M, and C groups, respectively) resulted significantly different between groups ($p = 0.03$); in particular, the M group required a significantly higher number of boluses compared to the D group ($p = 0.04$). Regardless of the treatment group, fentanyl boluses ($n = 42$) were administered during skin incision (3/42), incision, distraction, and suture of the joint capsule (18/42), elevation of the popliteal muscle from the medial tibial border (4/42), tibial osteotomy (8/42) and skin suture (9/42). Mean surgery and anesthesia times were 118 ± 21 and 242 ± 38 min in group D, 123 ± 26 and 234 ± 47 min in group M, and 111 ± 26 and 210 ± 33 min in group C, respectively. No differences were detectable between the three groups for surgery and anesthesia times ($p = 0.42$ and $p = 0.08$, respectively).

The postoperative HR was significantly influenced by the time ($p = 0.003$) and by the interaction of treatment and time ($p < 0.0001$), but not by the treatment ($p = 0.35$). It was significantly lower in the D group if compared to M and C groups from 0 to 1 h after extubation, and at 1.5 h if compared to group C (Fig. 2-A). The postoperative SAP, MAP, and DAP were significantly influenced by the time ($p < 0.0001$), but not by the treatment group ($p = 0.39$, $p = 0.62$, $p = 0.95$, respectively) nor by

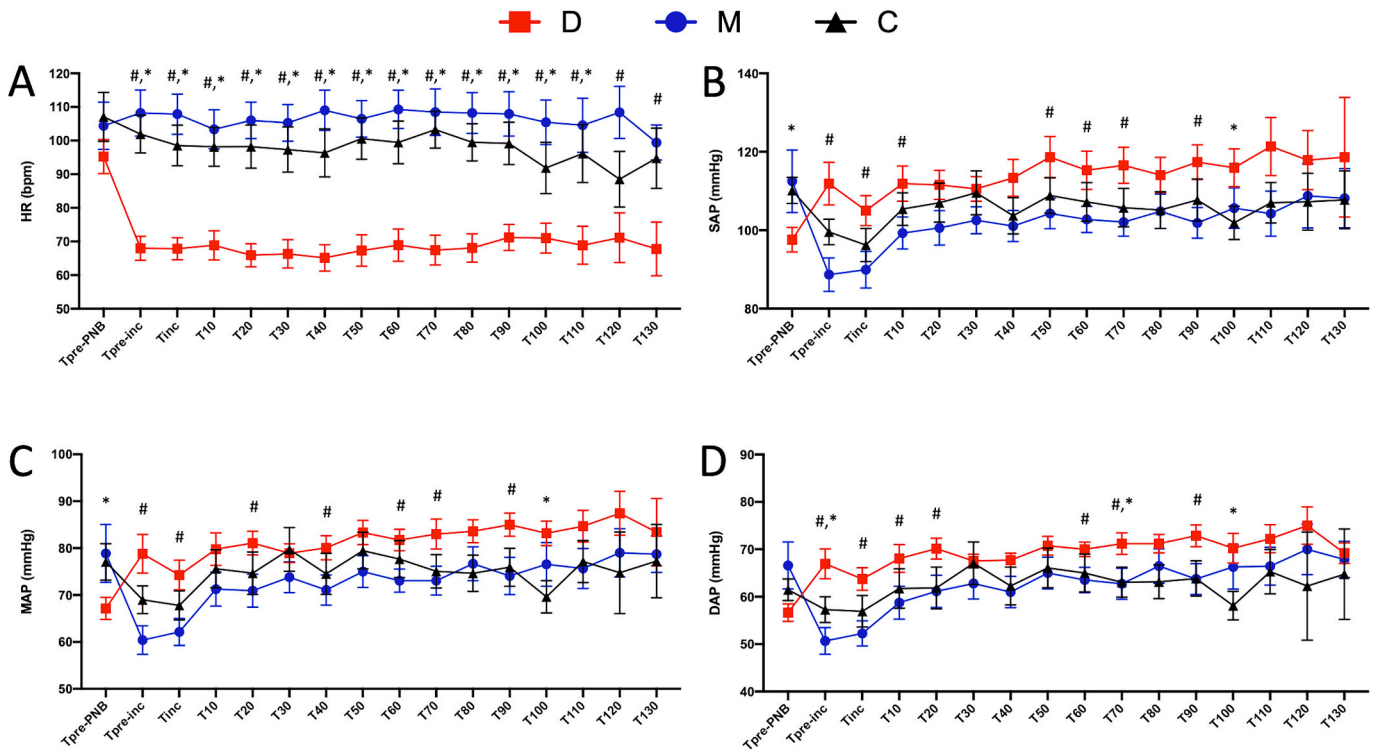

Fig. 1. Graphic representation of mean ± standard deviation cardiovascular parameters recorded at different intraoperative time points (Tpre-PNB, 5 min before peripheral nerve blocks execution; Tpre-inc, immediately before surgical incision; Tinc, surgical skin incision; intraoperative time points at 10 min intervals) in dogs that were administered perineural dexmedetomidine-ropivacaine (group D), magnesium sulphate-ropivacaine (group M) or ropivacaine (group C). In A, heart rate (HR; beats per minute, bpm) measurements; in B, systolic arterial blood pressure (SAP, mmHg) measurements; in C, mean arterial blood pressure (MAP, mmHg) measurements; in D, diastolic arterial blood pressure (DAP, mmHg) measurements. Statistics: # significant difference between D and M groups; * significant difference between D and C groups.

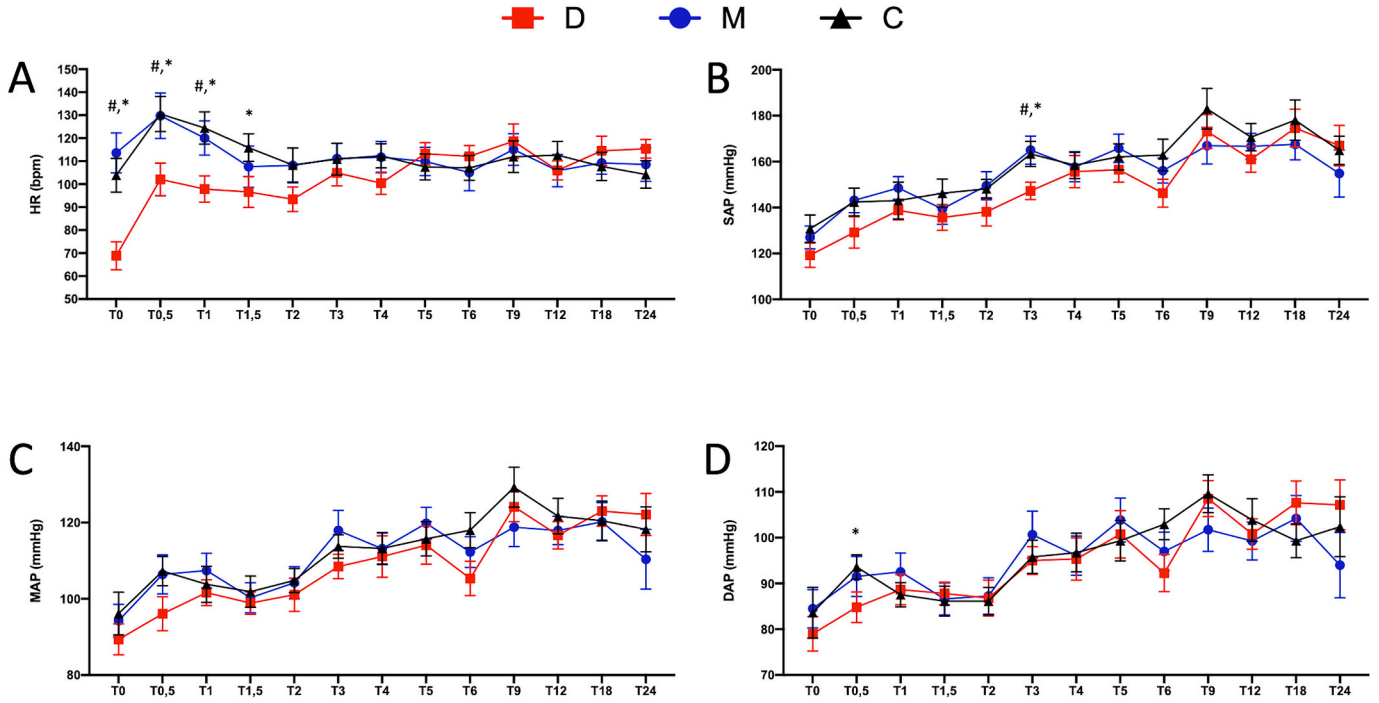

Fig. 2. Graphic representation of mean ± standard deviation cardiovascular parameters recorded at different postoperative time points in dogs that were administered perineural dexmedetomidine-ropivacaine (group D), magnesium sulphate-ropivacaine (group M) or ropivacaine (group C). In A, heart rate (HR; beats per minute, bpm) measurements; systolic arterial blood pressure (SAP, mmHg) measurements; in B, mean arterial blood pressure (MAP, mmHg) measurements; in C, diastolic arterial blood pressure (DAP, mmHg) measurements. Statistics: # significant difference between D and M groups; * significant difference between D and C groups.

its interaction with time ($p = 0.43$, $p = 0.40$, $p = 0.28$, respectively). Nonetheless, in the D group, SAP was significantly lower compared to that obtained in groups M and C at 3 h post extubation (Fig. 2-B). No significant differences could be detected between the three treatment groups for postoperative MAP (Fig. 2-C). In the D group, DAP was significantly lower compared to values obtained in group C at 0.5 h post extubation (Fig. 2-D). Differences between and within groups on postoperative HR, SAP, MAP, and DAP are summarized in Supplementary Table 2.

The postoperative sedation scores were significantly affected by time ($p < 0.0001$), but not by treatment ($p = 0.16$) nor by its interaction with time ($p = 0.36$). The SF-GCMPS scores were significantly affected by time ($p < 0.0001$), but not by treatment ($p = 0.25$) and its interaction with time ($p = 0.14$). Nonetheless, the M group had a significantly higher SF-GCMPS score at 4 ($p = 0.002$; Fig. 3-A) and 5 h after extubation ($p = 0.01$; Fig. 3-B), if compared to the C group. The VAS scores were significantly affected by time ($p < 0.0001$) and its interaction with treatment ($p = 0.009$), but not by treatment itself ($p = 0.29$). Indeed, Group D showed significantly higher scores compared to the C group at 0.5 and 1 h after extubation ($p = 0.03$ and $p = 0.008$, respectively; Fig. 3-C and Fig. 3-D, respectively). Furthermore, group M showed significantly higher scores compared to the D group at 3 h after extubation ($p = 0.03$; Fig. 3-E), and at 4 h ($p = 0.009$; Fig. 3-F) if compared to the C group. Differences within groups on SF-GCMPS and VAS scores are summarized in Supplementary Table 3. Rescue methadone was administered in 9/45 dogs: 2 patients in the D group, 5 in the M group, and 2 in the C group. In the D group, one dog received rescue methadone at 4 h and one dog at 2 h after extubation. In the M group, two dogs received rescue methadone at 1.5 h after extubation, while the other 3 dogs received rescue methadone at 3, 4, and 5 h after extubation, respectively. In the C group, one dog received rescue methadone at 3 h after extubation and one dog received 2 boluses, at 3 and 12 h after extubation. The number of dogs that required postoperative rescue analgesia was not significantly different between groups ($p = 0.29$). The scores assigned for the assessment of the degree of motor blockade were significantly affected by time ($p < 0.0001$), but not by treatment ($p = 0.25$) and its interaction with time ($p = 0.06$); nonetheless, the C group had significantly higher scores compared to the M group at 2 h after extubation, and at 6 and 9 h if compared to the D group. Differences between and within groups on scores of the degree of motor blockade are summarized in Supplementary Table 3. The duration of motor blockade was 6 (1−12) hours in the D group, 4 (2−12) hours in the M group, and 3 ± 1.5 (median 3; range 1–6) hours in the C group; no significant differences could be detected between groups ($p = 0.07$). The time to first spontaneous food intake was 4 (2–12) hours in the D group, 4 (1.5–18) hours in the M group, and 4 ± 1 (median 4; range 2–6) hours in the C group; no significant differences could be detected between groups ($p = 0.71$).

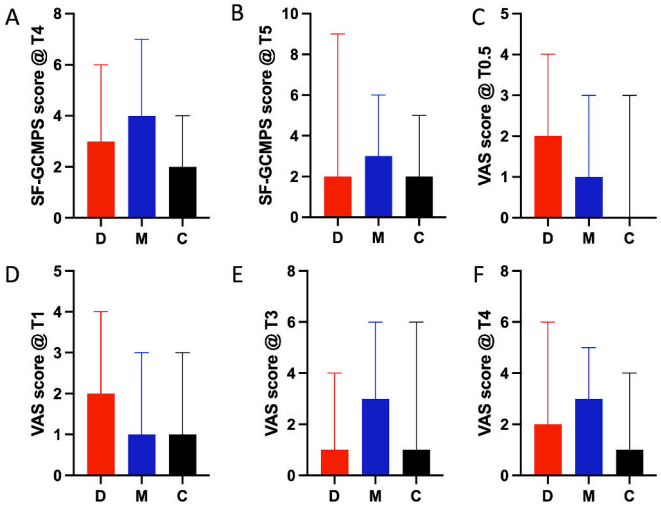

Fig. 3. Graphic representation of median SF-GCMPS and VAS scores in dogs that were administered perineural dexmedetomidine-ropivacaine (group D), magnesium sulphate-ropivacaine (group M), or ropivacaine (group C). In A, median SF-GCMPS scores at 4 h after extubation; in B, median SF-GCMPS scores at 5 h after extubation; in C, median VAS scores at 0.5 h after extubation; in D, median VAS scores at 1 h after extubation; in E, median VAS scores at 3 h after extubation; in F, median VAS scores at 4 h after extubation.

4. Discussion

This study failed to demonstrate that the administration of perineural dexmedetomidine or magnesium sulphate combined with ropivacaine in ultrasound-guided PNBs of the sciatic and saphenous nerves improves the quality of perioperative analgesia in dogs undergoing TPLO surgery, compared to perineural ropivacaine alone. Furthermore, dogs receiving perineural magnesium sulphate combined with ropivacaine experienced a more pronounced intraoperative nociceptive response if compared to dogs that were given perineural dexmedetomidine combined with ropivacaine; the first hypothesis must therefore be rejected.

Low doses of perineural dexmedetomidine have been used in association with ropivacaine in human patients undergoing orthopedic surgeries to reduce the consumption of analgesics and prolong postoperative analgesia (Liu et al., 2022). In a previous study, 0.5 μg/kg of dexmedetomidine per nerve block combined with ropivacaine did not reduce intraoperative fentanyl and postoperative methadone requirements in dogs undergoing sciatic and femoral nerve blocks for TPLO surgery (Marolf et al., 2022). For this reason, in the present study, a higher dose of dexmedetomidine (1 μg/kg per nerve block) has been proposed, but it failed to significantly reduce intraoperative fentanyl and postoperative methadone requirements, and to improve SF-GCMPS and VAS scores, if compared to perineural 0.3% ropivacaine. In humans, magnesium sulphate is a useful adjuvant to ropivacaine for PNBs, to prolong the duration of postoperative analgesia and reduce postoperative rescue analgesics, if compared to perineural ropivacaine alone (Elyazed and Mogahed, 2018). To the authors' knowledge, this is the first study evaluating the perineural administration of magnesium sulphate in dogs and it failed to demonstrate an equivalent effect in patients undergoing TPLO surgery. This result agrees with a previous study, that reported no analgesic benefits when magnesium sulphate was combined with epidural ropivacaine in dogs undergoing hip arthroplasty (Lardone et al., 2017). To avoid any complications for client-owned dogs, the authors decided to use magnesium sulphate at 2 mg/kg per nerve block; this dose was proven to be safe in terms of neurotoxicity in dogs (Simpson et al., 1994). Furthermore, magnesium sulphate is hyperosmolar, and in the present study, it was diluted with 0.9% sodium chloride to reach a final concentration of 0.2%, as previously recommended (Humphrey et al., 2015). Nonetheless, it cannot be excluded that a higher magnesium sulphate dose and concentration might have effectively enhanced the analgesic effect of ropivacaine. A possible explanation for the lack of a significant improvement in the quality of perioperative analgesia is that perineural ropivacaine might already have adequate analgesic efficacy in dogs undergoing TPLO surgery. Its long action (Schulman and Strichartz, 2012) could have masked the beneficial effects of both dexmedetomidine and magnesium sulphate in providing superior postoperative analgesia. At the institution where this clinical study was conducted, ropivacaine is routinely used for PNBs due to its longer-lasting effect and because it ensures perioperative comfort in dogs undergoing TPLO surgery, although it does not have a fast offset on nerve fibers, that is an ideal aspect when investigating the additive analgesic effects of adjuvant drugs. Furthermore, preoperative methadone and meloxicam were administered to all dogs included in this study and this decision could have made even more challenging the detection of differences in terms of the consumption of rescue analgesics and

postoperative pain scores. Further studies are needed to determine whether higher doses of perineural dexmedetomidine and magnesium sulphate would increase the analgesic effect and prolong motor blockade in dogs undergoing PNBs of the sciatic and saphenous nerves.

Surprisingly, dogs receiving a combination of perineural magnesium sulphate and ropivacaine required a significantly higher number of fentanyl boluses compared to dogs that were given a dexmedetomidine-ropivacaine perineural combination. Regardless of the treatment group, most fentanyl boluses were administered during arthrotomy and skin incision and suturing. In dogs, the stifle joint capsule could be innervated by additional branches coming from the femoral and/or obturator nerves (O'Connor and Woodbury, 1982). It might be hypothesized that a higher number of dogs where supplementary sensory fibers arise from the femoral and obturator nerves were included in the M group, resulting in an incomplete block with the worst quality of intraoperative antinociception. This aspect might have also influenced the significantly higher postoperative pain scores in the first 5 h after extubation and, although statistically non-significant, the greater methadone requirement registered in the M group. On the other hand, it has been reported that local injection of magnesium sulphate produces dose-dependent peripheral hyperalgesia in rodents, mediated by the activation of peripheral transient receptor potential ankyrin1 and NMDA receptors in primary afferent fibers, and peripheral production of nitric oxide (Srebro et al., 2015). In humans, magnesium sulphate promotes local analgesia after intra-articular administration (Koltka et al., 2011), but also local pain sensation after intramuscular injection (Herroeder et al., 2011), and this inconsistency could be explained by differences in the site of magnesium sulphate injection, the given dose, and species (Srebro et al., 2015). Thus, in the present study, the perineural administration of magnesium sulphate may have increased the peripheral nociceptive transmission, which could justify the higher perioperative analgesics consumption.

Regarding the score of motor blockade, it was significantly higher in the C group compared with the M group at 2 h after extubation, and at 6 and 9 h if compared with the D group, but the duration of motor blockade resulted in no significant differences between groups. These findings were unexpected but supported by the results of previous studies, which reported no beneficial effects of perineural dexmedetomidine (Marolf et al., 2021; Marolf et al., 2022) or epidural magnesium sulphate (Lardone et al., 2017) added to 0.5% ropivacaine in prolonging the duration of motor blockade in dogs. In the present study, a less concentrated ropivacaine solution (0.3%) has been proposed, because it has a similar efficacy but a shorter duration than 0.5% ropivacaine (Fenten et al., 2015; Tayari et al., 2017) and this could have been helpful in identifying any possible effects of adjuvant drugs in prolonging the motor blockade. Although statistically non-significant, a shorter duration of motor blockade was detected in the C group, however, a higher number of dogs would be probably needed to verify this difference.

It is reported that perineural administration of dexmedetomidine combined with ropivacaine has the potential to induce bradycardia, hypotension, and sedation in humans (Lin et al., 2013). In the present study, as previously hypothesized, a significant decrease in HR and a significant increase in arterial blood pressure were observed, comparing the Tpre-PNB values with those obtained after the administration of a perineural combination of 1 μg/kg per nerve block of dexmedetomidine and 0.3% ropivacaine. The HR was also significantly lower in the D group compared with the M and C groups intraoperatively and during the first 1.5 h post extubation. These findings might suggest that the cardiovascular effects of dexmedetomidine may appear when dexmedetomidine is administered perineurally at 2 μg/kg (1 μg/kg/nerve block site). In dogs, perineural dexmedetomidine administered at the aforementioned dose reached a plasmatic concentration similar to that measured after the administration of an interscalene brachial plexus block with 150 μg of dexmedetomidine and ropivacaine in humans, a combination that caused the lowering in heart rate (Fritsch et al., 2014; Marolf et al., 2021). In the present study, the cardiovascular effects related to perineural dexmedetomidine administration did not appear clinically relevant, since no dogs experienced bradycardia, cardiac arrhythmias, or hypotension. Another reported effect of dexmedetomidine is the ability to reduce the isoflurane requirement in dogs (Acevedo-Arcique et al., 2014). In this study, the administration of perineural dexmedetomidine combined with ropivacaine for the PNBs of the sciatic and saphenous nerves was associated with a significant decrease in FE'Iso compared with the other treatment groups at most of the intraoperative time points. The clinical variables used to assess the anesthetic depth were subjective, but it could be hypothesized that dexmedetomidine administered perineurally may have been absorbed into the circulation, resulting in systemic effects such as sedation. The decrease in norepinephrine release in the central nervous system caused by presynaptic α2-adrenergic receptor stimulation (Miller et al., 1968) and neuronal hyperpolarization induced by the activation of postsynaptic α2-adrenergic receptor (Aghajanian and VanderMaelen, 1982) could have contributed to the reported reduction in isoflurane requirement. However, the dexmedetomidine sedative effect seemed time-dependent since it was not clinically relevant after extubation.

There are some additional limitations in the current study that need to be addressed. First, the success of the sciatic and saphenous nerve blocks was not confirmed through the evaluation of sensory function or with the perfusion index calculation (Gatson et al., 2016); however, the ultrasonography facilitated the correct needle positioning and helped to visualize the spread of the solution around the target nerves. Furthermore, all dogs presented residual motor blockade after extubating. Second, an *a priori* sample size calculation was not performed based on all the outcome variables, and the potential for a type II error cannot consequently be excluded. Indeed, it is possible that a sample size calculation powered for motor block duration could have shown significant differences also in terms of this parameter. Finally, the study did not include a validated scale for evaluating the ability of dogs to walk and the degree of motor blockade. Nonetheless, the subjective scale used was simple to be applied and without great difficulties in assigning unambiguously the scores.

5. Conclusions

The addition of 1 μg/kg dexmedetomidine or 2 mg/kg magnesium sulphate to perineural 0.3% ropivacaine in ultrasound-guided PNBs of the sciatic and saphenous nerves did not improve the quality of perioperative analgesia in dogs undergoing TPLO surgery, and they did not prolong the motor blockade. Perineural dexmedetomidine, at the dose proposed in this study, promotes the appearance of clinically negligible systemic effects. This suggests that different doses of perineural dexmedetomidine and magnesium sulphate should be considered to increase the analgesic effect and prolong motor blockade in dogs undergoing PNBs of the sciatic and saphenous nerves with 0.3% ropivacaine.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Federica Alessandra Brioschi: Writing – original draft, Resources, Methodology, Investigation, Data curation, Conceptualization. **Vanessa Rabbogliatti:** Writing – review & editing, Resources, Investigation. **Giuliano Ravasio:** Writing – review & editing, Supervision, Resources, Project administration. **Martina Amari:** Writing – review & editing, Resources, Investigation. **Luigi Elia:** Writing – review & editing, Resources, Investigation. **Ilaria Gritti:** Writing – review & editing, Resources, Investigation. **Francesco Ferrari:** Writing – review & editing, Resources, Methodology, Investigation, Data curation,

Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rvsc.2024.105355.

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