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Evaluation of the effects of a single bolus of cisatracurium as part of an anesthetic protocol in cats undergoing orthopedic surgery

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Abstract

Non-depolarizing neuromuscular blocking agents (NMBAs) are commonly used in human anesthesia but remain uncommon in veterinary medicine. This study evaluated the effects of 0.5 mg/kg cisatracurium IV on muscle relaxation, cardiovascular variables and postoperative pain in cats undergoing orthopedic surgery. Twenty-four cats were randomly assigned to a control group (Group C) or a treatment group receiving cisatracurium (Group M) immediately after induction. Neuromuscular function was monitored using a calibrated train-of-four (TOF) device. Postoperative pain was assessed with the short form of the Glasgow Feline Composite Measure Pain Scale (CMPS-Feline). The mean time to suppression of muscle contraction was 2.6 ± 0.8 min, with peak suppression (90%) at 3.0 ± 0.7 min, a mean duration of 23.3 ± 4.4 min, and complete recovery at 27.3 ± 8.6 min. Group M required lower sevoflurane concentrations to maintain anesthesia compared to Group C ($p < 0.001$) and had a shorter mean surgical time (25.3 ± 3 min vs. 31.5 ± 4 min; $p < 0.001$). Pain scores were also lower in Group M ($p = 0.01$). These findings demonstrate that cisatracurium effectively induces neuromuscular block (NMB) and improves surgical conditions, resulting in lower postoperative pain scores in cats undergoing femoral fracture repair.

Keywords Cisatracurium, Neuromuscular blockade, Sevoflurane, Anesthesia, Cat

Introduction

Inhalant anaesthetics are widely used in veterinary practice thanks to their quick onset, rapid recovery and adjustable depth of anaesthesia. Despite inhalant anesthetics induce unconsciousness at relatively low concentrations, higher concentrations are required to suppress responses to noxious stimuli and achieve muscle relaxation [1]. However, at higher concentrations inhalant anesthetics may reduce cardiovascular and respiratory function. Sevoflurane use in cats causes dose-dependent cardiopulmonary depression, including decreased mean arterial pressure and vascular resistance [2, 3].Therefore,

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multimodal analgesia and the addition of analgesics and muscle relaxants are employed to mitigate these adverse effects and fulfil the three fundamental requirements of anaesthesia: the induction of unconsciousness, analgesia, and muscle relaxation [4, 5].

Non-depolarising neuromuscular blocking agents (NMBAs) are used to improve skeletal muscle relaxation, facilitate orotracheal intubation, improve compliance with mechanical ventilation and facilitate surgical procedures [6, 7]. While the use of NMBAs is quite widespread in human anesthesia, their application in veterinary medicine is still limited, being reported primarily in dogs to facilitate orthopedic and ophthalmic surgery [8–14]. Although cats have been used as ex-perimental models to investigate NMBAs pharmacology, clinical data remains scarce, and their use is still limited in cats compared to dogs [15–21]. The limited use of NMBAs is likely due to the lack of monitoring devices and insufficient training in their use. The risk of complications such as residual neuromuscular block (NMB), histamine release and potential cardiovascular side effects, may further limit their use [22–25]. The onset, dosing and duration of action of NMBs are also poorly understood [16, 20, 26–28]. Such information is essential to fully understand the variability in response to NMBAs and their potential routine use in orthopedic surgery. Cisatracurium is a non-depolarizing neuromuscular blocking agent (NMBA) of the benzylisoquinoline group and represents the purified form of one of the ten stereoisomers of atracurium. It acts as a competitive acetylcholine antagonist at post-synaptic nicotinic receptors, preventing channel opening and action potential generation, resulting in muscle paralysis and producing fewer adverse effects compared to atracurium [29–31]. The aim of the study was to assess the effects of 0.5 mg/kg of cisatracurium on the peak onset time, mean duration and time to full recovery from NMB, as well as the sevoflurane requirements and postoperative pain in cats undergoing orthopedic surgery. We hypothesized that cisatracurium-induced NMB would reduce sevoflurane requirement, shorten surgical time, and decrease postoperative pain.

Materials and methods

Animals

All treatments, housing and animal care followed EU Directive 2010/63/EU on the protection of animals used for scientific purposes. The protocol and procedures were approved by the Ethics Committee of the Department of Veterinary Medicine and Animal Production, University of Messina, Italy (prot.no. 074/2022). Informed consent was obtained from each cat owner before inclusion in the study. The study population consisted of privately owned cats presented with hind limb lameness. Prior to enrolment, all cats underwent clinical, orthopedic and laboratory examination (serum biochemistry and hematology). All subjects with a simple fracture of the femoral diaphysis (classified as 32-A1 in the AO/ASIF system according to Unger et al. [32], detected during clinical and/or orthopedic examination and confirmed by radiography, were included in the study. Between January 2023 and November 2024, a total of 29 cases of long bone fractures in cats were recorded. The orthopedic examination and radiographic evaluation were performed by the same orthopedic surgeon and radiologist, respectively. All subjects with complex non-diaphyseal fractures or fractures at other sites, exposed fractures, dog bite fractures, those with clinical, radiographic and laboratory evidence of systemic disease (cardiac, renal, hepatic, endocrine, neurological or neoplastic) and those with ASA class greater than II were excluded from the study (5 subjects).

Sample size was calculated with the G*Power 3.1 Software (Hein-rich-Heine-Universitat Dusseldorf, Düsseldorf, Germany). A sample size of 12 cats in each group was included in the study. The Sample size was estimated based on the primary endpoint: time to full recovery from NMB. According to previous studies [12, 16], this time ranges from 12.7 to 27 min, with standard deviations up to 10 min. Assuming a clinically relevant difference of 10 min and a conservative SD of 10 min, 17 cats per group would have been required to achieve 80% power and a significance level of 0.05.

Treatments and monitoring

A prospective, randomized, blinded clinical trial was performed in which twenty-four subjects (n = 24) were enrolled and divided into two groups: a control group (Group C) that received saline (n = 12) and a treatment group (Group M) that received cisatracurium (n = 12). Subjects were fasted for 12 h but had free access to water up to 2 h before anesthesia. All subjects were premedicated with dexmedetomidine 3 µg/kg (Dexdomitor® 0.5 mg/ml, Vetoquinol Italia SRL, IT) and methadone 0.3 mg/kg (Comfortan 10 mg/ml; Eurovet Animal Health BV, UK) both administered intramuscularly (IM). After premedication, animals were maintained in a quiet environment for approximately 15 min and were preoxygenated with 100% oxygen via facemask, while being monitored for adverse effects such as retching, vomiting, pale mucous membranes, decreased body temperature and muscle tremors. A 24-gauge catheter (0.74 mm; Farmacare SrL, Cannula; San Pietro in Casale (BO), Italy) was aseptically inserted and fixed to the cephalic vein for drug administration. Anesthesia was induced with alfaxalone (Alfaxan 10 mg/ml Dechra Veterinary Products SAS, FR) 3 mg/kg intravenously (IV) over approximately 60 s. Cats were positioned in lateral recumbency, and body temperature was maintained between 38.5 °C and 37.0 °C with a circulating warm water blanket (Soarmed Medical-Tech

Co., Ltd., Tai-wan). Once an adequate anesthetic depth was achieved, orotracheal intubation was performed with an appropriately sized endotracheal tube (ETT); the patients was transferred to the operating room and was then connected to an Ayre's T pediatric breathing circuit. Maintenance of anesthesia was achieved with sevoflurane (Sevoflo 100% Ecuphar S.r.l., Italy) administered in 100% oxygen. All patients were mechanically ventilated in pressure-controlled mode with a peak inspiratory pressure (PIP) of 8 cmH_2O, an inspiratory-to-expiratory ratio (I:E) of < 1:2, a respiratory rate (RR) of 14 breaths per minute, and an end-inspiratory pause (EIP) of 1.7 s, using a mechanical ventilator integrated into the anesthesia station (GE Datex-Ohmeda Avance 6.8; Helsinki, Finland). The vaporizer dial was initially set to 2% sevoflurane. The patient clipping and aseptic preparation with surgical draping were performed. Non-invasive blood pressures (systolic, diastolic and mean arterial pressure; SAP, DAP and MAP, respectively, mmHg) were measured by the oscillometric method using a pediatric cuff (Suntech® Vet20, USA) with a width equal to 40% of the tail diameter at the point of application. Peripheral hemoglobin oxygen saturation (SpO_2%) was assessed using a tongue-placed pulse oximetry probe, and heart rate (HR; beats/minute; pulse rate) was assessed via ECG monitoring. A calibrated thermistor was inserted into the esophagus to monitor body temperature (T, °C) (Datex-Ohmeda S/5). Respiratory rate (RR, breaths/minute), end-tidal CO_2 ($EtCO_2$, mmHg) and end-tidal fraction of sevoflurane (EtSEVO) were measured by a side-stream capnograph. All the above variables were constantly monitored and displayed on the anesthesia machine (GE Datex-Ohmeda Avance 6.8 with Datex-Ohmeda S/5; M-CAiOV; Helsinki, Finland). Clinical variables such as HR, SAP, MAP, DAP and T were recorded 15 min after premedication (baseline T0), while $EtCO_2$, SpO_2 and EtSEVO were recorded from induction time (Ti). All variables were recorded after muscle relaxant administration at the following time-points: after 5 (T5), 10 (T10), 15 (T15), 20 (T20), 25 (T25), 30 (T30), 35 (T35) and 40 (T40) minutes. Duration of surgery and anesthesia were also monitored. Surgical time was defined as the interval between skin incision and completion of skin suturing. The analyzer was calibrated at the start of anesthesia with the calibration gas supplied by the manufacturer (Quick Calibration Gas, Ref: 755583; GE Healthcare). Sodium chloride 0.9% (250 ml intravenous sodium chloride 0.9% solution Ecoflac, Braun) was administered at a rate of 2 ml/kg/h via a syringe infusion device (Compact 98 Syringe Driver, BRAUN, Germany and 0 A) throughout the duration of anesthesia. After the patient's preparation is complete, cats in group M were monitored with the TOF monitor (TOF-Watch® SX, Organon, Italy). Two subcutaneous needles were inserted into the medial aspect of the elbow, the proximal electrode at a distance of 2–3 cm from the distal electrode above the ulnar nerve (humeral epicondyle) to evoke muscle contractions [24, 25, 33]. The limb used for stimulation was different from the one where the cannula was placed. The TOF monitor was calibrated before NMBAs were administered to cats [24, 25, 30]. The free movement height was configured to establish a control height value of 100%. Train-of-four (TOF) stimulation involved the administration of four supra-maximal pulses over 2 s (2 Hz), was repeated every 13 s. The level of relaxation determined by comparing the ratio of the intensity of the fourth contraction to the first contraction (ratio T4:T1) were recorded. At this time, group M was received intravenous cisatracurium at a dose of 0.5 mg/kg (Nimbex 2 mg/ml; GlaxoSmithKline, Italy) over a period of 5 s. Before administration of NMBAs, catheter was flushed in with water for injectable preparations. During the TOF monitoring, the following time parameters related to NMB were calculated: time to suppression of muscle contraction, time to peak (90%) (TOF ≤ 10%), duration of peak and time to complete recovery from NMB, defined as TOF = ratio T4:T1 ≥ 0.9. Deep NMB was defined as the complete absence of response to all four stimulations (No twitch = > 95% occupancy) [20, 22, 24.

In all subjects, maintenance of anesthesia was achieved by the vaporization of sevoflurane inhalation. Sevoflurane concentration was adjusted according to cardiovascular parameters and autonomic responses to surgical stimulation. All anesthetic procedures were conducted and monitored by the same anesthetist, who was unblinded to group allocation. However, he was not be involved in postoperative care or the assessment of postoperative outcomes.

All surgeries were performed by a single experienced veterinary surgeon who was blinded to the treatment. All femoral fractures were treated using a locking compression plate (LCP) from the same manufacturer. After reducing the fracture site, the plate was applied in accordance with ORIF (open reduction and internal fixation) standards. Each case was assessed individually, allowing the surgeon to select the most appropriate plate to ensure optimal bone alignment and post-operative stability [32, 34]. The size of the plate was selected based on the patient's weight: 2.0 plates were used for patients weighing up to 2.5 kg and 2.4 plates for those weighing more than 2.5 kg. Three bicortical screws were used for each stump in each patient. If the increase in HR and SAP was greater than 20% from baseline intraoperative rescue analgesia was administered with a fentanyl bolus (2 µg/kg) [12]. The time required for complete recovery from neuromuscular blockade was defined as TOF = T4:T1 ratio ≥ 0.9. Neostigmine 0.01 mg/kg (Neostigmine 0,5 mg/ml; Carinopharm; gmbh) was slowly administered

(about one minute) to limit the recurrence of residual neuromuscular blockade. Then, the administration of sevoflurane was stopped, and the subjects were disconnected from the circuit when chest expansion and oxygen saturation were adequate. The orotracheal tube was removed when the swallowing reflex returned. At the end of surgery, all patients received subcutaneous tramadol at a dose of 4 mg/kg (Altadol 50 mg/mL Formevet S.r.l., Milan, Italy). Meloxicam (Metacam, Boehringer Ingelheim Animal Health Italia S.p.A., Noventana, Italy; 0.2 mg/kg on the first day, then 0.1 mg/kg, q24h for 10 days) was also administered in all patients. In the postoperative period, the short form of the Glasgow Feline Composite Measure Pain Scale (CMPS-Feline) was applied to all patients at 2, 4, and 6 h after extubation to assess postoperative pain [35–38]. Pain assessments were performed by three observers who were blinded to the anesthetic protocol. The items are scored in ascending order of pain intensity, with a maximum total score of 20. When the pain score exceeded 5/20, rescue analgesia was administered (buprenorphine 20 µg/kg; Bupaq Multidose 0.3 mg/ml, TREI S.p.A., a Livisto company).

Statistical analyses

Statistical analysis was performed using SPSS 21.0 (IBM Company, Italy). The normality assumption of the clinical data was tested using the Shapiro-Wilk test. Clinical variables, HR, SAP, MAP, DAP, $EtCO_2$, SpO_2, T° and EtSEVO requirement, were expressed as mean ± standard deviation (SD). Differences were analyzed using two-way repeated measures ANOVA. Bonferroni post hoc analysis was planned for multiple comparisons. Scores from the CMPS-Feline scale, reflecting postoperative pain responses were compared within and between groups using the Friedman test, followed by Dunn's post hoc test for multiple comparisons. For categorical data, median and range were reported. To assess the level of agreement between observers, Kendall's coefficient of concordance (W) was computed. A p value of < 0.05 was defined as the cut-off for statistical significance.

Results

During the period 2022–2024, a total of thirty-six cats ($n = 36$), undergoing orthopedic surgery for femoral fractures of traumatic origin were assessed for inclusion. Subjects with systemic disease ($n = 4$) were excluded, as were subjects who were not ASA class II ($n = 6$) and those whose owners did not consent to inclusion in the study group ($n = 2$). The sample size was 24 and the power was 0.80, considered to be representative of the study population. The study group consisted of sixteen males (66.66%) and eight females (33.33%) of the domestic shorthair breed. Differences in weight, age and ASA class between groups are reported as mean and standard deviation in Table 1.

Table 1 Demographic data from groups: differences in weight and age between the control group (C group) and the muscle relaxant treated cats (M group). Results are expressed as mean and standard deviation; $p < 0.05$ was considered statistically significant

Variable	Group C	Group M	*p* value
Weight (kg)	2.9 ± 1.2	3.2 ± 0.7	*0.91*
Age (months)	35 ± 12	37 ± 11	*0.60*

Table 2 Surgery and anesthesia times in two monitored groups. Values are expressed as mean ± SD. ♣Significant difference between Groups; $p < 0.05$ was considered statistically significant

	Group C	Group M	*p* value
Surgery time (minutes)	31.5 ± 4♣	25.3 ± 3	0.001
Anesthesia time (minutes)	46 ± 3♣	54 ± 4	*0.01*

All cats were fed commercial diets and had both indoor and outdoor lifestyles. One cat in group C was excluded from the study due to complications during surgery. Monitoring of NMB in the cisatracurium treated group (group M) showed that the mean time to suppression of muscle contraction was 2.6 ± 0.8 min and the mean time to peak (90%) was 3 ± 0.7 min after intravenous administration of the muscle relaxant. The mean duration of the peak was 23.3 ± 4.4 min. The mean time to complete recovery from neuromuscular blockade (T4:T1) to ≥ 90% TOF was 27.3 ± 8.6 min. No adverse events were observed.

The duration of surgery differed between the two groups ($p < 0.001$), with a mean of 31.5 ± 4 min in group C and 25.3 ± 3 min in group M, Table 2.

The study monitored changes in sevoflurane (EtSEVO, %) concentration at different time points. In both the C and M groups, there was a statistically significant reduction in EtSEVO at all time points within group. Comparison of Et-SEVO values between the two groups showed a statistically significant difference, with lower values in the M group than in the C group ($p < 0.001$) from T5 to T30, Table 3.

Table 3 End-tidal fraction of sevoflurane (EtSEVO, %) and its significance. Values are expressed as mean ± SD. Significance between groups: ♣C group vs. M group ($p < 0.001$). *Significant differences within group ($p < 0.001$). Monitoring times: induction time (Ti) and 5 (T5), 10 (T10), 15 (T15), 20 (T20), 25 (T25), 30 (T30), 35 (T35) and 40 (T40) minutes after cisatracurium administration

Time (minutes)		T_i	T_5	T_{10}	T_{15}	T_{20}	T_{25}	T_{30}	T_{35}	T_{40}
EtSEVO, %	Group C	2.1 ± 0.2	1.47 ± 0.2*	1.44 ± 0.2*	1.45 ± 0.1*	1.46 ± 0.2*	1.43 ± 0.2*	1.45 ± 0.1*	1.44 ± 0.2*	1.48 ± 0.2*
	Group M	2.08 ± 0.3	1.18 ± 0.2*♣	1.12 ± 0.2*♣	1.17 ± 0.1*♣	1.17 ± 0.1*♣	1.18 ± 0.1*♣	1.15 ± 0.1*♣	1.39 ± 0.1*	1.41 ± 0.2*

Table 4 Mean ± SD of heart rate (HR, beats/min), end-tidal CO_2 ($EtCO_2$, mmHg), peripheral hemoglobin saturation (SpO_2%), non-invasive blood pressure (systolic, diastolic and mean arterial pressure; SAP, DAP and MAP, respectively; mmHg) and body temperature (°C), in group C and in group treated with cisatracurium (group M). In parentheses after the group identifier in the group column: before premedication: induction time (Ti) and 5 (T5), 10 (T10), 15 (T15), 20 (T20), 25 (T25), 30 (T30), 35 (T35) and 40 (T40) minutes after cisatracurium administration. *Significant differences within groups ($p < 0.01$).♣Statistical difference between group C vs. group M ($p < 0.01$); $p < 0.05$ was considered statistically significant

Variables	Groups	T0	Ti	T5	T10	T15	T20	T25	T30	T35	T40
HR	C	133 ± 6	109 ± 12*	102 ± 9*	101 ± 5*	98 ± 5*	100 ± 6*	102 ± 6*	98 ± 6*	100 ± 6*	103 ± 5*
beats/min	M	137 ± 5	113 ± 6*	105 ± 6*	104 ± 8*	104 ± 8*	98 ± 4*	97 ± 4*	97 ± 3*	99 ± 3*	103 ± 3*
EtCO$_2$	C		35 ± 3	35 ± 2	33 ± 2	34 ± 1	33 ± 2	35 ± 2	33 ± 1	34 ± 2	35 ± 2
mmHg	M		33 ± 3	35 ± 2	34 ± 1	34 ± 2	34 ± 1	34 ± 1	34 ± 2	34 ± 1	35 ± 2
SPO$_2$	C		98 ± 1	97 ± 2	98 ± 1	97 ± 1	97 ± 1	98 ± 1	97 ± 1	98 ± 1	98 ± 1
%	M		97 ± 1	96 ± 1	96 ± 1	97 ± 1	98 ± 1	96 ± 1	98 ± 1	97 ± 2	98 ± 2
SAP	C	132 ± 5	125 ± 8*	110 ± 5*	107 ± 5*	104 ± 7*	108 ± 6*	106 ± 7*	107 ± 6*	107 ± 7*	108 ± 7*
mmHg	M	129 ± 5	132 ± 10	108 ± 4*	105 ± 5*	106 ± 4*	107 ± 5*	105 ± 5*	106 ± 6*	110 ± 5*	107 ± 6*
MAP	C	108 ± 9	103 ± 4*	95 ± 8*	83 ± 7*	79 ± 6*	77 ± 6*	80 ± 3*	79 ± 3*	83 ± 3*	87 ± 6*
mmHg	M	93 ± 5	101 ± 6*	89 ± 5	77 ± 6*	80 ± 7*	76 ± 5*	72 ± 6*♣	73 ± 3*	92 ± 8	85 ± 5*
DAP	C	79 ± 6	80 ± 6	76 ± 5	69 ± 5*	66 ± 4*	65 ± 4*	71 ± 4*	66 ± 2*	74 ± 4*	64 ± 5*
mmHg	M	75 ± 5	83 ± 4*	69 ± 6*♣	61 ± 4*♣	68 ± 4*	63 ± 3*	59 ± 4*♣	61 ± 4*	75 ± 6	66 ± 7*
Body Temperature	C	38.6 ± 4									37.6 ± 4
°C	M	38.5 ± 6									37.3 ± 5

Table 5 Glasgow feline composite measure pain scale (CMPS-Feline). Values at 2, 12 and 24 h after extubation, are expressed as median and range. *Significant within-group differences (p<0,05). ♣Significant differences be-tween groups ($p < 0.000$)

	2 h	4 h	6 h
Group M	2 (0/5)♣	1 (0/4)*♣	1 (0/3)*♣
Group C	3 (2/5)	3 (2/5)*	3(1/5)*
♣*P* value	*<0,05*	*<0,01*	*<0,01*

During anesthesia, the body temperature of all cats decreased by approximately one degree, remaining within optimal ranges. Furthermore, no significant differences in body temperature were observed between the groups. All clinical variables assessed at different time points are shown in Table 4. No cat required rescue analgesia during surgery.

According to the CMPS-Feline pain scoring system, significant differences were observed in postoperative pain assessment between the groups (Table 5). In Group M, a reduction in pain scores was observed at 4 and 6 h compared with 2 h ($p = 0.001$). Group C also showed a reduction at 4 and 6 h ($p = 0.05$ and $p = 0.01$, respectively). None of the groups exceeded the cutoff value, indicating that no rescue analgesia was required. However, significant differences were observed between the two groups at all assessment times, with Group M showing the lowest scores ($p = 0.01$).

In our study, no adverse effects were observed in the monitored clinical variables in relation to the administration of cisatracurium. No adverse events were seen in the recovery phase.

Discussion

The findings of this study suggest that a single bolus of cisatracurium in cats undergoing orthopedic surgery can induce optimal muscle relaxation, thereby reduce surgical time while maintaining stable clinical variables. Its integration into a balanced multimodal anesthesia protocol was also associated with lower sevoflurane concentrations and postoperative pain scores.

Cisatracurium is approximately three times more potent than atracurium and has a slower onset and longer duration of action. Like atracurium, cisatracurium undergoes Hofmann elimination, making its clearance largely independent of renal and hepatic function and therefore suitable for patients with liver or kidney disease [6, 8, 16, 27, 39]. Laudanosine, a metabolite common to both agents, has been associated with hypotension and convulsions in dogs [40, 41]. However, this risk is minimized by the greater potency of cisatracurium, which requires lower doses and consequently results in lower plasma concentrations of laudanosine compared to atracurium.

Unlike atracurium and the other isomers, cisatracurium is the only benzylisoquinoline NMBA that does not induce histamine release or cardiovascular side effects, even after high doses in both human and veterinary medicine [16, 20, 27, 28, 42]. In humans, cisatracurium does not affect plasma histamine concentrations or produce major cardiovascular effects at doses up to 8 times the ED95 in healthy patients undergoing elective surgery [27, 28]. Previous pharmacological studies in anesthetized cats evaluated the effects of intravenous bolus injections of atracurium, cisatracurium and other five isomers under experimental conditions [16, 20]. According

to these studies, administration of cisatracurium did not produce cardiovascular side effects or an increase in histamine levels even at higher doses (up to 5.3 mg/kg) of approximately 85 times the ED95 (0.06 mg/kg) in cats [16]. However, this is the first clinical study reporting cardiovascular effects of intravenous bolus injections of cisatracurium in cats undergoing orthopedic surgery. A slight decrease in HR was observed in group M, but this remained within normal reference ranges and there were no statistically significant differences between the two groups [43]. During anesthesia, all cats experienced a mild decrease in body temperature of approximately 1 °C. This moderate hypothermia did not appear to affect the anesthetic depth or the pharmacological effects of the administered drugs.

Blood pressure also showed a slight decrease but remained within physiological limits, with statistically significant differences between the two groups only for MAP at T25 and DAP at T5, T10 and T25. The observed reductions in HR and blood pressure suggest adequate anesthetic depth and the absence of intraoperative noxious stimulation [44].The M group required longer anesthesia due to the time needed to monitor its effects and ensure full patient recovery. Some authors claim that laryngeal recovery may be slower than recovery at the extremities. Therefore, it is probably safer to document a TOF ratio of at least 100% for several minutes prior to extubation [22].

Regarding the time parameters associated with NMB, the results of this study differ from previous reports on the use of cisatracurium in cats undergoing surgery. In our study, the mean time to suppression of muscle contraction was 2.6 ± 1.8 min and the mean time from cisatracurium administration to onset of maximal peak (90%) was 3 ± 1.7 min, similar to the onset time of 3.7 ± 0.1 min reported by Wastila et al. [16] and slightly longer than the median onset time of 2 min (range 1–6) reported by Van Wijnsberghe et al. [20]. The mean duration of the maximum peak was 23.3 ± 4.4 min, slightly longer than the duration of action of 20.4 ± 10.1 min reported by Van Wijnsberghe et al. and significantly longer than the 12.7 ± 0.9 min reported by Wastila et al. [16, 20]. The variety of protocols used in Van Wijnsberghe's study [20] may have influenced the results. In our study, all subjects received a single dose of cisatracurium, whereas in Van Wijnsberghe's study, subjects received multiple doses of cisatracurium to maintain adequate central eye position during surgery (2/11 received four additional doses, 1/11 received three additional doses, and 4/11 received two additional doses). Furthermore, in both the Van Wijnsberghe and Wastila studies [16, 20], the reported times refer to cisatracurium doses of 0.15 mg/kg and 0.06 mg/kg, respectively, which were significantly lower than the 0.5 mg/kg used in our study. Choosing low NMBA doses may preferentially affect extraocular muscles before skeletal muscles, facilitating globe centralization [12, 20, 21, 25]. In our study, the dose used was chosen based on the desired intensity, duration of NMB and according to the surgical requirements. A dose of 0.5 mg/kg was chosen to achieve an adequate degree and duration of blockade for the treatment of the fracture. According to Wastila et al. [16], the dose used does not produce histamine-like cardiovascular effects or cumulative effects. The mean time to complete recovery from NMB (TOF = ratio T4:T1 ≥ 0.9) in this study was 27.3 ± 8.6 min. The onset and duration of NMB observed in the treatment group were adequate for intraoperative management, as the NMB effect covered the surgical time.

However, clinical variables associated with NMB may also be influenced by other drugs that affect muscle contractility and/or cardiac output, such as benzodiazepines, acepromazine, alpha-2 agonists and inhaled anesthetics [20, 45, 46]. To date, no study has compared the time parameters of cisatracurium induced NMB with different anesthetic protocols.

It is important to note that NMBAs do not affect consciousness or pain perception and should therefore never be used alone, but always in combination with anesthetics and analgesics [13, 14]. Inhalational anesthetics increase the intensity and duration of cisatracurium induced NMB, whereas propofol has little or no effect on this blockade in both humans and dogs [9, 11–14]. The inhalant-sparing effect of NMBAs in dogs has been reported in the literature, but only limited information is available for cats [11]. In our study, group M required significantly lower sevoflurane concentrations to maintain anesthesia compared to Group C ($p < 0.001$). Surgical time was also shorter in group M than in group C (group C: 31.5 ± 4 min; group M: 25.3 ± 3 min).

The muscle paralysis induced by cisatracurium may facilitate both tissue and bone manipulation. In ophthalmic surgery it centralizes the eyeball, improving surgical precision and reducing ocular trauma [12, 20, 21, 25]. Similarly, in our study, muscle relaxation facilitated fracture reduction and fixation reducing tissue stress. This could explain the lower scores on CMPS-Feline observed in group M compared to group C and the shorter surgical time observed in group M. Reducing operating time also reduces the risk of intra-operative infection and can contribute to better resources management and overall healthcare costs reduction [7].

In our study, the degree of neuromuscular blockade induced by cisatracurium was monitored and quantified using a peripheral nerve stimulator through TOF stimulation. However, previous studies have reported that spontaneous recovery assessed solely by TOF monitoring does not reliably exclude the presence of postoperative residual curarisation (PORC) [19, 22–24]. Therefore, to

minimise the risk of undetected residual paralysis, neostigmine (0.01 mg/kg IV) was administered to all cats in group M at the end of surgery, when the TOF ratio (T4:T1) reached 0.9, as previously recommended [20, 22–24]. Previous experimental studies in cats reported minimal cardiovascular effects following cisatracurium administration and recovery, supporting the cautious use of reversal agents without routine anticholinergic administration [16, 20, 25]. In contrast, rocuronium or vecuronium are associated with a higher incidence of cardiovascular effects. In the present study, anticholinergic agents were readily available and would have been administered if clinically indicated. However, at the low dose used, no clinically relevant muscarinic effects as bradycardia were observed. Heart rate remained within physiological ranges so prophylactic administration was not performed.

Although the results of our study were obtained with a single bolus of cisatracurium at a dose of 0.5 mg/kg, it is well known from the literature that additional doses of cisatracurium up to 0.25 mg/kg can be used in longer surgeries or when the TOF value (T4:T1) is ≤ 0.5 [20]). This approach allows flexibility in adapting the use of cisatracurium to specific clinical needs, while maintaining effective control of NMB. Finally, no adverse effects were recorded, and no rescue analgesia was required either intraoperatively or postoperatively. The results of our study support the use of cisatracurium as part of a multimodal anesthetic protocol, providing information on physiological variables, anesthetic management and suggesting efficacy and safety of NMB in cats undergoing orthopedic surgery at the doses used.

Despite our findings, there are some limitations to this study. Firstly, we focused on surgery lasting approximately 30 min. Although we observed a significant reduction in surgical time, we cannot confirm that the same results would apply to longer surgeries. Further research is needed to determine whether the observed effects are maintained, attenuated or enhanced with longer surgical times. Another limitation is that neither serum concentrations of muscle relaxants nor plasma levels of histamine and pH were assessed, so we cannot directly correlate clinical outcomes with serum concentrations of muscle relaxants. Future studies should include these measurements to provide a more complete and detailed understanding of the pharmacodynamics and pharmacokinetics of cisatracurium. Finally, the inclusion of 24 cats provided a homogeneous and representative sample, but the limited size and single-center design represent further limitations. Future studies should be carried out on a larger number of animals to consolidate the results obtained. It will also be important to evaluate the use of cisatracurium in combination with other anesthetic agents and in other types of surgery. These approaches will provide a deeper understanding of the benefits and optimal use of cisatracurium in veterinary surgical practice [8, 14, 20, 21].

Conclusions

In conclusion, the results of this study demonstrate the efficacy of a single bolus of cisatracurium in inducing NMB and allowing maintenance of anesthesia with lower sevoflurane concentrations in cats undergoing orthopedic surgery. This approach also resulted in a reduction in surgical time, likely due to improved surgical conditions. The duration and recovery time from NMB were adequate for surgical requirements, making cisatracurium a viable and safe option for anesthetic management in this setting.

Abbreviations

TOF	Train-Of-Four
NMB	Neuromuscular block
NMBAs	Non-depolarising neuromuscular blocking agents
ETT	Endotracheal tube
ASA	American Society of Anesthesiologists
IM	Intramuscular
IV	Intravenously
PIP	Peak inspiratory pressure
EIP	End-inspiratory pause
I:E	Inspiratory-to-expiratory ratio
RR	Respiratory rate
SAP,MAP, DAP	Systolic, Diastolic and Mean arterial pressure
SpO_2	Haemoglobin oxygen saturation
HR	Heart rate
T	Temperature
$EtCO_2$	End-tidal CO_2
EtSEVO	End-tidal fraction of sevoflurane
CMPS-Feline	Glasgow Feline Composite Measure Pain Scale
SD	Standard deviation
ED95	Effective Dose 95

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Authors' contributions

CI has participated on the conceptualization, methodology, validation, investigation, data curation and as writing the original draft, reviewing and editing the manuscript. MT has participated on the conceptualization, data curation and formal analysis, as well as writing the original draft, reviewing and editing the manuscript. NI has participated on the methodology, investigation, project administration and resources. DI has participated on the investigation and data curation and formal analysis. GB has participated on the investigation and project administration and resources. VZ has participated on the data curation and formal analysis as well as reviewing and editing the manuscript. SDP has participated on the data curation and formal analysis as well as writing the original draft, reviewing and editing the manuscript. FM has participated on the project administration and resources as well as writing the original draft, reviewing and editing the manuscript.

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Data availability

The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participant

The protocol and procedures were approved by the Ethics Committee of the Department of Veterinary Medicine and Animal Production, University of Messina, Italy (prot.no. 074/2022). Written informed consent was obtained from the owner of each cat prior to the inclusion of the cat in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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