Peribulbar Sub-Tenon's Anaesthesia With Levo-Bupivacaine and Cis-Atracurium Besilate in Ophthalmic Intraocular Surgery in Cat: Clinical Study.

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Abstract

Background

this study aims to evaluate the efficacy of Levo-bupivacaine with the addition of a small dose of cisatracurium by sub-Tenon's injection on akinesia and mydriasis. Then, to evaluate if such a small dose of cisatracurium could determine a systemic neuromuscular blockade, despite the way of administration. Forty cats were anesthetized for intra-ophthalmic surgery with butorphanol 0,2 $mgkg^{-1}$, dexmedetomidine 15 mcg/kg and midazolam 0,2 $mgkg^{-1}$ IM and intubated to receive oxygen and isofluorane by mechanical ventilation. The animals were divided in four groups. Group L received 1.25 $mgkg^{-1}$ L-bupivacaine, administered by peribulbar injection; group CL received the same dose of L-bupivacaine, combined with 0.01mg/kg of cisatracurium; group C received 0.01 mg kg^{-1} of peribulbar cisatracurium; group GC received 0.01 mg kg^{-1} of cisatracurium intravenously. Physiological variables and oculomotor activity were measured before and up to 30 minutes after peribulbar injection.

Results

The data below, expressed with median and range, show that physiological variables remained in the physiological range. Among the treatments, the LC group showed akinesia, higher midriasis and a decrasing intraocular pressure (IOP); the onset time of akinesia was significantly shorter in group LC than in group L 4(3/5) min and 8(6/10) min respectively, p=0.000; the duration of akinesia was longer in group LC than in group L, 70(68/72) and 60(57/63min), respectively p=0.000. In group C we observed the appearance of akinesia after 5(5/5) minutes from the peribulbar administration and it lasted for 20(20/20) minutes (p=0.000), compared to groups L and LC. In group GC we registered akinesia after 5(5/5) minutes, but the duration observed was shorter 5(5/6). In groups C and GC, additional L bupivacaine peribulbar injection was required. The train of four (TOF) was ≥ 0.9 throughout the study in all of the groups.

Conclusions

A combination of cisatracurium and L-bupivicaine, used for peribulbar sub-Tenon's anesthesia, provides effective akinesia, midriasis of the eye, shortens the onset of akinesia and prolongs its duration, thus providing excellent conditions for intra-ophthalmic surgery, without incurring in a systemic blockade.

Background

General anaesthesia usually induces eyeball ventromedial deviation which may hamper the vision of the surgical field in subjects undergoing ocular surgery. Nowadays, regional anaesthetic techniques, which provide akinesia, mydriasis and periocular analgesia, are commonly used for ophthalmic surgery.[1–4] Regional anaesthetic techniques include retrobulbar and peribulbar anaesthesia. Peribulbar anaesthesia reduces the incidence of haemorrhages at the cone level and injuries to the optic nerve, and induces

akinesia and mydriasis more efficiently compared to retrobulbar anaesthesia.[5–7] The onset of akinesia related to peribulbar injections of local anaesthetic agent combined with a low dose of neuromuscular blocking is lower compared to that of the local anaesthetic agent alone. [8–11] Nevertheless, many serious complications (e.g.: retrobulbar hemorrhage, globe perforation) may occur also following peribulbar injections. To avoid these complications, sub-Tenon's anaesthesia has been developed and used during ophthalmic surgery in humans, dogs and cats. [5, 12–13]

Levobupivacaine, a long-acting local anaesthetic agent, is the levorotatory isomer of racemic bupivacaine. As regard with anaesthetic potency, levobupivacaine is similar to bupivacaine but has less toxic potential both on the central nervous system and on the heart. Reduced toxic potential of levobupivacaine compared to bupivacaine supports the use of levobupivacaine in those clinical situations in which the risk of systemic toxicity, related with overdosing or unintentional intravascular injection, is high, such as during epidural or peripheral nerve blocks. [14] Based on these findings, levobupivacaine is used for peribulbar anaesthesia in elderly human patients undergoing vitreous and retina surgical procedures.[15–16]

Cisatracurium, an isomer of atracurium, is a non-depolarizing neuromuscular blocking agent with a duration of action of approximately 27 minutes. Cisatracurium may be reversed by edrophonium, neostigmine, and pyridostigmine.[17–19] The clearance of cisatracurium occurs through Hoffmann elimination, bypassing hepatic metabolism and renal filtration. Consequently, cisatracurium may be safely used in patients with liver and kidney diseases. Non-depolarizing neuromuscular blocking agents administered intravenously are useful adjuvants for general anaesthesia but mechanical ventilator is required to support patient's ventilation, because these drugs cause respiratory muscle paralysis. To avoid this side effect, atracurium and cisatracurium are used in peribulbar aneasthesia to obtain extraocular muscle akinesia.[8–11]

This study was necessary: to achieve, a balanced anesthesia in the cat, adequate to ophthalmic intraocular surgery in cat, to reduce side effects, improve the comfort of the surgeon and ensure the success of surgery.The aim of this study is to evaluate the onset of eyeball centralization, akinesia duration and mydriasis degree after sub-Tenon's injection of levobupivacaine alone and combined with low dose of cisatracurium in cats undergoing intraocular ophthalmic surgery. Moreover, the study aims to assess if the low-dose of cisatracurium administered through sub-Tenon's injection can determine systemic neuromuscular blockade.

Methods

The study was approved by the Review Board for Animals Care of the the University of Messina. Procedures were performed in accordance with Italian law (D.M. 116192), Europe law (O.J. of E.C. L 358/1 12/18/1986), and USA laws (Animal Welfare Assurance No A5594-01, Department of Health and Human Services, USA). Prior to the cats enrolment in the study, the owners provided informed consent.

thirty female cat and ten males of 3,5 ± 0,5 kg ,were admitted to our hospital for the following ophthalmic surgeries: penetrating corneal ulcers (n = 32) and cataract (n = 8). The patients were chosen for their docile temperament and they were randomly divided into four groups of treatment of ten subjects each (L, LC, GC, and C group) by drawing a ticket. All cats were sedated using butorphanol 0.2 mg kg^{-1} (Dolorex 1%; Intervet, Aprilia Italy), dexmedetomidine 15 µg kg^{-1} (Dexdomitor 0.5%, Pfizer Animal Health, Roma Italy) and midazolam 0.2 mg kg^{-1} (Ipnovel 0,5% Roche, Basilea Switzerland) combined and administered intramuscurarly. Following sedation, a 0.64 × 19-mm, 24-G venous (DELTA VEN, Deltamed Italy) catheter was inserted in the cephalic vein for medication and fluid administration. Artificial tear eye drops were applied on corneal surface every thirty minutes until the start of surgery (Artelac splash; Baush & Lomb, Italy). Anaesthesia was induced with propofol (Proposure 1%, Merial Italy) at effect intravenously. All cats received 2 mg kg-^{1} of lidocaine (Lidocaina 2%, Zoetis, Roma Italy) sprayed on the glottis and the endotracheal intubation was performed with a cuffed tube. Anaesthesia was maintained with isoflurane (ESTEVE; Barcelona, Spain) delivered in 100% oxygen via a non-rebreathing circle system (Mapleson B in parallel of Lack). Controlled respiration was supported by intermittent positive pressure ventilation. The mechanical ventilator (Servoventilator 900 C, Siemens Elema Sweden) was set using the following parameters: respiratory rate 20 breaths min^{-1}, volume 1.5 L min^{-1}, tidal volume of ~ 18 mL kg^{-1}, inspiratory/expiratory ratio (I:E) 1:2, and airway pressure 20 cmH_2O.

Then, all the cats were administered peribulbar sub-Tenon's anaesthesia in the eye to be operated using a 0.4 × 13 mm 27 G sterile needle (Latex Free Benefis®Italy). The anaesthetic mixture was applied both in the inferior temporal corner and in the upper nasal corner by inserting the needle between orbit and eyeball (Davis *et al*, 1986). The L group received L-bupivacaine 1.25 mg kg^{-1} (0.75% Chirocaina; Abbott, USA); LC group received 1.25 mg Kg^{-1} of L-bupivacaine combined with cisatracurium 0.01 mg kg^{-1} (0.2% Nimbex; Glaxo, Smithkline spa Italy); C group received 0.01 mg kg^{-1} of cisatracurium; GC group received 0.01 mg kg^{-1} of cisatracurium intravenously. All peribulbar anaesthesia were performed with the same volume of drug (1 ml), with the addition of saline solution 0,9%. If ineffective block occurred, additional local anaesthetic peribulbar block with L-bupivacaine was administered. A single observer, blinded to treatment, recorded the following parameters: heart rate (HR – beats min^{-1}), respiratory rate (RR – breaths min^{-1}, end-tidal carbon dioxide tension ($EtCO_2$ - mmHg), arterial haemoglobin oxygen saturation (SpO_2 - %), non-invasive blood pressure (NIBP - mmHg) by placing a cuff around the base of the tail, and the concentration of inspired and expired isofluorane (IT/ET isofluorane) using a multiparameter model (AMI s.r.l., Leonardo model Italy).

The evaluation of neuromuscular transmission was performed by detecting the TOF (Train of four) using a machine (TOF-Watch® SX; Organon, Italy) set automatically before each use at 50 mA and 1-0.1 Hz. The stimulating electrodes were applied at the medial part of the elbow (at the level of the ulnar nerve), whereas the recording of potentials was obtained by applying the electrodes above the carpus muscles. All parameters were measured immediately before sedation (time 0), after sedation (S), except TOF, SpO_2, and $EtCO_2$, and at 5, 10, 15, 20, 25 and 30 minutes after anaesthesia.

The intraocular pressure (IOP - mmHg) was measured with Tono-Pen Vet (Reichert Italy). The IOP baseline value was recorded after instillation of one drop of oxybuprocaine (0.4% Novesina; Novartis Italy) in awake animals. Afterward, the IOP was measured after sedation, at 5 and 10 minutes after peribulbar anaesthesia, and before the start of surgery with cats in sternal recumbency. The degree of mydriasis was evaluated by measuring the horizontal pupil diameter (mm) with Jameson calipers (E2410 Storz®, Italy) in awake animals, after sedation, at 5 and 10 minutes after anaesthesia, and before the start of surgery. The horizontal pupil diameter was measured (mm) by a single observer in the same room, lit with a 40W lamp. After sedation, eyeball centralization (akinesia) was evaluated by three independent observers that recorded if the eye was rotated or centrally positioned. Any deviation of the eye from central position was considered as rotated.[1–4] Onset and duration of akinesia (minutes) of extraocular muscles were recorded by a single observer.

All cats after full recovery have been discharged from hospital.

Statistical analysis was performed using SPSS 15.0 IBM software for Windows. A Kendall's test of concordance Shapiro-Wilk test and a power calculation of sample were performed. The data, expressed with median and range, were compared using Friedman test to evaluate changes along the time line and compared differences among groups. Statistical significance was set at $p < 0.05$.

Results

High level of concordance inter-observer (W = 1) was recorded in all groups and data were not normally distributed; The sample ,of subjects examined, is not representative enough of the population. HR, NIBP remained within physiologic ranges in all groups; $EtCO_2$ and SpO_2 values were 32–34 mmHg and 98–100% respectively (details were not reported in Table 1) The onset time of akinesia in group LC was significantly shorter than in group L, 4(3/5) and 8(6/10) minutes respectively (p = 0.000) (Table 1). The duration of akinesia in group LC was longer than in group L, 70(68/72) and 60(57/63) minutes respectively (p = 0.000) (Table 1).

In group C we observed the appearance of akinesia after 5(5/5) minutes from the peribulbar administration and it lasted for 20(20/20) minutes (p = 0.000), compared to groups L and LC(Table 1) (Table 1).

In group GC we registered akinesia after 5(5/5) minutes, but the duration observed was shorter 5(5/6). In groups C and GC, additional L bupivacaine peribulbar injection was required.

IOP was significantly lower (p = 0.000) in the LC group than in the L group at 5 and 10 minutes after peribulbar anaesthesia. In groups GC and C, the IOP was reduced in comparison to baseline and remained consistent after peribulbar and intravenously cisatracurim administration (Table 1). The degree of mydriasis was significantly higher (p = 0.000) in the LC group than in the L group at 5 and 10 minutes after peribulbar anaesthesia; in C and GC groups, the pupil diameter increased after sedation and there were variations after that peribulbar cisatracurium was administered(Table 1). Throughout the study, the

TOF (T1:T4) was ≥ 0.9 in all groups. The concentration of inspired and expired isofluorane was about 0.5-1% among the groups.

Table 1 legend: physiological and ophthalmic variables recorded in the groups: LC = levobupivacaine 2.5 mg kg^{-1} combined with cisatracurium 0.01 mg kg^{-1} (peribulbar); L = levobupivacaine 2.5 mg kg^{-1} (peribulbar); GC= cisatracurium 0.01 mg kg^{-1} (EV); C= cisatracurium 0.01 mg kg^{-1} (peribulbar). S = sedation; 5' – 30' = measurements during anaesthesia. Underlined = significant differences between values at different times. Bold = significant difference between groups (P<0.05).

		Time	*After sedation*	*After anaesthesia*					
Measured Data Median range	*Drugs*	*0'*	*S*	*5'*	*10'*	*15'*	*20'*	*25'*	*30'*
IOP (mmHg)	*LC*	*20(16/22)*	*18(16/20)*	*16(15/17)*	*15(13/17)*				
	L	*18(16/20)*	*17(15/19)*	*17(15/19)*	*17(15/19)*				
	GC	*17(16/18)*	*16(16/17)*	*16(15/17)*	*16(15/17)*				
	C	*18(16/20)*	*18(16/20)*	*18(17/18)*	*16(15/17)*				
Horizontal pupil diameter (mm)	*LC*	*5(4/6)*	*6(5/7)*	*8(7/9)*	*8(7/9)*				
	L	*5(4/6)*	*6(5/7)*	*6(5/7)*	*6(5/7)*				
	GC	*4(4/6)*	*5(5/6)*	*5(5/6)*	*5(5/6)*				
	C	*6(4/6)*	*6(5/7)*	*8(7/9)*	*8(7/9)*				
Akinesia	*LC*	Eye rotated	Eye rotated	Akinesia	Akinesia	Akinesia	Akinesia	Akinesia	Akinesia
	L	Eye rotated	Eye rotated	Eye rotated	Akinesia	Akinesia	Akinesia	Akinesia	Akinesia
	GC	Eye rotated	Eye rotated	Akinesia	Akinesia	Akinesia	Akinesia	Akinesia	Akinesia
	C	Eye rotated	Eye rotated	Akinesia	Akinesia	Akinesia	Akinesia	Akinesia	Akinesia
Onset of akinesia (min)	***LC***	*4(3/5)*							
	L	*8(6/10)*							
	C	*5(3/7)*							
	GC	*5(5/5)*							
Duration of akinesia (min)	***LC***	*70(68/72)*							
	L	*60(/57/63)*							
	C	*20(20/20)*							
	GC	*5(5/6)*							

Discussion

Levobupivacaine, combined with cisatracurium and administered by sub-Tenon's peribulbar injection, has provided a clinically effective degree of mydriasis, a faster eyeball centralization (akinesia), and maintained normal IOP values.[8–9]The onset of akinesia induced by levobupicaine combined with small quantity of cisatracurium is faster compared to that of levobupivacaine alone.[10–11] In our opinion, this effect is due to the presence of the Felderstruktur.[20–21] This is an anatomical ocular structure, provided with small grape-like nerve endings, which respond with a slow tonic contraction to non-depolarizing agents, such as cis-atracurim[10–11]. Furthermore, the duration of akinesia induced by levobupicaine alone is shorter. The eyeball centralization and mydriasis facilitate the phacoemulsification and surgical procedures, whereas normal IOP is mandatory for the success of ophthalmic surgery. The administration of a combination of neuromuscular blocking agent and local anaesthetic drug by sub-Tenon's peribulbar injection is an effective option for the execution of many veterinary intra-ocular ophthalmic procedures, and it allows to use low doses of general anaesthetic drugs, without undergoing side effects, such as a systemic neuromuscular blockade [13, 14] Dexmedetomidine combined with midazolam and butorphanol is a suitable sedation protocol for cat undergoing ophthalmic surgery because it does not increase IOP and ensures mydriasis.[20] Furthermore, dexmedetomidine and butorphanol provide good sedation because they act on the same membrane G-protein.[22–24] Nevertheless, dexmedetomidine combined with butorphanol significantly decreases tear production 15 minutes after sedation.[25–27] In the present study, we used high dose of dexmedetomidine to obtain a profound sedation to perform basal TOF measurement. Despite this high dose of dexmedetomidine, hemodynamic and respiratory parameters remained within physiological ranges. Then, in other contests, this dosage is not necessary and it can be reduced. The peribulbar anaesthesia is a reliable alternative to retrobulbar anaesthesia. To perform peribulbar anesthesia, the practitioner injects the drugs around the orbit and, consequently, the risk of haemorrhages at the cone level or lesions of the optic nerve is greatly reduced, compared to retrobulbar anesthesia.[5] As regard with analgesia and akinesia, no clear differences between peribulbar and retrobulbar anaesthesia were demonstrated in human beings. Furthermore, few side effects were recorded with both anaesthetic techniques.[6–7] In the veterinary literature, Shilo-Benjamini et al. (2013) highlighted that single peribulbar technique was better than double peribulbar and retrobulbar techniques, because single peribulbar injection provided "large" distribution of injected drug and, consequently, it could determine 86% of regional anaesthesia. Furthermore, IOP at 15 minutes after peribulbar injection was higher compared to baseline values.[5] In our study, IOP decreased after peribulbar injection. The likely reason of this difference is that, unlike Shilo-Benjamini et al. (2013), we enrolled live animals. Nevertheless, we cannot exclude that decrease in IOP was related to the lower injected volume compared to that previously used.[5] Moreover, surgical procedures were easily performed and no anaesthetic side effects were recorded. All patients had an excellent adaptation to the automatic ventilator, with $EtCO_2$ ventilation setting between 32–34 mmHg. The SPO_2 remained consistent at optimal levels (98–100%). No systemic neuromuscular blockade was recorded in all groups by measuring TOF. However, if neuromuscular blocking agents are administered, the use of an automatic ventilator is advisable.

A limitation to this kind of study could be the scarcity of cases to recruit and properly submit to intraocular surgery, since it has been a clinical and non-experimental study.

Conclusion

The anaesthetic management contributes to the success of ophthalmic surgery. Peribulbar anaesthesia combined with low doses of isoflurane is an effective method for anesthetizing cats undergoing intra-ophthalmic surgeries. The addition of 0.01 mg kg^{-1} of cis-atracurium to sub Tenon's administration of levobupivacaine improves the onset and quality of the local block and the degree of mydriasis, reduces IOP, and, consequently, facilitates the execution of ophthalmic surgeries. Low-dose of cis-atracurium administered through sub-Tenon's injection does not determine systemic neuromuscular blockade.

Abbreviations

IOP; intraocular pressure

HR; heart rate

min ;minutes

RR; respiratory rate

$EtCO_{2;}$carbon dioxide tension

mmHg; millimetres of mercury

$SpO_{2;}$ arterial haemoglobin oxygen saturation

% ; percentage

NIBP; non-invasive blood pressure

IT/ET; concentration of inspired and expired isofluorane

TOF; Train of four

S; sedation

min; minutes

Declarations

Availability of data and materials

The collection material and the recorded data is available and kept by the first author, Dr. Giovanna Costa glcosta@unime.it

Competing interests

No competing interests

Consent for publication

All authors give their consent to publication

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Authors' contributions

Giovanna Costa: project preparation, data recording and statistical processing. Preparing the manuscript;

Bernadette Nastasi: data recording and preparing the manuscript;

Marcello Musicò data recording and preparing the manuscript

Fabio Leonardi data recording and preparing the manuscript

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