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Application of neuromuscular blockade using Rocuronium for performing different surgeries and its reversal by Neostigmine-Glycopyrrolate combination in dogs

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ABSTRACT

This study was executed in the clinical setup to investigate the effects of Rocuronium and its reversal by Neostigmine and Glycopyrrolate (Myopyrolate) combination in Propofol-Isoflurane anaesthetized dogs. Rocuronium-induced neuromuscular blockade was applied to 21 clinical cases. Out of which, 19 cases were of orthopaedic surgeries and 2 cases of ovariohysterectomy. After the animal had stabilized on the mixture of isoflurane and oxygen, the relaxation of muscle was induced using Rocuronium @ 0.5 mg/kg b.wt. Immediately IPPV was provided in volume control mode. Neuromuscular blockade was reversed using a single syringe combination drug having both Neostigmine and Glycopyrrolate (Myopyrolate) @ 0.05 mg/kg b.wt and @ 0.01 mg/kg b.wt, respectively. Rocuronium caused the centering of the ocular globe gradually in less than 30 sec. During orthopaedic surgeries, the reduction of fractured ends became easy without much tissue trauma. In ovariohysterectomy surgeries, the appropriate level of abdominal muscle relaxation further helped in the easy exteriorization of the ovarian stump. The onset time for Rocuronium was 17.64±1.10 sec and its duration of action was 27.82±0.72 min. The use of Rocuronium along with IPPV caused minimal alteration of the physiological parameters with no clinical consequences and thus can be considered a complication-free anaesthetic protocol for interventions demanding muscle relaxation.

Keywords: Anaesthesia, Glycopyrrolate, IPPV, Muscle relaxation, Neostigmine, Rocuronium

With the introduction of neuromuscular blocking agents, a light level of anaesthesia with good analgesia and adequate muscle relaxation became a possibility, thus any degree of relaxation could be achieved irrespective of the anaesthetic depth. The neuromuscular blocking drugs act specifically on the neuromuscular junction, thereby causing paralysis or relaxation of voluntary striated muscles. These drugs have no other important effect on the body except on the neuromuscular junction and produce fast and effective muscle relaxation with no or minimal effect on the central nervous system and circulatory system. Non-depolarising neuromuscular blocking agents are preferred in veterinary clinical practice because of the lesser side effects and comparatively longer duration of action than depolarising neuromuscular blocking agents. These are mostly mono or biquaternary hydrophilic salts and have a relatively slow time of onset. Anticholinesterases are used for the reversal of muscle relaxation provided by non-depolarising neuromuscular blocking agents. Rocuronium is an amino steroid competitive, non-depolarizing neuromuscular blocking agent with a rapid to intermediate onset depending on the dose and an intermediate duration of action. Rocuronium is metabolized primarily by the liver in dogs and a small fraction is eliminated by the kidney. It is freely soluble in water and has a longer shelf-life. Rocuronium does not appear to induce malignant hyperthermia. The reversal agents in case of non-depolarising neuromuscular block, when used in the proper manner do not allow the residual neuromuscular block to set in and thus recurarization does not occur. The effects of neuromuscular block provided by Rocuronium can be effectively antagonized with acetylcholinesterase inhibitors such as neostigmine. The effects of increase in the concentration of acetylcholine produced by acetylcholinesterase inhibitors are not specifically limited to the neuromuscular junction, but also occur at other cholinergic sites of the patient's body. The muscarinic effects include emesis, enhanced intestinal tone, bronchoconstriction, salivation and bradycardia. To prevent muscarinic effects, specifically bradycardia, glycopyrrolate or atropine may be given in small animals along with acetylcholinesterase inhibitors. The neostigmine-glycopyrrolate combination is preferred as it has a slower onset and a longer duration of effect.

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MATERIALS AND METHODS

A total 21 clinical cases of dogs of either sex were administered a neuromuscular blocking agent, Rocuronium following anaesthesia under general anaesthesia. All the dogs were withheld feed for about a 12 h period and water for about 4 h. All the animals were premedicated with Butorphanol tartrate @ 0.2 mg/kg b.wt. I/M, then after a gap of 30 min Atropine sulphate was administered @ 0.02 mg/kg b.wt. I/M; again after a gap of 10 min, the animal was premedicated with Diazepam @ 0.5 mg/kg b.wt. I/V and immediately followed by Propofol I/V administered till effect, for the induction of general anaesthesia.

Surgical anaesthesia had been induced with propofol and airway of the animal was secured by endotracheal intubation and animal was quickly transferred to the inhalant anaesthetic with a mixture of isoflurane and oxygen. Animal had been stabilized and the relaxation of muscle was induced by Rocuronium @ 0.5 mg /kg b. wt., IV; the animal was immediately shifted to intermittent positive pressure ventilation till the neuromuscular block wanes off. Neuromuscular block induced by Rocuronium was reversed at the first sign of asynchrony on the bellow and the multiparameter monitor. A single-syringe combination drug having both Neostigmine and Glycopyrrolate (Myopyrolate) was administered @ 0.05 mg/kg b.wt. I/V and @ 0.01 mg/kg b.wt. I/V, respectively. Various procedures done under the above-mentioned protocol are listed in Table 1. The various parameters were investigated at different time intervals based on Table 2.

Table 1. Surgical procedures performed during the study

Surgical procedure	No. of cases
Intra medullary pinning	5
Bone plating	4
Intra medullary pinning with cerclage wire	3
Rush pinning	5
Plate and rod combination	2
Ovariohysterectomy	2

Table 2. Time intervals for taking and recording various observation

Time interval	Time /stage
T_0	Base value
T_1	Just after induction
Rocuronium administered	
T_5	5 minutes after rocuronium injection
T_{10}	10 minutes after rocuronium injection
T_{15}	15 minutes after rocuronium injection
T_{20}	20 minutes after rocuronium injection
Neuromuscular block was reversed	
T_{40}	40 minutes after rocuronium injection

The haematobiochemical parameters were monitored in three phases (Pre, Intra and Post operative). Various parameters like heart rate, non-invasive blood pressure, SpO_2, ECG, rectal temperature and IOP (intraocular pressure) (Supplementary Table 1) were recorded. Additionally, pulmonary parameters like respiration rate, end-tidal oxygen concentration, fractional inspired oxygen concentration, end-tidal carbon dioxide, fractional inspired carbon dioxide concentration, end-tidal isoflurane, fractional inspired isoflurane concentration, minimum alveolar concentration were recorded with the help of anaesthetic gas monitor and multi-parameter monitor.

IPPV mode of the ventilator was used in the study and ventilator settings were kept as tidal volume @ 10 ml/kg b. wt., inspiratory and expiratory ratio as 1:2 and respiration rate of fifteen breaths per minute in all the animals. Postoperatively different recovery parameters were recorded which included total time of surgery under IPPV, i.e. time to weaning from the ventilator (the time period from keeping the animal on a ventilator until weaning from the ventilator), palpebral reflex time (the period from the stoppage of isoflurane in the anaesthetic circuit to the time when the animal starts showing palpebral reflex), pedal reflex time (the period from the stoppage of isoflurane in the anaesthetic circuit to the time when the animal started showing pedal reflex was recorded as pedal reflex time), time to first head raise and standing (the time period from discontinuation of isoflurane until the animal raised his head and acquired the standing stance respectively after stoppage of anaesthetic gas) (Supplementary Table 2). Statistical analysis was done with Graph Pad Instat Software, Version 3.01, 32 bit.

RESULTS AND DISCUSSION

There was a steady decrease in the body temperature from the baseline value till T_{40}. The decrease in rectal temperature at T_5, T_{10}, T_{15}, T_{20} and T_{40} time intervals was statistically significant (Table 3). The trend was similar to that observed by Redondo *et al.* (2012), who in their study on dogs recorded a 2.0ºC fall in the body temperature of the animals in the first hour of the surgery and further observed that in the premedication phase, animal was under the influence of analgesics and sedatives, therefore, the basal metabolism and amount of heat produced in the body of the animal were both reduced and heat dissipation was increased.

No major fluctuation in the Intraocular pressure (IOP) was observed during the course of the study and it remained well within physiological limits.

The insignificant decrease in intraocular pressure (IOP) might be due to the fact that the isoflurane causes a slight decrease in IOP and the neuromuscular blocking agent (NMBA) administered to the dog, which did not further have any effect on IOP (McMurphy *et al.* 2004). It was also reported that anticholinergic drugs did not have or have very little incremental effect on IOP (Frischmeyer *et al.* 1993 and Kovalcuka *et al.* 2013). Benzodiazepines like midazolam and diazepam cause minimum or no effect on IOP but at the same time, these drugs can effectively negate the incremental effect of propofol on IOP (Hofmeister *et al.* 2006 and Kovalcuka *et al.* 2013).

Table 3. Mean±SE of Rectal temperature (°F), Heart rate (beats/minute) Respiration Rate (per minute) at various time intervals

Parameter	T_{BASE}	T_1	T_5	T_{10}	T_{15}	T_{20}		T_{40}
	BASE	GA		NMBA (IPPV)			25-35 MIN	POST REVERSAL
Rectal Temp (°F)	101.24 ± 0.19	100.88 ± 0.17	99.92 ± 0.25***	99.25 ± 0.23***	98.71 ± 0.23***	98.03 ± 0.22***	REVERSAL	97.27 ± 0.26***
Heart rate (beats/min)	106.76 ± 3.45	125.00 ± 3.97***	131.82 ± 2.02***	122.94 ± 1.86***	120.41 ± 2.02**	117.35 ± 2.05*		116.05 ± 2.03*
Respiration rate (per min)	25.23 ± 1.47	20.11 ± 0.66***	15.0 ± 0.0***	15.0 ± 0.0***	15.0 ± 0.0***	15.0 ± 0.0***		11.23 ± 0.47***

*, Mean difference within the groups is significant when compared with base value (p< 0.05); **, Mean difference within the groups is significant when compared with base value (p< 0.01); ***, Mean difference within the groups is significant when compared with base value (p< 0.001).

Heart rate increased significantly from the base value to the T_1 and it further increased significantly ($p<0.001$) at T_5 just after rocuronium was administered to the animal and thereafter gradually decreased insignificantly up to $T_{40.}$ A slight increase in heart rate just after administration of rocuronium was in agreement with the findings of Khuenl-Brady *et al.* (1996) who reported a slight transitory increase in the heart rate after administration of Rocuronium, which might be attributed to the mild vagolytic activity of rocuronium in humans. After T_5 there was a gradual non-significant decrease in heart rate up to T_{40}; but the heart rate was always within physiological limits. Xue *et al.* (1998) documented that Rocuronium bromide had very little effect on cardiovascular parameters and it did not cause any histamine surge in humans. Booij (1997) and Miranda *et al.* (2008) stated that rocuronium in higher doses might be associated with a little increment in heart rate and appreciable increment in blood pressure due to its vagolytic property. All the ECG parameters were within the normal physiological range.

Mean arterial pressure (MAP) is the most important parameter for monitoring blood pressure during anaesthesia. No statistically significant change in MAP was observed at any time interval during the course of this study. Decrease in the value of MAP at the time interval T_1 which was just after induction might be due to Propofol (Table 4). There was a slight increase in MAP at T_5, which was just after Rocuronium was injected, as compared to T_1 and a similar trend was observed by Dugadale *et al.* (2002) in their study on dogs. All the values of MAP were within the normal physiological range at all the time intervals. Oxygen saturation of haemoglobin was between 98% to 100% at all the time intervals during this study.

The requirement of vaporizer concentration (%) showed a significant decline after neuromuscular blockade with Rocuronium was administered. Thus, a clear Isoflurane-sparing effect was observed during this study. Kumar (2017) conducted a study of NMBAs namely Atracurium and Vecuronium in dogs and found a similar inhalant-sparing effect of the neuromuscular blocking agent. In addition to this neuromuscular blockade produced by neuromuscular blocking agents could be potentiated by inhalant anaesthetic agents (Nagahama *et al.* 2006, Sakata *et al.* 2019), further, substantiating the fact that neuromuscular blocking agents had an inhalant sparing effect.

There was a statistically significant decrease ($p<0.001$) in the respiration rate at the T_1 time interval, that was just after induction, thereafter respiration rate remained constant at T_5, T_{10}, T_{15} and T_{20} as the animal was on a ventilator during these time intervals and the respiration rate was fixed at 15 breaths per minute. Furthermore, there was a statistically significant decrease ($p<0.001$) in the respiration rate at T_{40}, as the neuromuscular block had already been reversed between T_{20} and T_{40} and the animal had been weaned from the ventilator but was still on inhalant anaesthesia. The decreased respiration rate at T_{40} was normal under anaesthesia.

A similar decrease in the respiratory rate following premedication with diazepam and induction by propofol was observed by Naryal (2020). The fall in respiratory rate following induction with propofol was also observed by Musk *et al.* (2005) and Hammond and England (1994) in their respective studies on dogs. The value of fractional-inspired isoflurane (FiISO) showed a gradual decline from T_5 to T_{40} which directly corresponds to the vaporizer concentration at different time intervals (Table 5). The value of end-tidal isoflurane (EtISO) showed a gradual statistically significant decline from T_5 to T_{20} time interval and then a slight rise at T_{40}. Kumar (2017) in his study on dogs under NMBA stated that as the animal kept on inhalant anaesthesia got stabilized on isoflurane the absorption of the inhalant gas declined in the tissue thereby increasing

Table 4. Mean ± SE of Mean Arterial pressure (mmHg) at various time intervals. (n=21)

Parameter	T_{BASE}	T_1	T_5	T_{10}	T_{15}	T_{20}		T_{40}
	BASE	GA		NMBA (IPPV)				POST REVERSAL
MAP (mmHg)	95.41 ± 2.43	89.29 ± 3.04	92.47 ± 2.48	88.47 ± 2.12	89.64 ± 2.15	91.23 ± 1.44	25-35 MIN REVERSAL	94.35 ± 1.54

Table 5. Mean ± SE of Pulmonary parameters at various time intervals

Parameter	T_1	T_5	T_{10}	T_{15}	T_{20}		T_{40}
	GA (BASE)	NMBA (IPPV)				25-35 MIN	POST REVERSAL
Isoflurane vapour pressure (%)	3.58±0.11	2.26±0.06***	1.79±0.07***	1.5 ± 0.0***	1.5±0.0***	R	1.5±0.028***
SpO_2 (%)	98.82±0.29	98.64±0.20	98.23±0.30	98.70±0.21	98.58±0.23	E	99.35±0.18
$EtCO_2$ (mmHg)	38.29±1.13	39.41±1.03	40.41±1.30	41.23±1.36	41.11±1.02	V	42.58±1.17
$FiCO_2$ (mmHg)	0.05±0.05	0.11±0.07	0.11±0.07	0.23±0.10	0.17±0.09	E	0.17±0.09
EtO_2 (mmHg)	77.35±1.26	79.23±0.69	80.70±0.85	80.47±0.99	79.52±1.03	R	80.52±1.04
FiO_2 (mmHg)	83.94±0.63	85.17±0.25*	86.41±0.32**	86.47±0.49**	85.58±0.44*	S	86.17±0.38**
Et_{iso}(mmHg)	2.70±0.04	2.03±0.03***	1.85±0.02***	1.64±0.02***	1.16±0.03***	A	1.59±0.03***
Fi_{iso}(mmHg)	3.70±0.10	2.54±0.09***	2.22±0.02***	2.06±0.02***	1.94±0.03***	L	1.84±0.04***
Mac (%)	1.82±0.02	1.44±0.02***	1.28±0.01***	1.15±0.01***	1.10±0.00***		1.08±0.00***

*, Mean difference within the groups is significant when compared with the T_1 value ($p< 0.05$); **, Mean difference within the groups is significant when compared with the T_1 value ($p< 0.01$); ***, Mean difference within the groups is significant when compared with the T_1 value ($p< 0.001$).

the value of EtISO with increased duration of anaesthesia. The value of MAC showed a statistically significant decline (*p<0.001*) in the value from T_5 to T_{40}. The value of MAC was calculated by an inbuilt algorithm of AGM and directly corresponds to the vaporizer concentration (vol %) at different time intervals. The trend for a decrease in MAC value was in agreement with the study of Miyakazi *et al.* (2016), who reported a decrease in the MAC value of isoflurane in rats after neuromuscular blockade with Pancuronium.

Concentration of haemoglobin (Hb) and packed cell volume (PCV) showed a significant decrease (*p<0.01*) from the pre-operative base value to the intraoperative period and then again decreased (*p<0.001*) during the postoperative period (Supplementary Table 3). Decrease in the concentration of haemoglobin and PCV was attributed to the vasodilation at the microcapillary level and due to this dilatation; many RBCs enter these microcapillary and thereby decreasing the haemoglobin and PCV values measured in the blood sample from peripheral veins (Naghibi *et al.* 2002). Dunne *et al.* (2002) also observed anaemia in a large number of cases of human surgical patient during perioperative and postoperative period. The values of total leukocytic count (TLC) and total erythrocytic count (TEC) showed a significant decrease (*p<0.001*) from the pre-operative base value to the intraoperative period and then again decreased significantly (*p<0.01*) during the postoperative period. Decrease in the values of TLC, Hb and PCV could be the result of pooling of blood cells in the circulatory system into the spleen or other reservoirs due to sympathetic activity (Wagner *et al.* 1991). Popovici *et al.* (2014) stated that the decrease in TLC might be due to the migration of white blood cells from circulation to the site of surgery.

A statistically significant increase was observed in the level of glucose in the intraoperative and postoperative periods compared to the value of glucose in the preoperative period. The increase in the glucose level during and after surgery might occur due to a hyper metabolic response to the stress, in which the production of glucose was increased with simultaneous insulin resistance (Duncan 2012). In addition, Maeda *et al.* (2018) in their study on dogs opined that hormones related to stress namely cortisol, epinephrine and mediators of inflammation were responsible for elevated levels of glucose during the perioperative period. Inhalant anaesthetic agents like isoflurane and sevoflurane also depress the glucose metabolism of the blood by decreasing the secretion of insulin hormone from the pancreas. (Diltoer and Camu 1988, Vore *et al.* 2001 and Tanaka *et al.* 2005). The agent used for intravenous anaesthesia like propofol had also been associated with glucose metabolism suppression leading to an increased level of glucose (Kitamura *et al.* 2009). Dikshit and Prasad (1971) reported that due to the fall in basal metabolic rate and muscle activity during anaesthesia the use of glucose by the muscle tissue was decreased thereby causing an increased concentration of blood glucose in the body.

There was statistically non-significant decrease of Alanine transaminase (ALT) in the intraoperative and postoperative periods compared to the base values (Supplementary Table 4). Similarly, there was statistically significant decrease (*p<0.05*) Aspartate aminotransferase (AST) in the intraoperative and postoperative periods compared to the base value. The preoperative high values of AST and ALT might be due to muscle injury (Alvarez and Whittemore 2009). All the values of ALT and AST at different time intervals were well within the normal physiological limits. A similar trend of decrease in ALT and AST postoperatively was also recorded by Popovici *et al.* (2014) in their study on dogs undergoing orthopaedic surgery. Improved supply of blood to the liver as a result of administering propofol might have caused a fall in the ALT and AST in dogs (Khurana 2014).

All the animals recovered smoothly both from anaesthesia and neuromuscular block during the study. Under inhalant anaesthesia, the ocular globe of the animal was in the ventro-medial position. As rocuronium was administered to the animal, the ocular globe gradually changed to a central position within 30 seconds. The central position of the ocular globe facilitates many kinds

of surgical interventions and examinations in the eyes. Auer and Moens (2007) in their study observed similar results with the neuromuscular blocking agent, i.e. Rocuronium. Briganti *et al.* (2013) reported that rocuronium facilitated centering of the eyeball as a result of relaxation of extraocular musculature in dogs anaesthetized with isoflurane and the duration of relaxation depended on the dose of the rocuronium.

During orthopaedic surgeries, the reduction of fractured ends became effortless with minimal time thus reducing overall operative time. Easy reduction of the fracture with minimal tissue trauma was possible and bone nibbling was not required for reduction of the fracture ends. Popovici *et al.* (2014) in their study used rocuronium for orthopaedic surgeries in dogs and concluded that rocuronium provided very good muscle relaxation. In ovariohysterectomy surgeries, the appropriate level of abdominal muscle relaxation and overall easiness in surgical handling was observed which further helped in the easy exteriorization of the ovarian stump. Neves *et al.* (2014) reported a similar result in their study on female dogs using rocuronium with acepromazine-propofol-isoflurane anaesthesia protocol. Kumar *et al.* (2019) compared Atracurium and Vecuronium in their study on dogs and observed similar results pertaining to muscle relaxation for orthopaedic and ocular surgeries.

Rocuronium @ 0.5 mg/kg b. wt. IV in dogs produced neuromuscular blockade within 17.64±1.10 sec of administration and provided muscle relaxation for 27.82±0.72 min. Rocuronium-induced muscle relaxation provided the centering of the ocular globe within a few seconds without any significant effect on IOP, therefore its use in ophthalmic surgery can be explored. The use of Rocuronium along with IPPV caused minimal alteration of the physiological parameters with no consequences clinically and thus can be considered a complication-free anaesthetic protocol for interventions demanding muscle relaxation.

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