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Influence of atracurium on selected cardiovascular and respiratory variables and surgical times in dogs undergoing laparoscopic ovariectomy with a standardised ventilation pattern

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ABSTRACT: Respiratory and cardiovascular changes in normocapnic dogs undergoing laparoscopic ovariectomy are described in this report. To-date, changes during a standardised ventilation pattern, irrespective of end-tidal CO_2 ($EtCO_2$) levels, have not been reported. This study was undertaken to describe these changes. Forty bitches undergoing laparoscopic ovariectomy were enrolled in a prospective double-blind randomised clinical trial. They were first anaesthetised with medetomidine-butorphanol-propofol and then maintained with isoflurane in oxygen-air. Ventilation pattern was pressure-controlled, volume-limited. After stabilisation, atracurium 0.4 mg/kg (ATR group, n = 20) or saline 0.04 ml/kg (SAL group, n = 20) was administered intravenously. Capnoperitoneum was then established with an intra-abdominal pressure setting of 10 mmHg. Collected data included heart rate (HR), non-invasive blood pressure, $EtCO_2$, oxygen saturation of haemoglobin, and tidal volume and neuromuscular blockade (train-of-four). Data were recorded before administration of atracurium or saline, and at 2, 5, and 10 min thereafter. Subsequently, insufflation of CO_2 was commenced. After capnoperitoneum was established, data were recorded at 2, 5 and 10 min. Time of capnoperitoneum induction and duration, time of ovary searching and excision and total time of capnoperitoneum and surgery were also recorded. For statistical analysis, the Shapiro Wilk test, ANOVA with repeated measures and Student's t-test for independent samples were used ($P < 0.05$). Significant increases in $EtCO_2$ were observed in patients 5 min after atracurium administration and 5 min after capnoperitoneum was established in the ATR group, when compared to the SAL group. No other differences were found. Administration of atracurium in dogs undergoing laparoscopic ovariectomy with a standardised ventilation pattern did not result in clinically important differences in selected cardiovascular and respiratory variables and surgical times in comparison with non-relaxed dogs. Thus, the use of atracurium in laparoscopic ovariectomy does not result in any benefit for patients or surgeons.

Keywords: bitch; capnoperitoneum; spaying; relaxation

Laparoscopy is a minimally invasive technique for viewing the internal structures of the abdominal cavity. Laparoscopic ovariectomy in small animals has become popular due to its minimal invasiveness. Nevertheless, the influence of abdominal distension due to CO_2 insufflation must be considered as it can alter cardiovascular and respiratory functions of the patient during the anaesthesia (Weil 2009). Carbon dioxide is absorbed into the blood. Higher levels of arterial CO_2 tend to increase heart rate, blood pressure, and cardiac output. Insufflation of gas increases intra-abdominal pressure (IAP) in the patient, with the potential to cause decreased tidal volume and hypoventilation by cranial displacement of the diaphragm and decreased residual capacity of the lungs (Nunn 1990). A decrease caused by capnoperitoneum is marked in cases where intra-abdominal pressure exceeds

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16 mmHg. No significant changes are observed when the pressure is approximately 10 mmHg (Ishizaki et al. 1993; Luz et al. 1994). Therefore, intra-abdominal insufflation pressure higher than 15 mmHg should be avoided in dogs (Duke et al. 1996; Bailey and Pablo 1999). In humans, low intra-abdominal insufflation pressure in laparoscopic procedures is recommended so as to promote lower post-operative pain perception and minimal alteration of cardiovascular and respiratory system functions (Joshipura et al. 2009).

Neuromuscular blocking agents (NMBA) are commonly used in human or veterinary laparoscopic procedures as neuromuscular block (NMB) allows easier surgical access to the abdominal cavity as well as organ manipulation (Hanley 1992). Moreover, the use of NMBA allows abdominal insufflation with lower pressure or improves the surgical conditions when higher pressure is used (Staehr-Rye et al. 2014).

Atracrium is a commonly used NMBA in human and veterinary anaesthesiology. Some authors report that its use potentiates the release of histamine (Hughes and Chapple 1981). Nevertheless, common therapeutic doses do not have a significant influence on basic cardiovascular parameters (i.e. heart rate or arterial blood pressure) (Lavery et al. 1986; Larijani et al. 1992; McMurphy et al. 2004).

Van Goethem et al. (2012) described a comparable study to the one reported here. In their patients, NMB did not significantly improve laparoscopic ovariectomy times and except for a 5% decrease in arterial blood pressure did not change any of the evaluated anaesthetic and surgical variables.

This study was aimed at investigating the effects of the NMBA atracurium on selected cardiovascular and respiratory variables and surgical times in dogs undergoing laparoscopic ovariectomy with standardised ventilation pattern, while Van Goethem et al. (2012) described changes in dogs maintained in normocapnia using a different ventilator pattern.

We hypothesised that there might be significant differences in selected variables between groups with and without NMBA administration.

MATERIAL AND METHODS

All procedures were carried out with the consent of the Animal Welfare Ethics Committee of the University of Veterinary and Pharmaceutical Sciences, Brno.

Animals. Forty adult client-owned bitches of different breeds undergoing laparoscopic ovariectomy were enrolled in this study. All owners signed an informed consent before study entry. Only dogs with normal anatomy of the uterus and ovaries during laparoscopic evaluation remained in the study. A standard questionnaire was completed before surgery. Questions included dog age, number of oestrus cycles, date of last oestrus, occurrence of pseudopregnancy, general health and vaccination status.

The dogs were 4.2 ± 3.2 years old (mean ± SD, range 0.5–11.0) and weighed 34.3 ± 11.5 kg (15.0–64.0). The dogs were clinically healthy and were allocated randomly to one of ATR (atracurium) and SAL (saline) groups (n = 20 each). All dogs were fasted overnight prior to anaesthesia, but had free access to water.

A prospective, randomised, double-blind clinical trial was performed.

Surgery. All surgeries were performed by the same surgeon (M. Crha) who was blinded to the administration of atracurium or saline. Dogs were positioned in a strictly horizontal position and the table was laterally tilted (90°) depending on the side of interest. A standard midline laparoscopic approach was performed using three portals (Rothuizen 1985). After capnoperitoneum was established, intrabdominal pressure was maintained at 10 mmHg (Laptflow 40, Smith & Nephew, Germany). A Veress needle for CO_2 insufflation and three trocars (two 5 mm and one 10 mm) were placed. A 5 mm telescope was introduced and the abdomen was inspected. Two grasping forceps were used to locate and manipulate the ovarian bursa. Both ovaries were removed with a bipolar sealing device (Harmonic Blade Endo-Surgery, Ethicon, Germany). At the end of surgery, CO_2 was spontaneously evacuated from the abdomen through portals and the portal incisions were closed routinely.

Anaesthesia. All dogs were anaesthetised using a standard protocol. After premedication with medetomidine (0.01 mg/kg *i.v.*; Domitor 1 mg/ml, Orion, Finland) and butorphanol (0.4 mg/kg *i.v.*; Butomidor 10 mg/ml, Richter Pharma AG, Austria) anaesthesia was induced with propofol (12 mg/kg *i.v.*; Norofol 10 mg/ml, Norbrook, Northern Ireland). Thereafter, all dogs were orotracheally intubated and connected to an anaesthetic machine (Venar, Chirana, Slovak Republic). Anaesthesia was maintained with isoflurane (1.5–2.0 vol.%, Isofluran, Torrex Chiesi, Austria) vaporised in an oxygen-

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air mixture (1–2 l/min, semi-closed rebreathing circle system, fraction of inspired oxygen (FIO_2) 0.6. After connection to a circle breathing system, pressure-controlled volume-limited automatic ventilation was started. An initial respiratory frequency of 10 breaths/min, peak inspiratory pressure of 15 cmH_2O and positive end-expiratory pressure of 2 cmH_2O were chosen.

After patient stabilisation, atracurium (0.4 mg/kg *i.v.*; Tracrium, Glaxo Smith Kline, Italy) (ATR group, n = 20) or saline 0.04 ml/kg (SAL group, n = 20) was administered intravenously.

Capnoperitoneum was then established by insufflation of carbon dioxide through a Veress needle inserted into the abdominal cavity paramedially. Intra-abdominal pressure was thereafter set and automatically maintained at 10 mmHg.

Monitoring. Collected data included heart rate (HR), non-invasive blood pressure (NIBP), end-expiratory partial pressure of CO_2 (end-tidal CO_2, $EtCO_2$), oxygen saturation of haemoglobin (SpO_2) and tidal volume (V_T) and neuromuscular blockade (train-of-four, TOF).

Heart rate was monitored by 3-lead ECG, leads were applied on the front and left hind limbs. Non-invasive blood pressure (Cardel 9401, Midmark, UK) was measured using a cuff applied to the front limb; cuff width was 40% of the circumference of the limb. Mean arterial pressure was measured. The sensor for $EtCO_2$ measurement was attached to the end of the patients' endotracheal tube and $EtCO_2$ was measured using a side-stream technique. Oxygen saturation of haemoglobin was measured using a sensor applied to the tip of the patients' tongue. Heart rate, $EtCO_2$ and SpO_2 were measured using vital-sign monitors (Datex Cardiocap II, Datex-Ohmeda, Finland).

Tidal volume was measured using a spirometric module attached to the patients' endotracheal tube and connected to an inhalation anaesthetic machine (Venar, Chirana, Slovakia).

Neuromuscular blockade was measured using a TOF technique (Flaherty and Auckburally 2007). The needle electrodes of a peripheral nerve stimulator (TOF-Watch SX, Organon, Ireland) were placed subcutaneously over the left peroneal nerve. Four supramaximal stimuli of 10 mA and 0.2 s duration were delivered at 2 Hz over 2 s. Each TOF was repeated every 30 s. Disappearance of the twitch response to all four stimuli was considered complete neuromuscular block.

Surgical times – time of capnoperitoneum induction and duration, time of ovary localisation and total time of surgery were also recorded. Time of capnoperitoneum induction was set as the time from the beginning of CO_2 insufflation into the abdominal cavity to the point when intra-abdominal pressure reached 10 mmHg. Time of capnoperitoneum duration was set as the time of reaching an intra-abdominal pressure of 10 mmHg to complete desufflation of intra-abdominal pressure to 0 mmHg at the end of surgery. Time of ovary searching was set as the time from insertion of the endoscope into the abdominal cavity to the visualisation of the left or right ovarium separately. Time of ovary excision was set as the time from the end of the search for the appropriate ovary to its complete resection. Total time of surgery measured as the time from skin incision to the placement of the last skin suture.

Follow-up. Dogs were sent home after complete anaesthetic recovery with owners instructed regarding postoperative care and the administration of carprofen (2 mg/kg *s.c.*; Rimadyl, Zoetis, Czech Republic).

Data collection and statistical analysis. Collected data included HR, NIBP, $EtCO_2$, SpO_2 and V_T and were recorded and collected before administration of atracurium or saline, and at 2, 5, and 10 min thereafter. Subsequently, insufflation of CO_2 was commenced. After capnoperitoneum was established, data were recorded at 2, 5 and 10 min. Neuromuscular blockade were recorded and collected 2, 5 and 10 min after administration of atracurium.

Data normality checking was carried out using the Shapiro Wilk test. Differences in anaesthetic variables (HR, NIBP, $EtCO_2$, SpO_2 and V_T) were evaluated using analysis of variance (ANOVA) with repeated measures. Differences in surgical times (time of capnoperitoneum induction and duration, time of ovary localisation and total time of surgery) were evaluated using Student's t-test for independent samples.

Data are reported as mean ± standard deviation (SD) (ranges). Differences were considered significant where $P < 0.05$. Statistical analysis of data was performed with SPSS software (IBM, USA).

RESULTS

There were no significant differences between ATR and SAL groups with respect to sex, body mass, age, character of oestrus cycles, time since

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last oestrus and pseudopregnancy. In the ATR group twenty dogs, 3.7 ± 3.4 (0.5–11.0) years old and weighing 28.5 ± 8.8 (15.0–49.5) and in the SAL group twenty dogs, 4.7 ± 3.0 (0.8–9.0) years old and weighing 36.2.3 ± 9.4 (23.0–64.0) were included. All dogs were clinically healthy.

Anaesthetic variables

There were no significant differences between ATR and SAL groups with respect to HR, NIBP, SpO_2 and V_T. There were also no significant differences in ATR and SAL groups in selected variables measured before and after capnoperitoneum was established (Figures 1, 2, and 3).

Significant increases in $EtCO_2$ were observed in patients of the ATR group compared to the SAL group at 5 min after atracurium administration (P = 0.04), and at 5 min after capnoperitoneum was established (P = 0.027) (Figure 4). Five minutes after atracurium administration $EtCO_2$ increased by 10% (ATR group), and after saline administration it decreased by 9% (SAL group). Five minutes after capnoperitoneum was established $EtCO_2$ increased in the ATR group by 22%, while in the SAL group it decreased by 6%. No other differences were found.

Surgical times

Administration of NMBA did not significantly change any of the recorded surgical times.

Capnoperitoneum was established in the ATR (atracurium) group after 183 ± 126 (68–301) and in the SAL (saline) group after 228 ± 102 (62–322) seconds, respectively. Total time of capnoperitoneum was 28 ± 10 (20–45) min in the ATR group and 29 ± 4 (25–35) min in the SAL group, respectively.

In the ATR group the search for and excision of the right ovary took 50 ± 30 (14–99) s and 155 ± 55 (109–252) s, respectively. In the SAL group the search for and excision of the right ovary took 37 ± 21 (5–68) s and 157 ± 53 (85–212) s, respectively.

In the ATR group the search for and excision of the left ovary took 60 ± 79 (7–236) s and 150 ± 48 (88–230) s, respectively. In the SAL group the search for and excision of the left ovary took 76 ± 64 (1–190) s and 169 ± 52 (115–254) s, respectively.

Total surgery time was 33 ± 5 (29–40) min in the ATR group and 39 ± 9 (27–50) min in the SAL group, respectively. Total time of anaesthesia was 75 ± 5 (70–80) min in the ATR group and 78 ± 12 (65–95) min in the SAL group, respectively.

DISCUSSION

The present study demonstrates that the use of atracurium during laparoscopy with standardised ventilatory pressure-controlled volume-limited pattern does not result in any benefit for either the patient or the surgeon. We did not confirm the results of Staehr-Rye et al. (2014), who reported that deep neuromuscular blockade was associated with better surgical condition. In addition, administration of atracurium did not significantly influence the selected cardiovascular and respiratory variables.

Neuromuscular blocking agents are used in human and veterinary surgery to relax the muscles

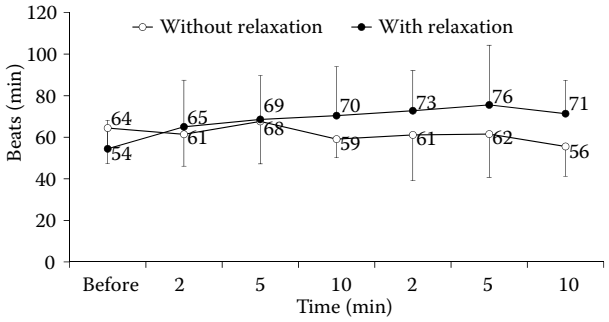

Figure 1. Changes in heart rate (mean ± SD) before and 2, 5, and 10 min after administration of atracurium (with relaxation, ATR group) or saline (without relaxation, SAL group) and 2, 5, and 10 min after capnoperitoneum was established

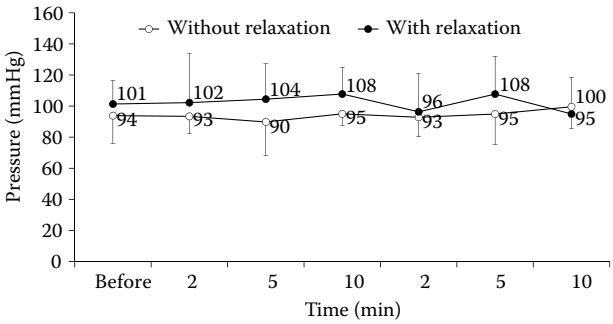

Figure 2. Changes in mean arterial pressure (non-invasive) (mean ± SD) before and 2, 5, and 10 min after administration of atracurium (with relaxation, ATR group) or saline (without relaxation, SAL group) and 2, 5, and 10 min after capnoperitoneum was established

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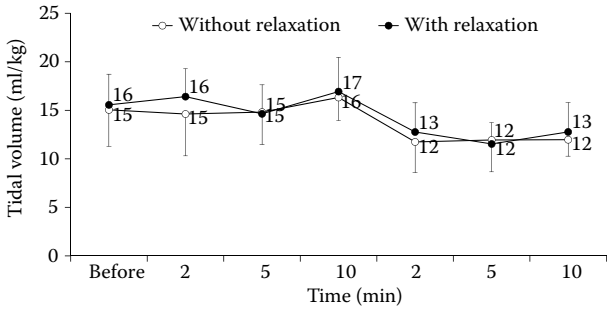

Figure 3. Changes in tidal volume (mean ± SD) before and 2, 5, and 10 min after administration of atracurium (with relaxation, ATR group) or saline (without relaxation, SAL group) and 2, 5, and 10 min after capnoperitoneum was established (pressure-controlled volume-limited ventilatory pattern)

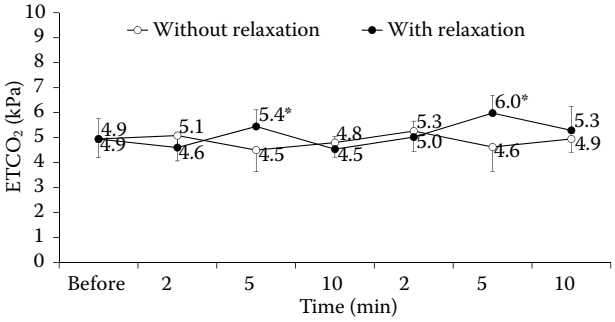

Figure 4. Changes in end-expiratory partial pressure of CO_2 (mean ± SD) before and 2, 5, and 10 min after administration of atracurium (with relaxation, ATR group) or saline (without relaxation, SAL group) and 2, 5, and 10 min after capnoperitoneum was established

*significantly higher $EtCO_2$ in the ATR group 5 min after administration of atracurium (P = 0.0268) and 5 min after capnoperitoneum was established (P = 0.0037) as compared with the SAL group

and make surgical procedures on the abdominal wall and organs easier (Hanley 1992). In our study, duration of separate parts of the surgical procedure and of capnoperitoneum and anaesthesia were measured. The conditions were identical between relaxed and non-relaxed dogs, and no significant differences were observed. This could be due to sufficient muscle relaxation caused by the alpha-2-agonist medetomidine. Medetomidine has been used for premedication of patients and it provides a good level of muscle relaxation (Vaha-Vahe 1989). Our results are in accordance with Van Goethem et al. (2012). In that study, medetomidine was used for premedication of animals and vecuronium for muscle relaxation. No significant differences were observed in surgery duration. In contrast to our study, Van Goethem et al. (2012) maintained normocapnia in all patients with different ventilation patterns – tidal volume and breathing rates. That could influence the results, although possibly only marginally. In our study, standard ventilation pattern was used – with constant breathing rate and peak inspiratory pressure. Therefore, the pressure on the abdominal cavity and its influence on the surgical procedure should be comparable in all patients.

CO_2, the most common insufflation gas in laparoscopic procedures, is resorbed into the blood and causes hypercapnia. Higher levels of arterial CO_2 increase the heart rate, blood pressure, and cardiac output (Nunn 1990). We did not measure the cardiac output in our patients due to the difficulty in procuring measurement devices. The heart rate and mean arterial blood pressure did not differ significantly between patients treated or non-treated with NMBA. There were no significant differences in the values measured before and after CO_2 insufflation (and IAP increase). The relatively low IAP (10 mmHg) could be the cause of such uniform results as it should not have a great influence on the cardiovascular system (Ishizaki et al. 1993).

The use of a standardised ventilatory pattern means that the likelihood of alterations in cardiovascular parameters should be comparable in all patients. Any differences are likely to be caused by the atracurium NMBA. Its administration should not significantly influence the heart rate nor the arterial blood pressure in dogs anaesthetised with isoflurane (McMurphy et al. 2004). This was confirmed in our study, as there were no significant differences in monitored cardiovascular parameters between the groups treated and non-treated with atracurium. Other drugs administered during anaesthesia also influence blood pressure and may have contributed to this finding. Isoflurane is known for its dose-dependent depression of blood pressure; therefore, the end-tidal concentration of isoflurane (Et_{iso}) was kept unchanged (between 1 and 2 vol.%) for the entire duration of the surgery (Merin et al. 1991). Medetomidine causes an initial hypertension in dogs followed by a return to approximately normal values (Murrell and Hellebrekers 2005). These changes were not observed in our study. There were no heart rate or blood pressure irregularities in any of our patients.

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Insufflation of gas increases IAP, with the potential of causing decreased tidal volume and hypoventilation (Nunn 1990). In our patients, the tidal volume decreased, however non-significantly. In contrary to the initial hypothesis, the difference between the tidal volume before and after CO_2 insufflation was not significant. Even the NMBA administration did not generate significant differences. One of the possible causes could be the sufficient medetomidine-related muscle relaxation (Vaha-Vahe 1989), which would not be potentiated by subsequent administration of atracurium (NMBA). The relatively low insufflation pressure (10 cmH_2O) could be another considerable cause. This pressure is just 5 cmH_2O lower than the peak inspiratory pressure used during artificial pulmonary ventilation (15 cmH_2O).

In atracurium-treated patients, a significant but transient $EtCO_2$ increase was observed 5 min after atracurium administration and 5 min after establishing the capnoperitoneum. This difference was not recorded at any other observation time and therefore it is highly unlikely to be clinically important. Atracurium produces airway constriction caused by histamine release in Basenji or Greyhound dogs (Mehr et al.1992). This airway constriction can alter the gas exchange (including elimination of CO_2 from the lungs). That would explain the transient increase 5 min after atracurium administration but not the increase 5 min after the increase in iatrogenic CO_2 levels (insufflation). Another explanation for the increase in $EtCO_2$ might be changes in lung compliance due to NMB in combination with PEEP. This might increase the dead space, end tidal volume and accordingly, $EtCO_2$. The lack of a further increase after 10 min may be due to "airway stabilisation" and gas exchange improvement (especially CO_2). That would prevent a greater difference between NMBA-treated and non-treated patients.

Chassard et al. (1996) concluded that neither high peak inspiratory airway pressure nor intrabdominal pressure during laparoscopy are affected by neuromuscular block. Our results confirm those conclusions. These findings also question the necessity of muscle relaxants in clinical anaesthetic practice during laparoscopic surgery.

CONCLUSION

Administration of atracurium in dogs undergoing laparoscopic ovariectomy with a standardised ventilation pattern did not result in clinically important differences in selected cardiovascular and respiratory variables and surgical times in comparison with non-relaxed dogs. Thus, the use of atracurium in laparoscopic ovariectomy does not result in any benefit for patients or surgeons. Therefore, we conclude that it is not a necessary part of anaesthetic protocols.

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