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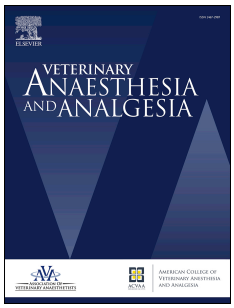

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PII: S1467-2987(24)00086-2

DOI: https://doi.org/10.1016/j.vaa.2024.05.009

Reference: VAA 953

To appear in: *Veterinary Anaesthesia and Analgesia*

Received Date: 14 June 2023

Revised Date: 25 May 2024

Accepted Date: 25 May 2024

Please cite this article as: Dupont J, Mignini B, Salciccia A, Serteyn D, Sandersen C, Comparison of inhaled salbutamol and salmeterol for the treatment of arterial hypoxaemia in anaesthetized horses: a randomized clinical trial, *Veterinary Anaesthesia and Analgesia*, https://doi.org/10.1016/j.vaa.2024.05.009.

RESEARCH PAPER

Comparison of inhaled salbutamol and salmeterol for the treatment of arterial hypoxaemia in anaesthetized horses: a randomized clinical trial

Julien Dupont[a], Benedetta Mignini[a], Alexandra Salciccia[a], Didier Serteyn[a], Charlotte Sandersen[a]

[a]Department of Clinical Sciences, Anesthesiology and Equine Surgery, Faculty of Veterinary Medicine, University of Liege, Liège, Belgium

Correspondence: Julien Dupont, Department of Clinical Sciences, Anesthesiology and Equine Surgery, Faculty of Veterinary Medicine, University of Liege, Quartier Vallée 2, Avenue de Cureghem 5, Bâtiment B41, Sart-Tilman, 4000 Liège, Belgium. E-mail: julien.dupont@uliege.be

Please use the above contact details for communication regarding ScholarOne business.

ORCID details

Julien Dupont (0000-0002-0857-1903), Benedetta Mignini (no ORCID account), Alexandra Salciccia (0000-0001-5902-5040), Didier Serteyn (0000-0002-2473-9737), Charlotte Sandersen (0000-0002-3404-2757)

Acknowledgements

JD obtained a fellowship from F.R.S.-FNRS Fund for Scientific Research (Veterinary MD. Ph.D Student Fellowship-VETE-CCD-grant number 34991014).

Authors' contributions

JD: study design, data analysis and writing of the manuscript. BM: data analysis and writing of the manuscript. AS: review of the manuscript. DS and CS: study design and review of the manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

Abstract

Objective To compare the efficacy of inhaled salbutamol with salmeterol for the treatment of arterial hypoxaemia in anaesthetized horses.

Study design Prospective, randomized, clinical study.

Animals A total of 108 client-owned horses (American Society of Anesthesiologists status I-V) anaesthetized for elective and emergency procedures.

Methods Horses were premedicated with acepromazine [intramuscularly 0.1 mg kg^{-1} or intravenously (IV) 0.05 mg kg^{-1}] and xylazine (0.6 mg kg^{-1} IV). Midazolam (0.06 mg kg^{-1} IV) and ketamine (2.2 mg kg^{-1} IV) were combined to induce anaesthesia, and isoflurane in oxygen/air mixture (inspired oxygen fraction 0.7) was used for maintenance of anaesthesia. Mechanical ventilation was initiated without delay using the following ventilator settings: tidal volume 10 mL kg^{-1}, respiratory rate eight breaths $minute^{-1}$, inspiratory-to-expiratory time ratio 1:2, no positive end-expiratory pressure. If arterial blood gas analysis revealed PaO_2 < 100 mmHg (13.3 kPa), the administration of either inhaled salbutamol (2 µg kg^{-1}) or salmeterol (0.5 µg kg^{-1}) was randomly assigned Blood gas analysis was repeated 15 and 30 minutes after treatment. The intervention was considered successful when PaO_2 after treatment ≥ 1.2 x PaO_2 before treatment (i.e. ≥ 20% increase). PaO_2 at 15 and 30 minutes was compared between groups using Mann-Whitney U test; $p < 0.05$ was considered significant.

Results Of the 108 horses, 60 received salbutamol, 65% and 60% responded successfully at 15 and 30 minutes, increasing their initial PaO_2 by 38 and 44%, respectively. The other 48 horses received salmeterol, 35% responded successfully at 15

and 30 minutes, increasing their initial PaO_2 by 3 and 4%, respectively. PaO_2 was significantly higher after salbutamol than salmeterol at 15 and 30 minutes.

Conclusions and clinical relevance Using the described protocol, inhaled salbutamol was more effective than salmeterol in improving PaO_2 in anaesthetized horses with value < 100 mmHg (13.3 kPa).

Keywords arterial partial pressure of oxygen; horse; salbutamol; salmeterol

Introduction

Hypoxaemia has long been recognised as a consequence of general anaesthesia in horses. Indeed, anaesthesia is responsible for the rapid development of lung atelectasis and pulmonary shunt (Nyman & Hedenstierna 1989; Nyman et al. 1990). Several strategies have been evaluated to improve oxygenation, but no consensus exists regarding the best treatment option (Auckburally & Nyman 2017).

Increasing the inspired oxygen fraction (F_IO_2) has a limited efficacy because pulmonary shunt is the leading cause of impaired oxygenation (Benator et al. 1973). The open lung concept and the associated alveolar recruitment manoeuvre (ARM) have been adapted to equine mechanical ventilation with promising results (Levionnois et al. 2006, Wettstein et al. 2006, Ambrosio et al. 2013, Hopster et al. 2016a, Ambrisko et al. 2017, Andrade et al. 2019, Andrade et al. 2022).

The use of several β_2-adrenergic agonists to improve oxygenation has been investigated in horses during general anaesthesia. Among them, inhaled salbutamol (albuterol) (2 μg kg^{-1}), a short-acting β_2-adrenergic agonist, is the most commonly used with a positive overall effect on oxygenation (Robertson & Bailey 2002, Patschova et al. 2010, Casoni et al. 2014, Clark-Price et al. 2022, Dupont et al. 2022). The exact mechanism of action is unknown, but it has been hypothesized that salbutamol could alter haemodynamic (Patschova et al. 2010, Clark-Price et al. 2022) or respiratory mechanics (Robertson & Bailey 2002, Dupont et al. 2022). Aerosolized salmeterol, a long-acting β_2-adrenergic agonist, has demonstrated bronchodilatory properties in conscious asthmatic horses but has never been studied under general anaesthesia (Henrikson & Rush 2001). According to the microkinetic diffusion theory, the longer

effect of salmeterol compared to salbutamol can be due to its higher lipophilicity and its consequent ability to accumulate in the cell membrane and remain accessible in the vicinity of the β_2-adrenergic receptor (Szczuka et al. 2009).

Since hypoxaemia remains one of the major challenges in equine anaesthesia. This study compared the efficacy of inhaled salbutamol and salmeterol in horses with an arterial partial pressure of oxygen (PaO_2) < 100 mmHg (13.3 kPa) at any time during anaesthesia.

We hypothesized that salmeterol would be equally effective but longer-acting than salbutamol when used to treat arterial hypoxaemia in anaesthetized horses.

Material and methods

Institutional approval for animal experimentation (Committee for the Ethical Use of Animals, University of Liege, number 2266) was obtained prior to this study. The Consolidated Standards of Reporting Trials (CONSORT) guidelines were applied.

Cases were recruited from client-owned horses anaesthetized at the Equine Hospital of the Faculty of Veterinary Medicine of the University of Liege from September 2020 to April 2022. Before inclusion, informed consent was obtained from the owners, allowing the collection of data and its publication in an anonymized format. Cases that met the following criteria were included: (1) age ≥ 6 months, (2) body weight (BW) ≥ 100 kg, (3) mechanical ventilation was initiated within 10 minutes following induction of anaesthesia and (4) PaO_2 < 100 mmHg (13.3 kPa) at any time during anaesthesia. Treatment with dexamethasone and/or clenbuterol in the preoperative period, administration of a neuromuscular blocking agent, Trendelenburg or reverse Trendelenburg position, laparoscopic procedure requiring abdominal insufflation,

diaphragmatic hernia repair, asthma or surgery ending prior to the second blood gas measurement following treatment (i.e. before 30 minutes following treatment) led to exclusion from the study.

Acepromazine [0.1 mg kg^{-1} intramuscularly or 0.05 mg kg^{-1} intravenously (IV); Placivet, Kela, Belgium] and xylazine (0.6 mg kg^{-1} IV; Nerfasin vet., Dechra, the Netherlands) were given for premedication, except for horses anaesthetized for exploratory laparotomy (colic) and caesarean section surgeries. These horses only received xylazine. Ketamine (2.2 mg kg^{-1} IV; Ketamidor, Ecuphar, Austria) and midazolam (0.06 mg kg^{-1} IV; Midazolam Mylan, Mylan, Belgium) were combined for the induction of anaesthesia. Maintenance of anaesthesia consisted of isoflurane (Isoflurin, Vetpharma Animal Health, Spain) vaporized in a mixture of oxygen (O_2) and medical air (F_IO_2 0.7), and the end-tidal percentage was adjusted to maintain an appropriate anaesthetic plane. The targeted F_IO_2 was obtained as follows: O_2 flow rate of 7 L $minute^{-1}$ was used until F_IO_2 reached 0.7, it was then reduced to 4 L $minute^{-1}$ and medical air was added. Ketamine boli (0.2 to 0.4 mg kg^{-1} IV) were administered in case of inadequate depth but no other drugs were used to maintain anaesthesia. Volume-controlled ventilation (VCV) was applied from the beginning of anaesthesia (Tafonius, Vetronics, UK) as follows: tidal volume (V_T) 10 mL kg^{-1}, respiratory rate (f_R) 8 breaths $minute^{-1}$, inspiratory-to-expiratory time ratio 1:2, no positive end-expiratory pressure. End-tidal carbon dioxide partial pressure ($P_E´CO_2$) was maintained between 35 and 50 mmHg (4.7 and 6.7 kPa) by adjusting f_R, inspiratory time was accordingly adjusted to maintain an inspiratory-to-expiratory time ratio of 1:2. Ringer's lactate solution (Vetivex, Dechra, the Netherlands)was administered IV (10 to 20 mL kg^{-1} $hour^{-1}$) and hypotension, defined as mean arterial pressure (MAP) < 60 mmHg, was treated with

dobutamine (Dobutrexmylan, Mylan, Belgium). The infusion rate started at 0.5 µg kg^{-1} $minute^{-1}$ and increased by 0.5 µg kg^{-1} $minute^{-1}$ every 5 minutes until MAP reached 60 mmHg, or until the infusion rate reached 3 µg kg^{-1} $minute^{-1}$. Noradrenaline (Noradrenaline, Aguettant, France) was added if MAP remained < 60 mmHg and dobutamine reached 3 µg kg^{-1} $minute^{-1}$. The latter infusion started at 0.1 µg kg^{-1} $minute^{-1}$ and increased by 0.1 µg kg^{-1} $minute^{-1}$ every 3 minutes until MAP reached 60 mmHg, or until the infusion rate reached 1 µg kg^{-1} $minute^{-1}$.

A cannula was placed in the transverse facial artery, the facial artery or the dorsal metatarsal artery to allow for repeated arterial blood sampling and continuous direct arterial pressure measurement. Arterial blood gas analysis was performed immediately after cannula placement and every 30 minutes thereafter. Electrocardiogram, pulse oximetry, invasive arterial blood pressure, airway pressure, flow-volume loops, inspired and expired percentages of oxygen and isoflurane, inspired carbon dioxide partial pressure and $P_{E'}CO_2$ were continuously recorded (Solomon, Vetronics, UK). Arterial partial pressure of carbon dioxide ($PaCO_2$), PaO_2, oxygen saturation of haemoglobin, total haemoglobin, packed cell volume, pH, base excess and plasma electrolytes were measured with a blood gas analyser (GEM 3500, Werfen, Belgium) directly after sampling, without correcting for actual body temperature.

If any arterial blood gas measurement revealed PaO_2 < 100 mmHg (13.3 kPa), the administration of either inhaled salbutamol or salmeterol was randomly assigned. A total of 126 pieces of paper were prepared, 63 bearing the inscription “salbutamol” and 63 with the inscription “salmeterol” were placed in an opaque envelope. Each time PaO_2 < 100 mmHg (13.3 kPa), a piece of paper was drawn by lot and not replaced.

Salbutamol (Ventolin, GlaxoSmithKline, Belgium) and salmeterol (Serevent, GlaxoSmithKline, Belgium) were both supplied in a metered-dose inhaler. Both drugs were administered through a dedicated port in the Y-piece of the breathing system, at the onset of inspiration. For salbutamol, each depression of the nozzle delivered 100 µg of active substance to the animal. A dose of 2 µg kg^{-1} was administered to the horses, rounded up to the next 50 kg. For salmeterol, each depression of the nozzle delivered 25 µg of active substance. A dose of 0.5 µg kg^{-1} (Henrikson & Rush 2001, Bullone et al. 2017) was administered, rounded up to the next 50 kg.

Arterial blood gas measurement was repeated at 15 and 30 minutes after treatment and PaO_2 was used to assess the efficacy of the treatment. If PaO_2 remained < 100 mmHg (13.3 kPa) 30 minutes after treatment measures were taken to correct persistent arterial hypoxaemia. Positive end-expiratory pressure was applied, starting at 5 cmH_2O and increasing by 5 cmH_2O every 5 minutes until 25 cmH_2O. It was maintained at 25 cmH_2O for 5 minutes before being tapered off by 5 cmH_2O every 5 minutes until 15 cmH_2O, and subsequently maintained at this level.

Statistical analysis

All analyses were performed using MedCalc for Windows, version 20.027 (MedCalc Software, Belgium). Variables were summarized as frequency for categorical variables; mean ± standard deviation (SD) for continuous, normally distributed variables; or median [interquartile range (IQR)] for continuous, non-normally distributed data.

Age, body weight (BW), sex, American Society of Anesthesiologists (ASA) status, type of surgery (laparotomy *versus* all the other procedures), recumbency, interval between induction and first arterial blood gas measurement revealing PaO_2 <

100 mmHg (13.3 kPa), and systolic, mean and diastolic arterial pressure (SAP, MAP, DAP), dobutamine requirement, respiratory variables [f_R, peak inspiratory pressure (PIP)], FIO_2 and PaO_2 when first arterial blood gas measurement revealed PaO_2 < 100 mmHg (13.3 kPa) were compared between the two groups.

Next, arterial blood pressure (SAP, MAP, DAP), dobutamine requirement, respiratory variables (f_R, PIP), FIO_2 and PaO_2 obtained 15 minutes after treatment were compared between both groups. The same comparisons were repeated for variables obtained 30 minutes after treatment.

Arterial blood pressures (SAP, MAP, DAP), dobutamine requirement, respiratory variables (f_R, PIP), FIO_2 and PaO_2 when first arterial blood gas measurement revealed PaO_2 < 100 mmHg (13.3 kPa) were then compared with values obtained at 15 and 30 minutes within each group. In addition, arterial blood pressure (SAP, MAP, DAP), dobutamine requirement, respiratory variables (f_R, PIP), FIO_2 and PaO_2 obtained at 15 minutes were compared with values obtained at 30 minutes within each group.

Finally, the ratio of PaO_2 at 15 minutes to PaO_2 before treatment, and the ratio of PaO_2 at 30 minutes to PaO_2 before treatment were calculated. Horses were divided between responders, where the ratio ≥ 1.2 (i.e. ≥ 20% increase), and non-responders, where the ratio < 1.2.

The normality of data distribution was assessed using Shapiro-Wilk test. Chi-square test was used to compare categorical data. Non-normally distributed independent data were compared using Mann-Whitney U test. For normally distributed independent data, homogeneity of variance was tested using Fisher's F-test and data were subsequently compared using Student's t-test or Welch test as appropriate. Non-

normally distributed dependent data were compared using Wilcoxon signed-rank test. Normally distributed dependent data were compared using paired Student's t-test. *p* - values < 0.05 were considered statistically significant.

Sample size was initially calculated based on the PaO_2 commonly observed in horses receiving oxygen insufflation (15 L $minute^{-1}$, oxygen hose inserted as deep as possible into the orotracheal tube) during recovery. Based on clinical experience, we considered 60 ± 40 mmHg (8 ± 5.3 kPa) and 80 ± 40 mmHg (10.7 ± 5.3 kPa) for salbutamol and salmeterol, respectively. An *a priori* sample size analysis revealed that 126 horses would be needed to detect a 20% difference in postoperative PaO_2 between treatments, with a power of 80% and $\alpha = 0.05$. However, intermediary statistical analysis was performed because of the apparent difference in efficacy noted during surgery between treatments. Results of this intermediary analysis are presented here.

Results

Study population

A total of 130 horses with PaO_2 < 100 mmHg (13.3 kPa) at any time during anaesthesia were identified during the study period. From this total, 22 horses were subsequently excluded: two were asthmatic and treated with dexamethasone and clenbuterol in the preoperative period, seven were administered a neuromuscular blocking agent, one underwent a laparoscopic procedure in Trendelenburg position, and surgery ended prior to the second blood gas measurement following treatment for 12 of them. A total of 108 were finally included in the study. There were 33 mares, 27 stallions and 48 geldings. Their median (IQR) age and BW were 150 (78-210) months and 540 (458-600) kg, respectively. Of the 108 horses, 57 were submitted for elective procedures (11 ASA I,

192 40 ASA II and six ASA III) while 51 were anaesthetized as emergencies (two ASA II E,
193 23 ASA III E, 23 ASA IV E and three ASA V E). Of the 108 horses included in the
194 study, 53 were anaesthetized for laparotomy while 55 underwent another type of
195 surgery. A total of 88 horses were positioned in dorsal recumbency, 11 horses in right
196 lateral recumbency and nine horses in left lateral recumbency.

197 Initial variables

198 The interval between induction and first arterial blood gas measurement that revealed
199 PaO_2 < 100 mmHg (13.3 kPa) was 41 (26–68) minutes. Arterial blood pressure,
200 dobutamine requirement and respiratory variables prior to this initial arterial blood gas
201 measurement were as follows: SAP 102 (87–113) mmHg, MAP 77 (67–90) mmHg,
202 DAP 65 ± 19 mmHg, dobutamine requirement 0 (0–0.5) µg kg^{-1} $minute^{-1}$, f_R 8 (8–8)
203 breaths $minute^{-1}$, PIP 23 (19–27) cmH_2O, FIO_2 0.72 (0.69–0.75) and PaO_2 81 (69–88)
204 mmHg [10.8 (9.2-11.7) kPa].

205 Treatment allocation

206 Salbutamol was administered to 60 horses while 48 horses were treated with salmeterol
207 when first arterial blood gas measurement revealed PaO_2 < 100 mmHg (13.3 kPa).

208 Age, BW, sex, ASA status, type of surgery (laparotomy *versus* all the other
209 procedures), recumbency, and duration of anaesthesia, SAP, MAP, DAP, dobutamine
210 requirement, f_R, FIO_2 and PaO_2 when first arterial blood gas measurement revealed
211 PaO_2 < 100 mmHg (13.3 kPa) did not differ between the two groups. PIP immediately
212 before this arterial blood measurement was significantly higher in the salmeterol than in
213 the salbutamol group (p = 0.04) (Table 1).

214 Treatment success

SAP, MAP, DAP, dobutamine requirement, F_IO_2, f_R and PIP were not significantly different between groups at 15 and 30 minutes after β_2-adrenergic agonist administration. PaO_2 was significantly higher in the salbutamol than in the salmeterol group at 15 ($p < 0.001$) and 30 ($p = 0.002$) minutes (Table 1).

The comparison of initial SAP, DAP, MAP, dobutamine requirement, f_R, PIP, F_IO_2 and PaO_2 with values obtained at 15 minutes revealed a significant increase in f_R in the salmeterol group ($p = 0.007$), and SAP ($p = 0.001$), MAP ($p < 0.001$) and DAP ($p = 0.001$) in the salbutamol group. In addition, PaO_2 significantly increased in the salbutamol (+ 38%; $p < 0.001$) and the salmeterol (+ 3%; $p = 0.006$) groups (Table 1).

The comparison of initial SAP, MAP, DAP, dobutamine requirement, f_R, PIP, FIO_2 and PaO_2 with values obtained at 30 minutes revealed a significant decrease in dobutamine requirement ($p = 0.03$) and increase in f_R ($p = 0.002$) in the salmeterol group, and increase in SAP ($p = 0.02$), MAP ($p = 0.008$), DAP ($p = 0.02$) and decrease in PIP ($p = 0.02$) in the salbutamol group. Moreover, PaO_2 significantly increased in the salbutamol (+ 44%; $p < 0.001$) and the salmeterol (+ 4%; $p = 0.005$) groups (Table 1).

Within each group, SAP, MAP, DAP, dobutamine requirement, PIP, f_R, F_IO_2 and PaO_2 did not differ between 15 and 30 minutes .

Among horses treated with salbutamol, 65% and 60% were classified as responders at 15 ($p < 0.001$) and 30 ($p < 0.001$) minutes, respectively, while 35% of horses that received salmeterol were classified as responders at 15 ($p = 0.006$) and 30 ($p = 0.005$) minutes.

Discussion

237 This study showed that salbutamol was more effective than salmeterol in improving
238 PaO_2 in anaesthetized horses with value < 100 mmHg (13.3 kPa).

239 Both salbutamol and salmeterol are inexpensive (i.e. salbutamol 0.43 euros,
240 salmeterol 3.41 euros for a 500-kg horse), easily and noninvasively administered by
241 inhalation through a dedicated port in the Y-piece of the breathing system and readily
242 available when the need arises during anaesthesia. In addition, their potential favourable
243 effects are rapidly apparent after administration. ARM is widely used to treat
244 hypoxaemia in anaesthetized horses. However, ventilator-induced lung injury (Hopster
245 et al. 2016b) and decreased intestinal perfusion secondary to impaired cardiac output
246 (Hopster et al. 2016a) have been associated with its use. This ventilatory strategy is not
247 without risk and inhaled β_2-adrenergic agonists should be viewed as a valuable
248 alternative.

249 Apart from tachycardia, which is rarely seen and most likely attributed to
250 systemic absorption and β_1-adrenergic receptor activation (Casoni et al. 2014),
251 salbutamol has not been associated with any other side effect when administered to
252 horses under general anaesthesia. Salmeterol and salbutamol are respectively 3388 and
253 21 times more selective for β_2 than β_1-adrenergic receptors (Baker 2010). The
254 haemodynamic side effects might therefore be less common with salmeterol compared
255 to salbutamol. Nevertheless, sustained tachycardia has been observed following
256 nebulized salmeterol in anaesthetized rhesus monkeys (Fozard & Buescher 2000) and
257 the occurrence of cardiovascular alterations cannot be excluded in other species. The
258 beneficial effect of salbutamol on oxygenation might be related to its haemodynamic
259 effects. Clark-Price et al. (2022) showed an increase in HR, and Patschova et al. (2010)
260 reported an increase in HR and cardiac output following salbutamol administration.

261 They attributed the favourable impact on oxygenation to these cardiovascular changes
262 and the subsequent improved pulmonary perfusion. Therefore, the greater selectivity of
263 salmeterol for β_2-adrenergic receptors may explain its limited efficacy for improving
264 oxygenation in anaesthetized horses since it has fewer haemodynamic effects. In this
265 study, arterial blood pressure was increased during the 30-minute period after
266 salbutamol administration. Nevertheless, SAP, MAP, DAP and dobutamine requirement
267 were similar in both groups.

268 A decrease in PaO_2 after treatment was observed in both groups. In the
269 salbutamol group, this occurred in 12 and 11% of cases at 15 and 30 minutes after
270 administration, respectively. In the salmeterol group, it happened in 38 and 30% of
271 cases at 15 and 30 minutes after administration, respectively. These changes were
272 attributed to the severity of lung atelectasis. Estimated shunt fraction, an oxygen
273 tension-based index, has proven to estimate venous admixture better than content-based
274 indices (Araos et al. 2012, Briganti et al. 2015). Nevertheless, PaO_2 was the only
275 oxygenation index used in this study and we cannot conclude that horses in which PaO_2
276 decreased after drug administration were those with the largest areas of lung atelectasis.
277 The most effective way of improving oxygenation in horses presenting very low
278 ventilation-perfusion ratios likely relies on lung recruitment. In those cases, inhaled β_2-
279 adrenergic agonists probably act on haemodynamic rather than respiratory mechanics.
280 Salbutamol might have a lower failure rate due to its greater β_1-adrenergic agonist
281 activity compared with salmeterol.

282 The 2 $\mu g\ kg^{-1}$ dose of salbutamol improves oxygenation in horses under general
283 anaesthesia (Robertson & Bailey 2002, Patschova et al. 2010, Casoni et al. 2014, Clark-
284 Price et al. 2022, Dupont et al. 2022); however, the dose of salmeterol (0.5 $\mu g\ kg^{-1}$) has

been extrapolated from studies conducted on conscious asthmatic horses (Henrikson & Rush 2001, Bullone et al. 2017). The potency ratio of salmeterol to salbutamol is somewhere between 4 and 100 (Bennett & Tattersfield 1997). We decided to use only the fourfold potency difference to determine equipotent doses of the two drugs in order to optimize the chances of observing any beneficial effect of salmeterol. However, a higher dose of salmeterol was required to relieve bronchoconstriction in anaesthetized rhesus monkeys (Fozard & Buescher 2000), and we cannot exclude the possibility that the dose of salmeterol was inadequate to improve oxygenation.

The time interval between β_2-adrenergic agonist administration and arterial blood gas measurement was set at 15 and 30 minutes. The onset and time-to-peak effect of salmeterol are 15 and 30–60 minutes, respectively (Henrikson & Rush 2001). However, waiting for the maximal response for more than 30 minutes might have exposed horses to worse oxygen deprivation. The time interval of 15 and 30 minutes was deemed suitable to assess the efficacy of salbutamol because its onset and duration of action are 5 and 30–180 minutes, respectively (Derksen et al. 1999).

f_R was adjusted to maintain $P_{E'}CO_2$ between 35 and 50 mmHg (4.7 and 6.7 kPa). Therefore, f_R increased in parallel with $P_{E'}CO_2$ over time in the salmeterol group. Increase in $P_{E'}CO_2$ can be caused by decreased CO_2 elimination or increased CO_2 production. Decreased CO_2 elimination can be caused by decreased alveolar ventilation, increased dead space ventilation or increased venous admixture (Portela et al. 2023). Because V_T was constant, and because f_R was adjusted to meet the targeted $P_{E'}CO_2$, it is unlikely that decreased alveolar ventilation was responsible for reduced CO_2 elimination. Neither dead space nor venous admixture were evaluated in this study. Elevated tissue perfusion secondary to dobutamine infusion can enhance CO_2 removal.

However, dobutamine requirements were similar in both groups, and decreased at 30 minutes compared to pre-treatment values in the salmeterol group.

Although PIP decreased at 30 minutes in the salbutamol group, values were within the recommended range of PIP required to deliver a suitable V_T to healthy horses under general anaesthesia (Kerr & McDonell 2009). Although the change in f_R and PIP reached statistical significance, the authors feel that these results are not clinically relevant.

To the best of the authors' knowledge, there are only few studies that quantify the treatment of hypoxaemia in terms of success rate. Therefore, our definition of treatment success (i.e $\geq$ 20% increase in PaO_2) is based on experience and clinical impression rather than scientific evidence.

The authors acknowledge several limitations in this study. First, because we hypothesized that salbutamol and salmeterol would be equally effective, it was not possible to estimate an appropriate sample size based on intraoperative PaO_2. We initially planned to measure PaO_2 during recovery and to rely on values commonly observed in horses receiving oxygen insufflation to calculate the sample size. However, we did not manage to measure PaO_2 during recovery on a regular basis and this variable has not been included in the study. Second, inclusion of cases was interrupted before reaching the calculated sample size. Third, performing the last arterial blood gas measurement 30 minutes after β_2-adrenergic agonist administration might have prevented salmeterol from reaching its full effect because its time-to-peak effect is between 30 and 60 minutes (Henrikson & Rush 2001). The authors cannot exclude the possibility that extending the data collection period may have changed the results of this

study. However, it was judged ethically questionable to expose client-owned horses to arterial hypoxaemia for more than 30 minutes.

Conclusions

Based on the percentage of responders at 15 and 30 minutes after treatment, this study showed that inhaled salbutamol was almost twice as effective as inhaled salmeterol in improving PaO_2 when administered to horses with value < 100 mmHg (13.3 kPa) during general anaesthesia.

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Table 1. Dobutamine requirement, invasive systolic, mean and diastolic arterial pressures (SAP, MAP, DAP), inspired oxygen fraction (FIO_2), respiratory rate (f_R), peak inspiratory pressure (PIP) and arterial partial pressure of oxygen (PaO_2) measured in 108 horses during general anaesthesia. Horses were treated with either inhaled salbutamol (2 µg kg^{-1}), n = 60 or salmeterol (0.5 µg kg^{-1}), n = 48. Data were collected before and at 15 and 30 minutes after drug administration. Values are reported as median (interquartile range) or mean ± standard deviation.

	Salbutamol			Salmeterol		
	Before treatment	15 minutes after treatment	30 minutes after treatment	Before treatment	15 minutes after treatment	30 minutes after treatment
Dobutamine requirement (µg kg^{-1} $minute^{-1}$)	0 (0–0.5)	0 (0–0.5)	0 (0–0.5)	0 (0–1)	0 (0–0.5)	0 (0–0.5)§
SAP (mmHg)	100 ± 20	110 ± 17*	105 (97-116)§	104 (86-119)	108 (97-114)	110 ± 17
MAP (mmHg)	77 ± 18	86 ± 14*	85 ± 17§	79 (68–92)	86 ± 16	85 ± 14
DAP (mmHg)	63 ± 17	72 ± 15*	71 ± 15§	64 (53–79)	72 ± 16	71 ± 14
FIO_2	0.72 (0.7–0.75)	0.71 (0.68–0.74)	0.71 (0.69–0.75)	0.72 (0.69–0.76)	0.71 (0.69–0.74)	0.72 (0.69–0.75)

f_R (breaths minute^{-1})	8 (8–8)	8 (8–10)	8 (8–10)	8 (8–8)	8 (8–10)*	8 (8–10)§
PIP (cmH_2O)	22 (17–26)¶	23 (18–27)	21 (19–27)§	24 ± 6¶	23 (21–27)	23 (22–26)
PaO_2 (mmHg)	82 (72–89)	113 (81–137)*†	118 (81–153)‡§	78 ± 12	82 (67–105)*†	83 (70–99)‡§
PaO_2 (kPa)	10.9 (9.6-11.9)	15.1 (10.8-18.3)*†	15.7 (10.8-20.4)‡§	10.4 ± 1.6	10.9 (8.9-14)*†	11.1 (9.3-13.2)‡§

*Significant difference ($p < 0.05$) between initial values and values 15 minutes after treatment. †Significant difference ($p < 0.05$) between salbutamol and salmeterol group at 15 minutes after treatment. ‡Significant difference ($p < 0.05$) between salbutamol and salmeterol group at 30 minutes after treatment. §Significant difference ($p <0.05$) between initial values and values 30 minutes after treatment. ¶Significant difference ($p < 0.05$) between salbutamol and salmeterol groups before treatment.

Declaration of interests

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

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: