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RESEARCH PAPER

Pulsed inhaled nitric oxide improves arterial oxygenation in colic horses undergoing abdominal surgery

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Abstract

Objective To evaluate the effect of pulsed inhaled nitric oxide (INO) on arterial oxygenation and subsequent blood lactate concentration in colic horses during abdominal surgery.

Study design Prospective, randomized, clinical trial.

Animals Thirty colic horses that underwent acute abdominal surgery at the University Animal Hospital in Uppsala, Sweden.

Methods Anaesthesia was induced according to the standard protocol at the clinic, including romifidine, butorphanol, diazepam and ketamine. Anaesthesia was maintained with isoflurane in oxygen. Fifteen horses were administered pulsed INO and 15 served as controls. After baseline data collection, pulsed INO delivery commenced. Arterial and venous blood were collected and analysed during surgery. Cardiorespiratory parameters were measured, and oxygen content and F-shunt were calculated.

Results Arterial oxygen tension (PaO_2) and arterial oxygen saturation (SaO_2) increased from 10.9 ± 5.7 kPa (82 ± 43 mmHg) and $93 \pm 6\%$ to 17.3 ± 6.9 kPa (134 ± 52 mmHg) ($p < 0.0001$) and $98 \pm 2\%$ ($p < 0.0001$), respectively, in horses receiving pulsed INO during anaesthesia. In the control group, PaO_2 and SaO_2 decreased from 13.9 ± 9.1 kPa (104 ± 68 mmHg) and $93 \pm 7\%$ to 12.1 ± 8.6 kPa (91 ± 65 mmHg) ($p = 0.0413$) and $91 \pm 8\%$ ($p = 0.0256$), respectively, during anaesthesia. At the end of anaesthesia, the oxygen content was significantly higher in horses receiving pulsed INO compared to controls ($p = 0.0126$). The calculated F-shunt decreased from $39 \pm 10\%$ to $27 \pm 6\%$ ($p < 0.0001$) in horses receiving pulsed INO, and remained unchanged in controls, $40 \pm 12\%$ to $44 \pm 12\%$. Blood lactate concentration decreased ($-17 \pm 21\%$) during anaesthesia in horses receiving pulsed INO ($p = 0.0119$), whereas no difference was measured in controls ($2 \pm 31\%$).

Conclusions and clinical relevance The present study showed that it is possible to effectively reduce the F-shunt and improve arterial oxygenation in colic horses during abdominal surgery by continuous delivery of pulsed INO.

Introduction

General anaesthesia in horses causes cardiopulmonary impairment, which frequently results in hypoxaemia (Nyman & Hedenstierna 1989; Nyman et al. 1990; Wagner 2008). During general anaesthesia, hypoxaemia is mainly resulting from the development of atelectasis in the dependent lung, and ventilation/perfusion ($\dot{V}_A/\dot{Q}$) mismatch is most noticeable when the horse is positioned in dorsal recumbency (Dobson et al. 1985; Nyman & Hedenstierna 1989; Nyman et al. 1990).

There are two hypothetical ways to improve the matching of ventilation and perfusion during anaesthesia: either the ventilation can be directed to lung regions that are well perfused or the perfusion can be redistributed to the well-ventilated lung areas. Most research in the anaesthetized horse has focused on the first way, i.e. improving the ventilation in the perfused lung regions. Nyman & Hedenstierna (1989) showed that neither mechanical ventilation (MV) nor positive end-expiratory pressure (PEEP) had a positive effect on $\dot{V}_A/\dot{Q}$ ratios. Selective MV of

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dependent lung regions with PEEP does decrease $\dot{V}_A/\dot{Q}$ mismatch and increase arterial oxygen tension (PaO_2) during general anaesthesia (Nyman et al. 1987; Moens et al. 1994). However, this method requires technical interventions which are difficult to apply in clinical conditions (Moens et al. 1992). More recently, it has been shown in clinical studies that MV with recruitment manoeuver (RM) and constant PEEP improved PaO_2 but simultaneously decreased arterial gastrointestinal oxygenation (Hopster et al. 2011, 2016). This method entails transiently high inspiratory pressures and opens up previously collapsed alveoli. Although the RM was considered to successfully open the lungs based on the increased PaO_2, the manoeuver had to be continually repeated to keep the lungs open. Additionally, the elevated mean airway pressure generated by PEEP decreased cardiac output (CO) and consequently decreased oxygen delivery to the tissues (Hopster et al. 2016).

The second way to improve the $\dot{V}_A/\dot{Q}$ matching is to regulate the lung perfusion. Inhaled nitric oxide (INO) is widely used in human medicine, e.g. for children and adults with acute hypoxaemic respiratory failure and neonates with pulmonary hypertension (Rossaint et al. 1993; Dobyns et al. 1999; Clark et al. 2000). INO works as a selective pulmonary vasodilator and does not cause systemic effects in the rest of the body (Frostell et al. 1991). However, few studies have been done on INO and horses. In one study by Young et al. (1999), continuous delivery of INO in horses showed no positive effect on oxygenation. Conversely, in another study done on neonatal foals with experimentally induced pulmonary hypertension, continuous delivery of INO did improve arterial oxygenation (Lester et al. 1999).

Heinonen et al. (2000) compared pulsed delivery of INO during inspiration to constant inspired concentration of NO in anaesthetized pigs and concluded that the NO gas effect was used more effectively, and environmental exhausts was reduced with pulsed delivery. This method of pulsed delivery of NO was developed in a study by Heinonen et al. (2001), in which pulsed INO turned out to be an effective way to counteract hypoxaemia in horses during general anaesthesia. Further studies showed that a pulse of INO during the first part of inspiration (30–45% of the inspiration time) improved arterial oxygenation in healthy horses (Heinonen et al. 2002; Grubb et al. 2008; Nyman et al. 2012; Grubb et al. 2013a,b). Additionally, Grubb et al. (2014) used multiple inert gas elimination technique and scintigraphy to demonstrate that blood flow was redistributed from dependent atelectatic lung regions to non-dependent ventilated areas during pulsed INO, resulting in a reduction of right to left vascular shunt. The improvement in arterial oxygenation during pulsed delivery of INO has been shown to be sustained throughout 2.5 hours of anaesthesia (Nyman et al. 2012) and no adverse effects, i.e. rebound, have been observed in the studies done on horses (Grubb et al. 2008; Nyman et al. 2012; Grubb et al. 2013a,b, 2014).

The present study is a progression from experimental conditions to a clinical setting. The aim was to evaluate the effect of pulsed INO on arterial oxygenation and subsequent blood lactate concentration in colic horses during abdominal surgery.

Materials and methods

The study was designed as a prospective randomized clinical trial, and informed owner consents were obtained. A sample size calculation indicated that the number of horses should be 11 in each group, based on the results of previous studies (Heinonen et al. 2001, 2002; Nyman et al. 2012; Grubb et al. 2013b, 2014) and with consideration that this study did not include healthy horses. In the end, a total of 30 horses were included in the study, which increased the power from 80% to 90%. The study was approved by the local ethics committee for animal experiments, Uppsala, Sweden (approval number C 201/14).

Horses

Inclusion criteria for the study called for horses to show signs of colic and undergo acute abdominal surgery at the Equine Clinic at the University Animal Hospital in Uppsala, Sweden, between May 2012 and December 2013. Horses with an approved owner consent were randomized so that every second horse was enrolled to the pulsed INO group. Horses younger than 6 months were excluded from the study.

Anaesthesia

The horses were anaesthetized following the standard protocol used at the Equine Clinic at the University Animal Hospital. Premedication included 1.1 mg kg^{-1} flunixin meglumine (Flunixin N-vet; N-vet AB, Sweden), 0.03 mg kg^{-1} acepromazine (Plegicil; Pharmaxim, Sweden), 0.1 mg kg^{-1} romifidine (Sedivet; Boehringer Ingelheim Vetmedica, Sweden) and 0.025 mg kg^{-1} butorphanol (Butador; Vetoquinol, Sweden). For induction, 0.03 mg kg^{-1} diazepam

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