Differences in blood glucose increase between horses receiving xylazine and detomidine for surgical and non-surgical clinical procedures

Diferenças no aumento da glicemia entre equinos recebendo xilazina e detomidina para procedimentos clínicos cirúrgicos e não-cirúrgicos

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Abstract

The aim of this prospective randomized clinical study was to compare blood glucose and cortisol levels between horses receiving xylazine and detomidine for surgical and non-surgical procedures. Horses from non-surgical groups received 0.5 mg/kg of xylazine (GX group, n=5) or 0.01 mg/kg of detomidine (GD group, n=5) for gastroscopic examination. Horses from the surgical groups received similar doses of xylazine (AX group, n=7) or detomidine (AD group, n=7), followed by anesthetic induction with 2 mg/kg of ketamine and 0.05 mg/kg of diazepam for an arthroscopic procedure under isoflurane anesthesia. Blood samples were obtained prior to the alpha-2 agonist administration (baseline) and after 10, 30, 60 and 90 minutes. All groups had a significant increase in blood glucose from 30 to 90 minutes after alpha-2 agonist administration, compared to baseline. After receiving the alpha-2 agonist, the AD group had blood glucose levels (118-150 mg/dL) significantly higher than GD (99-119 mg/dL) and AX (97-116 mg/dL) groups. Cortisol had no significant changes within a group. However, the AX group had cortisol levels (3.6-3.7 µg/dL) significantly lower than GX group (5.4-5.7 µg/dL) from 30 to 90 minutes after xylazine administration. We concluded that blood glucose levels were when detomidine was administered for surgical procedure, compared to xylazine also for surgical procedure, and non-surgical procedure. Serum cortisol was minimally affected by administration of xylazine and detomidine regardless procedures were surgical or non-surgical.

Keywords: Alpha-2 agonists. Cortisol. Gastroscopy. Arthroscopy. Horses.

Resumo

O objetivo deste estudo clínico, radomizado e prospectivo, foi comparar as concentrações sanguíneas de glicose e cortisol entre equinos recebendo xilazina e detomidina para procedimentos cirúrgicos e não-cirúrgicos. Os equinos dos grupos não-cirúrgicos receberam 0,5 mg/kg de xilazina (grupo GX, n=5) ou 0,01 mg/kg de detomidina (grupo GD, n=5) para realização de exame gastroscópico. Os equinos dos grupos cirúrgicos receberam doses semelhantes de xilazina (grupo AX, n=7) ou detomidina (grupo AD, n=7), seguindo-se a indução anestésica com 2 mg/kg de cetamina e 0,05 mg/kg de diazepam para realização de procedimento artroscópico durante anestesia com isofluorano. As amostras de sangue foram coletadas antes da administração do alfa-2 agonista (basal) e após 10, 30, 60 e 90 minutos. Todos os grupos tiveram um aumento significativo da glicemia, a partir de 30 até 90 minutos da administração do alfa-2 agonista, em relação ao basal. Após receber o alfa-2 agonista, o grupo AD apresentou glicemia (118-150 mg/dL) significativamente maior que os grupos GD (99-119 mg/dL) e AX (97-116 mg/dL). Não houve diferenças significativas da concentração de cortisol dentro de cada grupo. Entretanto, o grupo AX apresentou níveis de cortisol (3,6-3,7 µg/dL) significativamente mais baixos que o grupo GX (5,4-5,7 µg/dL), a partir de 30 até 90 minutos da administração de xilazina. Concluímos que a glicemia apresentou valor mais elevadoapós a administração de detomidina para realização de procedimento cirúrgico, comparado à xilazina administrada também para procedimento cirúrgico, e para procedimento não-cirúrgico. A concentração sérica de cortisol foi minimamente influenciada pela administração de xilazina e detomidina independentemente dos procedimentos serem cirúrgicos ou não-cirúrgicos.

Palavras-chave: Alfa-2 agonistas. Cortisol. Gastroscopia. Artroscopia. Equinos.

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Introduction

Horses develop a stress response to anesthesia and surgery, characterized by increases in plasma glucocorticoids, such as cortisol[1,2,3]. It commonly increases hepatic gluconeogenesis and inhibits glucose uptake by the cells, enhancing lipid-protein catabolism and resulting in hyperglycemia[4]. Therefore, blood glucose and cortisol levels may indicate if appropriate analgesia is being provided[3].

Alpha-2 agonists drugs (e.g. xylazine and detomidine) are commonly administered in horses for analgesia and reduction of the stress response by decreasing the sympatho-adrenal activity[5,6] and the adrenocorticotropic hormone release[7]. However, these drugs also have an anti-insulin effect caused by stimulation of alpha-2 receptors in pancreas, which commonly increases blood glucose levels[8,9]. Therefore, this response must be differentiated from the hyperglycemia induced by either a sympatho-adrenal response to nociceptive stimulus or glucocorticoids, when evaluating an analgesic therapy. However, there is no single index or variable, or combination of variables that consistently makes this differentiation by defining a stress response[10]. A traditional approach includes measurement of both blood glucose and cortisol levels[5,6,7,8,9].

Detomidine has a higher specificity for the alpha-2 receptors compared to xylazine, which suggests that detomidine would induce a more pronounced increase in blood glucose levels. However, the literature is not consistent regarding the ultimate effect of the association of alpha-2 agonists with different combinations of anesthetic drugs, mechanical ventilation and surgery on blood glucose and cortisol levels in horses[3,4,6,11,12,13,14]. In addition, some other determinants of a stress response are also associated with a clinical procedure, such as fasting, pain, tissue perfusion and energy availability[3,11,12,15,16]. All these features should be considered to avoid mistakes when interpreting blood glucose and cortisol in horses during a clinical procedure.

Therefore the aim of the present study was to compare the levels of blood glucose and cortisol in horses receiving xylazine or detomidine alone, for non-surgical procedures, or in combination with ketamine, diazepam and isoflurane for a surgical procedure. The hypothesis was that horses receiving detomidine have a higher increase in blood glucose than those receiving xylazine, regardless of the stressful stimuli, and that xylazine and detomidine similarly prevent cortisol increase after a surgical or a non-surgical procedure.

Materials and Method

This study was approved by the Institutional Animal Care Committee (protocol number 1555/2008). Client consent was obtained before inclusion of any horse into the study. Data of 24 mature male and female horses, weighing 439 ± 32 kg, undergoing gastroscopic examination (n=10) or bilateral arthroscopic procedures of the tibiotarsal joint for the removal of osteochondral fragments and drilling of cartilage (n=14) were registered. All procedures were performed in the morning period. Exclusion criteria comprised animals undergoing gastroscopic examination lasting more than 30 minutes or arthroscopic procedures lasting more than 90 minutes. Only clinically normal horses, based on their medical history, physical examination and laboratory analysis (complete blood count, plasmatic fibrinogen and total plasmatic protein levels) were included in the study.

All animals had a 14-gauge catheter (Safelet - Nipro Medical Ltda – Sorocaba-SP, Brazil) introduced into the right jugular vein to facilitate drug administration and blood sampling. Horses scheduled for gastroscopic examination were fasted for 18 hours with no water access for 12 hours. The exam was performed with animals under IV sedation with 0.5 mg/kg of xy-

lazine (Sedazine - Fort Dodge Animal Health - Fort Dodge-IA, USA) (GX group, n = 5) or IV 0.01 mg/kg of detomidine (Dormium V - Agener União Saúde Animal - Embu Guaçu-SP, Brazil) (GD group, n = 5). To ensure the random allocation of the horses among groups, xylazine or detomidine were administered according to a previous randomization, which was performed using a computer program (www.randomization.com). Group information was placed in sealed manila envelopes numbered from 1 to 10 by a person who did not participate in the study. Envelopes were opened in a consecutive order at the arrival of the horse at the scheduled time.

Horses scheduled for arthroscopic procedures were fasted for 12 hours prior to anesthesia, but water was available *ad libitum*. Animals were premedicated with IV administration of 0.5 mg/kg of xylazine (Sedazine - Fort Dodge Animal Health - Fort Dodge-IA, USA) (AX group, n = 7) or IV 0.01 mg/kg of detomidine (Dormium V - Agener União Saúde Animal - Embu Guaçu-SP, Brazil) (AD group, n = 7). The administration of xylazine or detomidine as preanesthetic medication was performed according to a previous randomization similar to that designed in horses undergoing gastroscopic examination. Ten minutes after premedication was administered, anesthesia was induced by 2 mg/kg of ketamine (Dopalen - Vetbrands Animal Health – Miramar-FL, USA) with 0.05 mg/kg of diazepam (Compaz – Cristália – Itapira-SP, Brazil) intravenously. After horses were positioned in lateral recumbency, orotracheal intubation was performed with a cuffed endotracheal tube of appropriate size. Anesthesia was maintained with isoflurane (Isoforine – Cristália – Itapira-SP, Brazil) at an end tidal concentration of 1.5 – 1.8% in 100% oxygen delivered through a large animal rebreathing circuit with a microprocessor-controlled anesthesia ventilator designed for horses (Línea C – Intermed - São Paulo-SP, Brazil). Animals were positioned in dorsal recumbency on a foam padding surgical table and all horses were mechanically ventilated. The respiratory rate, inspiratory:expiratory ratio and tidal volume were monitored (WinTracer version 3.3 beta - Intermed - InMetro [Instituto Nacional de Metrologia, Normalização e Qualidade certification of medical products compliance OCP 0004 – São Paulo-SP, Brazil) and adjusted to maintain the end-tidal carbon dioxide between 35 and 45 mmHg (PoetIQ - Criticare Systems Inc. - Waukesha-WI, USA). The side stream gas analyzer was calibrated before each surgery, and the sampling line was inserted between the orotracheal tube and the rebreathing system for continuous measurement of end-tidal concentrations of isoflurane and carbon dioxide. Self-adhesive patches were applied to the skin for recording the electrocardiogram and heart rate (Viridia CMS 66S - Hewlett-Packard – Andover-MA, USA). A 22-gauge catheter (Safelet - Nipro Medical Ltda – Sorocaba-SP, Brazil) was introduced into the facial artery and connected to a calibrated pressure transducer zeroed at the level of the left atrium. The systolic, diastolic and mean arterial blood pressures were monitored with a multiparametric data collection system (Viridia CMS 66S - Hewlett-Packard – Andover-MA, USA). Lactated Ringer´s solution was administered (10 mL/kg/h) throughout the anesthetic procedure.

All gastroscopic and arthroscopic procedures were performed by the same surgeon (LCLCS). The same gastroscope was used for each gastroscopic examination, and the same resection pattern and suture material were used for each arthroscopic surgery.

In all groups, venous blood samples were withdrawn prior to the alpha-2 agonist administration (baseline) and after 10, 30, 60 and 90 minutes. For horses undergoing gastroscopic examination, "10 minutes after alpha-2 agonist administration" corresponded to the time-point prior to the introduction of the gastroscope into the nostril of the horse, "30 minutes" comprised the time-point during the gastroscopic examination, and "60 and 90 minutes" corresponded to time-points

after the examination had ended. For horses undergoing arthroscopic procedures, "10 minutes after alpha-2 agonist" comprised the time-point prior to the induction of anesthesia, "30 minutes" comprised the time-point during 15 minutes of isoflurane anesthesia and prior to the start of surgery, and "60 and 90 minutes" comprised the time-points during arthroscopic surgery with no drilling of cartilage and with drilling of cartilage, respectively.

Blood samples for glucose measurements were immediately analyzed by amperometry in a portable glucometer (Accu-Check Aviva - Roche Diagnostics Corp. – Indianapolis-IN, USA), which was considered to have high agreement with the gold standard laboratory measurement of glucose in the plasma of equine emergency patients[17]. The samples for cortisol measurements were immediately centrifuged and serum was stored at -20ºC for posterior evaluation performed by radioimmunoassay (TKCO5 cortisol - Siemens Healthcare Diagnostics - Deerfield-IL, USA).

Statistical Analysis

Blood cortisol and glucose concentrations were analyzed within groups (baseline *versus* 10, 30, 60 and 90 minutes after alpha-2 agonists administration) and between groups (GX group *versus* GD group, AX group *versus* AD group, GX group *versus* AX group and GD group *versus* AD group) by using two-way analysis of variance (InStat 3.01 – GraphPad - San Diego-CA, USA). When appropriate, *post hoc* analysis was performed with Tukey test for analysis within groups and with *t*-Student test for analysis among groups. Within each group, the Pearson correlation coefficient was calculated between blood glucose and serum cortisol levels. A $p<0.05$ value was considered significant.

Results

No significant differences were observed between the groups for the baseline values of blood glucose and cortisol (Table 1).

Table 1 - Blood glucose (mg/dL) and serum cortisol levels (µg/dL) of GX, GD, AX and AD groups. Data are presented as mean ± SD

Group		Baseline	Post alpha-2 agonists (minutes)			
			10	30	60	90
GX	Glucose	89 ± 8	97 ± 7	111 ± 8	109 ± 6	105 ± 4
	Cortisol	4.5 ± 0.8	5.2 ± 0.7	5.4 ± 0.4	5.5 ± 0.8	5.7 ± 0.9
GD	Glucose	86 ± 7	93 ± 8	119 ± 9	112 ± 7	99 ± 3
	Cortisol	4.4 ± 0.7	4.5 ± 0.7	5.4 ± 0.8	5.1 ± 0.9	4.6 ± 0.7
AX	Glucose	86 ± 6	95 ± 8	116 ± 9	103 ± 9	97 ± 9
	Cortisol	4.5 ± 0.5	4.4 ± 0.8	3.6 ± 0.7	3.7 ± 0.7	3.6 ± 0.9
AD	Glucose	88 ± 5	99 ± 8	150 ± 9	133 ± 9	118 ± 9
	Cortisol	4.1 ± 0.6	3.9 ± 0.6	4.3 ± 0.7	3.4 ± 0.8	3.3 ± 0.8

GX group: horses undergoing gastroscopic examination after sedation with xylazine (0.5 mg/kg IV); GA group horses undergoing gastroscopic examination after sedation with detomidine (0.1 mg/kg IV); AX group: horses undergoing arthroscopic procedures after premedication with xylazine (0.5 mg/kg IV); AD group: horses undergoing arthroscopic procedures after premedication with detomidine (0.1 mg/kg IV). Baseline: prior to the alpha-2 agonist administration. For GX and GD groups: "10 minutes post alpha-2 agonist" comprised the time-point prior to the introduction of the gastroscope into the nostril of the horse; "30 minutes post alpha-2 agonist comprised the time-point during the gastroscopic examination; "60 and 90 minutes post alpha-2 agonist" comprised the time-point after the examination had ended. For AX and AD groups: "10 minutes after alpha-2 agonist" comprised the time-point prior to the induction of anesthesia, "30 minutes" comprised the time-point during 15 minutes of isoflurane anesthesia and prior to the start of surgery, and "60 and 90 minutes" comprised the time-points during arthroscopic surgery with no drilling of cartilage and with drilling of cartilage, respectively. *Within a group, values differ from baseline ($P < .05$); †within a time-point, values differ from the AD group ($P < .05$); ‡within a time-point, values differ from the GX group ($P < .05$). São Paulo/SP, 2009

In all groups, blood glucose increased significantly at 30, 60 and 90 minutes after alpha-2 agonist administration compared to baseline ($p<0.05$). Horses from the AD group had blood glucose significantly higher than horses from the GD and AX groups at 30 ($p=0.0002$, $p=0.0001$, respectively), 60 ($p=0.001$, $p=0.0003$, respectively) and 90 minutes ($p=0.0013$, $p=0.0037$, respectively) (Table 1).

No significant serum cortisol increase was observed within the groups. Horses from the GX group had cortisol levels significantly higher than horses from the AX group at 30 ($p=0.0003$), 60 ($p=0.0021$) and 90 minutes ($p=0.0023$) (Table 1). No significant correlation between blood glucose and cortisol levels was observed within or between the groups (GX group: $r=0.5875$, $p=0,0631$; GD group: $r=0.2981$, $p=0.0629$; AX group: $r=-0.5605$, $p=0.1355$; AD group: $r=-0.02061$, $p=0.9738$).

Discussion

The blood glucose increase is a well-known marked effect of alpha-2 agonists[1,6,8,9]. The present results, however, showed that during a surgical procedure and combined with other anesthetics, blood glucose levels have a higher increase (70%) when followed by detomidine (group AD) than after xylazine (group AX, 35% increase in blood glucose).

In part, this finding was attributed to the fact that detomidine has a higher specificity for the alpha-2 receptors (260:1) compared with xylazine (160:1)[18], and that it is the anti-insulin effect caused by stimulation of alpha-2 agonist receptors in pancreas that produces the hyperglycaemic effect[8,9]. However, the other anesthetics and surgical stimuli should also have contributed for these results, since blood glucose following detomidine plus diazepam, ketamine and isoflurane for surgery was higher than after detomidine alone for a non-surgical procedure (38% increase in blood glucose). Indeed, horses in the AD group had blood glucose levels higher than the normal range for the species (75.6 to 131.4 mg/dL)[19]. These higher values were observed only at 30 and 60 minutes, which can be attributed to the action time of detomidine. Ketamine administered for induction of anesthesia is a sympathomimetic drug that can possibly produce significant changes in blood glucose and cortisol[1]. However, previous studies reported that plasma glucose values following 1.1 mg/kg xylazine and 2.2 mg/kg ketamine were almost identical to those reported after xylazine alone[8,9].

Although horses are described to develop a stress response to anesthesia and surgery[1,2,3], this was not observed in the present study. However, in previous studies only halothane, but not isoflurane, was associated with a stress response to anesthesia through activation of the pituitary-adrenal axis, and significantly increase of plasma cortisol levels in horses[2,13,16,20,21]. This effect was not reported with isoflurane, which was described to produce minimal changes in biochemical and hormonal values in horses undergoing surgery[1,22]. In addition, alpha-2 agonists are capable to reduce the stress response in horses[5,6]. Although cortisol levels were lower in the AX group, which underwent surgery, compared to the GX group, which did not, these differences probably had little clinical relevance, as no significant differences were observed within a group. Benzodiazepine[20] and ketamine[1,4] administered in groups that underwent surgery had no significant impact on cortisol levels and this was supported by previous studies, describing no significant changes in cortisol levels of horses receiving detomidine, midazolam and ketamine followed by maintenance with isoflurane[14]. Furthermore, in another study, xylazine and ketamine administered prior to halothane anesthesia delayed cortisol increase for 80 minutes[13].

Besides anesthesia, the stress response is also associated with the pain stimuli, and reported to be proportional to the degree of surgical trauma[12,23]. Similar

to the present study, Robertson et al.[11] also reported minor changes in circulating metabolites and hormones in horses undergoing arthroscopic surgery. In addition, cortisol levels in the present study were also similar to horses undergoing standing laparoscopic cryptorchidectomy[24], and general anesthesia for non-abdominal surgery[1,12]. However, as expected, in horses undergoing colic surgery, cortisol levels were reported to be higher than in the present study[25,26].

Baseline values for blood glucose and cortisol levels were similar between groups, regardless of the time for fasting, and these values were within the range of normal values for horses[9,15,19,22,27]. In addition, diurnal variations of cortisol are described to be remarkable in the horse, considering the circadian pattern of cortisol release by adrenal gland[27], so only horses undergoing procedures in the morning period were included in the present study. The greatest blood glucose and cortisol changes occurred at 30 minutes after administration of alpha-2 agonist in all groups, but values higher than baseline were observed until the last time-point (90 minutes after administration of the alpha-2 agonist). This long-term change in blood glucose and cortisol was also reported in previous studies in horses[11,13].

In conclusion, blood glucose increase was higher in the anesthetized group receiving detomidine for a surgical procedure. Cortisol levels were lower in horses receiving xylazine for a surgical procedure, compared to the non-surgical group, but normal values for cortisol were always maintained. The greatest blood glucose changes occurred from 30 to 90 minutes after administration of alpha-2 agonist in all groups. The alterations observed in blood glucose in the present study should be considered when assessing pain and stress in horses receiving xylazine or detomidine.

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