Significant hematocrit decrease in healthy horses during clinical anesthesia

Redução significante dos valores de hematócrito em equinos saudáveis durante anestesia

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Abstract

Xylazine (XYL) and acepromazine (ACP) are known to decrease the hematocrit (HT) of horses when administered alone. However in routine anesthesia these drugs are administered by associations which ultimate effect in the HT is unknown but may cause false impressions about the hydration status, blood loss and red blood cell indices. The objective of this study was to characterize the values of HT in horses anesthetized with XYL, ACP, ketamine, midazolam, guaiphenesin, isoflurane and ephedrine. Twenty healthy horses were premedicated with either XYL 0.8 mg/kg (XYL group, n=10) or XYL 0.5 mg/kg plus ACP 0.05 mg/kg (XYL+ACP group, n=10). Anesthesia was induced with ketamine, midazolam and guaiphenesin and maintained with isoflurane. Ephedrine was infused for cardiovascular support. HT, vital parameters and blood gas values were evaluated at baseline, between each drug administration, after standing and 24 hours after baseline (24hBL). The HT started to decrease 17 and 40 minutes after premedication in XYL group and XYL+ACP group, respectively ($p<0.05$). The maximum decrease of 19% in XYL group and 17% in XYL+ACP group was observed after 1 hour of premedication ($p<0.05$). In both groups HT remained low for longer than 180 minutes and returned to baseline at 24hBL. A significant HT decrease should be considered in anesthetized healthy horses receiving XYL, ACP, ketamine, midazolam, guaiphenesin, isoflurane and ephedrine.

Keywords: Horse. Hematocrit. Packed cell volume. Xylazine. Acepromazine.

Resumo

A administração isolada de xilazina (XIL) e acepromazina (ACP) pode diminuir o hematócrito (HT) de equinos. Na rotina anestésica, estes fármacos são administrados em associações, cujo efeito final no HT não é conhecido, mas pode causar falsas impressões sobre o grau de hidratação, perda sanguínea e índices hematimétricos. O objetivo deste estudo foi caracterizar os valores de HT de equinos anestesiados com XYL, ACP, cetamina, midazolam, EGG, isofluorano e efedrina. Vinte equinos hígidos foram pré-tratados com XIL 0,8 mg/kg (grupo XIL, n=10) ou XIL 0,5 mg/kg associada à ACP 0,05 mg/kg (grupo XIL+ACP, n=10). A anestesia foi induzida com cetamina, midazolam e EGG e mantida com isofluorano. A efedrina foi utilizada para suporte cardiovascular. O HT, parâmetros vitais e hemogasometria foram avaliados no momento basal, entre administração de cada fármaco, após retorno à posição quadrupedal e 24 horas após momento basal (24hBL). A diminuição do HT iniciou-se 17 e 40 minutos após administração da medicação pré-anestésica no grupo XIL e grupo XIL+ACP, respectivamente ($p<0,05$). A queda máxima de 19% no grupo XIL e 17% no grupo XIL+ACP foi observada após 1 hora da administração da medicação pré-anestésica ($p<0,05$). Em ambos os grupos, o HT permaneceu baixo por mais de 180 minutos e retornou aos valores basais em 24hBL. Deve-se considerar a ocorrência de uma redução significativa do HT em equinos hígidos anestesiados com XYL, ACP, cetamina, midazolam, EGG, isofluorano e efedrina.

Palavras-chave: Equino. Hematócrito. Volume Globular. Xilazina. Acepromazina.

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Introduction

Xylazine (XYL) and acepromazine (ACP) are commonly administered in horses as preanesthetic medication, which significantly decreases hematocrit (HT) by relaxation of the splenic capsule, vasodilation on this organ and subsequent sequestration of red blood cells[1,2,3,4,5,6]. Despite HT decrease is expected after administration of XYL and ACP, in routine anesthesia they are often administered associated with other drugs based on the concept of balanced anesthesia, which is not known if may result in a different effect on HT. Ketamine and ephedrine are capable to increase HT through a sympathomimetic effect, while inhalation anesthetics can produce this effect by increasing cortisol release in the circulation.[7] This alpha adrenergic activity of these drugs produces splenic contraction, injecting red blood cells in the circulation. Also, there may be an increase in vascular resistance and intravascular hydrostatic pressure, shifting fluid out of the vasculature to the extravascular space with an increase in HT by hemoconcentration[4,5,8,9].

Since it is not consistently found on the literature which is the ultimate effect of these drugs associations on HT levels, the hydration status, blood loss and red blood cells indices may not be properly estimated during anesthesia when XYL and ACP are used. Therefore, this study aimed to evaluate possible changes in HT of healthy horses promoted by two different anesthetic protocols consisting of XYL, ACP, ketamine, midazolam, guaiphenesin, isoflurane and ephedrine. The hypothesis is that the anesthetic protocol that includes ACP produces higher HT decrease than the anesthetic protocol that does not include ACP.

Material and Method

This study was approved by the ethics and animal investigation committee at our institution (protocol number 985/06). The experiments were performed in 20 healthy cross-bred horses with (mean ± s.d.) 9 ± 5 years and weighing 431 ± 87 kg scheduled for arthroscopy surgery.

Food was withheld for 12 hours and water was always available before anesthesia. The left jugular vein was percutaneously catheterized using a 14 gauge catheter (Nipro Medical Ltda. – Sorocaba-SP, Brazil) for administration of drugs and lactated Ringer´s solution (10 ml/kg/h). Horses were randomly assigned into 2 groups according to the preanesthetic medication administered: XYL group (n=10) received xylazine (0.8 mg/kg i.v.; Sedazine – Fort Dodge Animal Health – Campinas-SP, Brazil) and XYL+ACP group (n=10) received xylazine (0.5 mg/kg i.v.; Sedazine – Fort Dodge Animal Health – Campinas/SP, Brazil) plus acepromazine (0.05 mg/kg i.v.; Acepran 1% - Univet S.A. – São Paulo/SP, Brazil). Ten minutes after preanesthetic medication, anesthesia was induced similarly in all horses with ketamine (2 mg/kg i.v.; Dopalen – Vetbrands Animal Health – Jacareí-SP, Brazil) plus midazolam (0.1 mg/kg i.v.; Dormire – Cristália Produtos Químicos Farmacêuticos Ltda. – Itapira-SP, Brazil), and two minutes after anesthetic induction, 10% guaiphenesin (100 mg/kg i.v.) was administered. Once the animal was recumbent and orotracheal intubation was performed, horses were positioned in dorsal recumbency on foam padding and connected to a large animal closed circular anesthetic circuit (Línea C – Intermed Produtos Médicos Hospitalares Ltda. - São Paulo-SP, Brazil). The lungs were mechanically ventilated with tidal volume of 10 ml/kg, positive end-expiratory pressure of 5 cmH_20 and respiratory rate (RR) (WinTracer version 3.3 beta, Intermed Produtos Médicos Hospitalares Ltda. - São Paulo-SP, Brazil) adjusted to maintain arterial partial pressure of carbon dioxide ($PaCO_2$) between 35-50 mmHg (ABL 555 – Radiometer – Copenhagen, Denmark). Anesthesia was maintained at an end-tidal isoflurane (Isoforine – Cristália Produtos Químicos Farmacêuticos Ltda. – Itapira-SP, Brazil) of 1.5-1.7% vaporized in 0.8 inspired oxygen fraction (FiO_2) (Po-

etIQ – Criticare Systems Inc. – Waukesha-WI, USA). Self-adhesive patches were applied to the skin for recording ECG and heart rate (HR) (Viridia CMS 66S – Hewlett Packard – Andover/MA - USA). The facial artery was catheterized with a 22 gauge catheter (Nipro Medical Ltda. – Sorocaba/SP, Brazil), connected to a calibrated pressure transducer and systolic, diastolic and mean arterial blood pressures (MABP) were recorded (Viridia CMS 66S – Hewlett Packard – Andover/MA – USA). Ephedrine infusion (0.02 mg/kg/min; Efedrin – Cristália Produtos Químicos Farmacêuticos Ltda. – Itapira-SP, Brazil) was initiated after 20 minutes of isoflurane anesthesia for cardiovascular support in horses with MABP < 60 mm Hg. Infusion was administered to maintain mean MABP at 65 – 70 mm Hg and time of infusion was registered.

The HT was measured by the microhematocrit centrifugation method by using venous blood samples collected from the jugular vein. HT, HR and RR were measured immediately before preanesthetic medication (baseline), 10 minutes after preanesthetic medication (10BL), 12 minutes after preanesthetic medication (2 minutes after induction; 12BL), 17 minutes after preanesthetic medication (5 minutes after guaiphenesin; 17BL), 40 minutes after preanesthetic medication (after the initial 20 minutes of isoflurane anesthesia; 40BL), 60 minutes after preanesthetic medication (after the initial 40 minutes of isoflurane anesthesia; 60BL), 10 minutes after standing (ST) and 24 hours after preanesthetic medication (24hBL). MABP and end tidal isoflurane were measured at 40BL and 60BL. Blood gas values were measured at baseline, 40BL and ST, and rectal temperature was measured at baseline, 40BL, 60BL and ST.

Data were statistically analyzed using analysis of variance (ANOVA) for repeated measurements (InStat 3.01 – GraphPad – San Diego-CA, USA) followed by Tukey test for comparison of different time points of the same group. t-Student test was used to evaluate possible differences between groups and statistical significance was considered as $p<0.05$.

Results

In both groups HT decreased significantly at 40BL, 60BL and ST compared to baseline. This effect had an earlier onset in XYL group (17BL, $p<0.05$) compared to XYL+ACP group (40BL; $p<0.01$). The greatest decrease in HT was observed at 60BL in both groups, consisting of a 19% fall in XYL group (29 ± 6.8%, $p<0.001$) and a 17% fall in XYL+ACP group (30 ± 4.5%, $p<0.001$). At 24hBL HT was similar than baseline values. There were no significant differences in HT between groups (Table 1).

In both groups horses had MABP lower than 60 mm Hg at 40BL. XYL+ACP group had values of MABP significantly lower than XYL group at 40BL ($p<0.05$). Both groups had significant increase of MABP at 60BL ($p<0.05$), which were higher than 60 mm Hg (Table 1).

Rectal temperature was significant lower at 40BL, 60BL and ST compared to baseline ($p<0.05$) in both groups. End tidal isoflurane was significantly lower in XYL+ACP group compared to XYL group at 60BL ($p<0.05$) (Table 1).

HR, RR and arterial blood gas values did not change significantly along the study and were within the range of normal values in both groups (Table 1).

XYL+ACP group received a total volume of ephedrine (582 ± 91 mL) significantly higher than XYL group (278 ± 87 mL) ($p<0.05$). No significant difference in time of infusion was observed among groups (34 ± 6 minutes in XYL group; 35 ± 5 minutes in XYL+ACP group).

Discussion

The most marked decrease in HT was 17% and 19%, occurring after 1 hour of premedication, in XYL and XYL+ACP groups, respectively.

Table 1 – Hematocrit, respiratory rate (RR), heart rate (HR), mean arterial blood pressure (MABP), rectal temperature, end tidal isoflurane and blood gas values of horses from XYL group (xylazine 0.8 mg/kg, i.v.) and XYL+ACP group (xylazine 0.5 mg/kg plus acepromazine 0.05 mg/kg, i.v.). Data are presented as mean ± standard deviation

Parameter	Group	Baseline	10BL	12BL	17BL	40BL	60BL	ST	24hBL
Hematocrit	XYL	36 ± 5.9	36 ± 7.4	35 ± 6.2	32 ± 5.8*	30 ± 6.0*	29 ± 6.8*	32 ± 7.9*	34 ± 4.5
(%)	XYL+ACP	36 ± 3.5	36 ± 3.0	37 ± 5.4	34 ± 4.3	31 ± 4.2*	30 ± 4.5*	31 ± 3.8*	36 ± 4.3
RR	XYL	17 ± 3	13 ± 2	13 ± 2	13 ± 2	10 ± 1	10 ± 1	17 ± 3	17 ± 2
(breaths/min)	XYL+ACP	16 ± 2	13 ± 2	12 ± 2	10 ± 2	9 ± 1	9 ± 1	11 ± 2	16 ± 3
HR	XYL	36 ± 6	32 ± 9	38 ± 8	37 ± 6	39 ± 7	40 ± 7	43 ± 6	38 ± 7
(beats/min)	XYL+ACP	35 ± 3	32 ± 7	34 ± 9	37 ± 8	42 ± 9	41 ± 6	38 ± 8	35 ± 7
MABP	XYL	-	-	-	-	56 ± 8	70 ± 8§	-	-
(mm Hg)	XYL +ACP	-	-	-	-	43 ± 5†	62 ± 2§	-	-
Rectal temp.	XYL	37.7 ± 0.4	-	-	-	36.0 ± 0.9*	35.7 ± 0.9*	36.2 ± 0.7*	37.8 ± 0.4
(oC)	XYL +ACP	37.4 ± 0.4	-	-	-	36.4 ± 0.8*	35.9 ± 0.6*	36.4 ± 0.6*	37.8 ± 0.5
End tidal	XYL	-	-	-	-	1.29 ± 0.3	1.20 ± 0.2	-	-
isoflurane (%)	XYL +ACP	-	-	-	-	1.26 ± 0.3	1.05 ± 0.2§	-	-
pH	XYL	7.40 ± 0.03	-	-	-	7.33 ± 0.08	-	7.40 ± 0.15	-
	XYL +ACP	7.39 ± 0.02	-	-	-	7.36 ± 0.04	-	7.42 ± 0.04	-
PaCO2	XYL	41 ± 6	-	-	-	46 ± 4	-	41 ± 5	-
(mm Hg)	XYL+ACP	40 ± 2	-	-	-	45 ± 5	-	43 ± 3	-
PaO2/FiO2	XYL	462 ± 44	-	-	-	418 ± 93	-	438 ± 73	-
	XYL+ACP	469 ± 35	-	-	-	403 ± 95	-	438 ± 39	-
SaO2	XYL	97 ± 1.9	-	-	-	99 ± 1.5	-	96 ± 1.9	-
(%)	XYL+ACP	97 ± 1.9	-	-	-	100 ± 0.7	-	95 ± 5.4	-
Plasmatic bicarbonate	XYL	25 ± 2.2	-	-	-	25 ± 2.8	-	27 ± 2.7	-
(mEq/L)	XYL+ACP	24 ± 1.6	-	-	-	25 ± 2.1	-	26 ± 2.5	-

Baseline - immediately before preanesthetic medication, 10BL - 10 minutes after preanesthetic medication and immediately prior to induction, 12BL – 12 minutes after preanesthetic medication and 2 minutes after induction, 17BL – 17 minutes after preanesthetic medication and 5 minutes after guaiphenesin, 40BL – 40 minutes after baseline and 20 minutes of isoflurane anesthesia, 60BL – 60 minutes after baseline and 40 minutes of isoflurane anesthesia, ST - 10 minutes after standing, 24BL - 24 hours after preanesthetic medication. * within a group, value is significantly different than the Baseline value for this variable ($p<0.05$). § within a group, value is significantly different than the 40BL value for this variable ($p<0.05$). † Within this time point, value is significantly different than other treatment ($p<0.05$). São Paulo/SP, 2008

In XYL group HT decrease (19%) was similar to the observed by Robertson[10] (15%) using XYL (1.1 mg/kg), KET (2.2 mg/kg) and halothane. In both studies, this XYL effect in HT was predominant over the other anesthetic drugs administered and started after about 20 minutes of XYL administration with duration longer than 3 hours. Unlike the present study Wagner et al.[11] did not observe any variation of HT in horses receiving bolus of XYL (0.15 mg/kg) and KET (0.3 mg/kg) followed by infusions of both drugs (0.02 mg/kg/min and 0.06 mg/kg/min, respectively). This context suggests that a minimum dose of i.v. XYL is probably necessary to produce relaxation of splenic capsule and vessels of horses and HT decrease.

In the XYL+ACP group despite the lower dose of XYL compared to XYL group, it was observed a

similar decrease in HT which was attributed to the addition of ACP. According to Wood et al.[3] HT decrease is considered to be an important effect after 30 minutes of ACP administration and i.v. doses as low as 0.0001 mg/kg are capable to decrease HT in 10% for up to 2 hours after administration. Reducing the dose to 0.00005 mg/kg i.v. totally eliminates this effect and increasing the dose to 0.006 mg/kg i.v increases this effect to 18%. Administration of higher doses prolonged this effect but did not produce significant increases in the magnitude of this effect[5,12]. Indeed, the 17% decrease on HT in XYL+ACP group was similar to the 20% decrease reported by Wood et al.[3] after administration of 0.01 mg/kg i.v. and by Parry and Anderson[5] after administration of a dose ten times higher (0.10 mg/kg i.v.). Similarly, Luna, Taylor and Massone[13] reported a significant decrease on HT (17%) after 20 minutes of ACP administration (0.03 mg/kg i.v.) that lasted 4 hours of anesthesia with ketamine, midazolam and halothane. According to Lang, Eglen and Henry[14], this limited amount by which HT decreases is probably explained by the dependence on the splenic storage capacity which, therefore, may plateau HT levels with increasing ACP doses. Therefore, it is suggested that HT levels decreased similarly in both groups, because both anesthetic protocols achieved splenic storage capacity, regardless of the preanesthetic medication administered.

After about 3 hours of premedication, when horses had already recovered the standing position, HT values had not returned to baseline in both groups, which would be expected on horses that received ACP based on Parry and Anderson[5] studies, that reported significant reductions in HT values in horses for 12 hours after ACP administration of 0.05 mg/kg i.v. and for 21 hours after 0.15 mg/kg i.v. In horses administered only XYL as preanesthetic medication, this effect was not expected since this drug has a shorter action, but similar results were obtained by Robertson[10], who reported HT decreasing for more than 3 hours.

The sympathomimetic effect of KET and EPH is capable to produce splenic contraction and increase HT[15,16]. The alpha-adrenolytic activity of XYL and ACP can promote splenic relaxation with consequent erythrocyte storage in the spleen[5] and this effect would have overwhelmed the splenic contraction caused by the adrenergic drugs. The association of midazolam to KET may also have contributed for the maintenance of HT levels after anesthetic induction which was also observed by Mello, Castro Jr. and Silva Filho[17]. Midazolam is capable to prevent the increase in catecholamine levels caused by ketamine[13] and probably avoided the adrenergic effects of this dissociative anesthetic in the spleen capsule and vessels and the increase in HT. In addition, guaiphenesin may have contributed for HT decrease due to a hemodilution effect.

The maintenance of HT after EPH infusion was also described in horses by Hellyer et al.[9] but with the dose of 0.06 mg/kg. Dobutamine, an inotrope administered in anesthetized horses for cardiovascular support, produces a marked HT increase, which would also be expected after EPH administration, since these drugs act by an alpha-adrenergic activity that may cause splenic contraction[9]. However, considering the results observed in both studies there is probably a dose-dependent contraction of the splenic vascular bed and capsule after EPH injection in horses similar to observed in dogs by Davies and Withrington[16] and the dose administered in horses to treat hypotension may be insufficient to cause a significant splenic contraction.

Anesthetic maintenance with isoflurane may also have contributed for HT increase by increasing endogenous catecholamine's release reported in horses anesthetized with inhalant agents[7]. However, this effect is more prominent in halothane anesthetized horses. In addition, the magnitude of this effect or the short duration of the inhalation anesthesia may not be capable to significant change HT in horses anes-

thetized with isoflurane, which was probably the case of the present study supported by Hellyer et al.[9] and Luna, Taylor and Massone[13].

MABP was significantly lower in XYL+ACP group compared to XYL group, which was attributed to the alpha-1 antagonism produced by ACP[18]. It led to a significant decrease in end tidal isoflurane and a significant higher volume of ephedrine infused in XYL+ACP group compared to XYL group to treat hypotension, which successfully increased MABP to normal values.

The transient and marked decrease of temperature during inhalation anesthesia was attributed to the depression of the thermoregulatory center caused by isoflurane and XYL, and also to the cutaneous vasodilation produced by ACP, which predisposed to the heat loss[19,20,21].

Conclusions

The intravenous premedication of horses with xylazine 0.8 mg/kg or with the association of xylazine 0.5 mg/kg plus acepromazine 0.05 mg/kg bwt can significantly decrease hematocrit by 20% for longer than 180 minutes with an anesthetic protocol consisting of ketamine, midazolam, guaiphenesin, isoflurane and ephedrine. This effect was transitory in healthy horses but should be considered by the veterinary in order not to infer false impressions about the hydration status, blood loss and red blood cell indices during anesthesia. Based on these results further studies in critical care horses are necessary to investigate if the hematocrit decrease caused by these anesthetic protocols is also transitory or may be deleterious in horses with preanesthetic conditions such as anemia, hypoxemia, septicemia or shock.

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