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Limited usefulness of the observation of eye bulb rotation and neuro-ophthalmic responses for assessing the depth of equine anesthesia: an observational study comparing three protocols

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Summary

The observation of the neuro-ophthalmic responses is an established basic tool for monitoring the depth of anesthesia in horses. However, their usefulness during balanced anesthesia in the clinic is questionable. The aim of this study was to compare the usefulness of neuro-ophthalmic responses during 3 commonly used anesthetic protocols. An observational study was performed on 22 horses, 5 maintained only with isoflurane (ISO group), 12 maintained with isoflurane and a constant rate infusion of ketamine (ISO+KET group), and 5 maintained with isoflurane and a constant rate infusion of detomidine (ISO+DET group). The occurrence of all five responses was noted: spontaneous palpebral and provoked palpebral response, corneal response, nystagmus and eye bulb rotation. The most consistent with the literature and most useful for anesthetic depth assessment was the observation of spontaneous palpebral reflex in all of the groups ($p = 0.788$) and the most significant differences were visible for the observation of the provoked palpebral reflex ($p = 0.015$) for all groups. The reflexes in the group ISO+DET were less consistent with the literature than in other groups, making them least useful. The group ISO seemed to have the reflexes' observations most consistent with the literature expectations. The corneal reflex was always present and nystagmus always absent which confirmed the observations from literature.

The above results suggest that neuro-ophthalmic responses, especially eye bulb rotation and provoked palpebral reflexes, should not be the only indicators in assessing the depth of anesthesia during maintenance with ketamine or detomidine with concurrent isoflurane.

Keywords: equine anesthesia, isoflurane, ketamine, detomidine, anesthesia monitoring, neuro-ophthalmic responses

General anesthesia in horses generates a high risk and is much more difficult to manage than in small animals (2). The mortality rate for general anesthesia in horses is estimated to be 1%, while in small animals is 0.11% and in human patients – 0.008% (2, 15). This is due to size and the risk of injury of the horse or person during induction and recovery: controlling a horse is physically challenging and potentially dangerous. Therefore, excitement during induction must be avoided, which is also important because the stimulation of the CNS (central nervous system) is likely to influence the responses to the anesthetics and worsen the maintenance. Anesthetic overdose can result in cardiopulmonary depression or cardiac arrest, and due to the physical features of horses, attempts at cardiopulmonary resuscitation are unlikely to be successful. This underlines the importance of monitoring the depth and stability of anesthesia in horses. There is also the potential for post anesthetic myositis after prolonged anesthesia due to reduced blood flow (and subsequent hypoxemia) to the muscles, which were in contact with the surgical table. This explains the importance of the monitoring of blood pressure.

The risk posed by anesthesia also depends on the choice of protocol. Inhalation anesthesia, which is somehow the only choice for longer procedures, poses a much higher risk (2.9%) than total intravenous anesthesia (TIVA, 0.3%) (15). TIVA is commonly used in shorter surgeries (up to 90 minutes) (15), but in other cases it is necessary to use volatile agents, which result in significant cardiovascular depression (20, 23). Inhalant anesthetics are also frequently used in high-risk patients (3, 5). To balance these risks, the partial intravenous anesthetic protocol (PIVA) is chosen the most often (1, 4, 11, 12).

Maintaining the appropriate depth of anesthesia requires accurate monitoring. The first step is to use the features that do not require special equipment. According to the literature (13, 16, 21, 26), neuro-ophthalmic responses (provoked and spontaneous palpebral reflexes, corneal reflexes, eye bulb rotation, and nystagmus) are basic tools used to determine the depth of anesthesia. It is said that those responses, transferred through the cranial nerves which have their origin directly in the central nervous system, are the most direct and sensitive indicator of the brain arousal. Such responses could show the changes in the anesthetic depth earlier than the cardiovascular or respiratory responses, which recruit much more nerves distally from the brain. They are also easy to measure: monitoring is purely observational and the provoked palpebral reflex is checked by a slight touch of the upper eye lid. The responses are noted as absent, present or weakened. It is believed that during sufficient anesthetic depth (which allows to perform surgery uneventfully) the corneal reflex and the rotation of the eye bulb should always be present, the nystagmus and the spontaneous palpebral reflex – always absent, while the provoked palpebral reflex should at least be weakened if present at all. Surprisingly, literature investigating this issue is scarce (23). Only a few studies on the use of neuro-ophthalmic responses as a monitoring tool in TIVA and the differences between inhalant anesthesia and PIVA have been published to date, none of which have focused on systematic comparisons or detailed descriptions.

The drug most frequently mentioned in the context of the limited utility of neuro-ophthalmic response is ketamine (22). Ketamine with alpha-2 agonists is the drug combination most commonly used for PIVA because of the sedative and analgesic effect of alpha-2-agonists and dissociative as well as analgesic features of ketamine (9, 10, 12, 17, 19, 26). Using one of them (or sometimes both) in constant rate infusion (CRI) while maintaining inhalant anesthesia allows reducing the concentration of volatile agents, limiting the depression of the cardiovascular system, and, combined with other factors such as an appropriate inspired oxygen fraction, the administration of additional sedative agents in the recovery period, results in a good recovery (23, 28, 30, 31). Other factors that can influence recovery include muscle responses to prolonged surgical table time, the pharmacokinetics of the anesthetics and related medications, and post-op pain management. However, it has been observed that using an anesthetic mixture including ketamine disturbs the occurrence of the neuro-ophthalmic responses used to assess the depth of anesthesia; its effect, if used simultaneously with volatile anesthetics, is unknown (22). Similarly, alpha-2 agonists are popular adjuvants for use in PIVA, but their effects on neuro-ophthalmic responses also remain to be determined (1).

The main focus of our study was to test the hypothesis that the usefulness of neuro-ophthalmic responses might depend on the anesthetic protocol. We expected more variability in measurements during conditions where the CRI of ketamine or CRI of detomidine was used, compared to isoflurane alone. We also sought to identify other factors that might influence the occurrence of the neuro-ophthalmic responses.

Material and methods

Study design. Twenty-two adult horses referred to the clinic for elective surgeries were included in this study. The horses were classified to ASA (American Society of Anesthesiologists) status I or II during the physical examination (27). They underwent different types of surgeries (Tab. 1), and the anesthetic protocol was chosen according to the type of procedure (and its estimated pain level) and results of presurgical physical exams. Since all the horses were clinical cases and were anesthetized according to one of three routine anesthetic protocols, special permission from the Ethical Committee was not required. Before the procedures, all horse owners signed the consent for further clinical activities, including surgery and anesthesia and were informed about the possible complications.

The anesthetic responses were measured in 22 horses during surgery. The ages of the patients were between 3 and 17 years, and the bodyweights were between 400 and 600 kg. Among the horses, 19 were half-blood Polish horses, and 3 were pureblood Arabians.

Procedure. Patient preparation. At least one day before the surgery the patients had blood samples collected from the jugular vein for analysis. Electrocardiography was also performed and evaluated. In all 22 cases, no pathological changes were detected in these examinations. A basic ophthalmological examination was also performed to rule out diseases, pathological changes, and dysfunctions that could have affected further observations. Food, but not water, was withheld for 12 hours before the surgery. Before beginning the anesthetic procedures, the horses were cleaned and the

Tab. 1. Patients enrolled in the study and the types of surgeries performed on each horse in each group

No. of patient	Type of surgery	Group allocation
Horse 1	Resection of SDFT (superficial digital flexor tendon)	ISO
Horse 2	Removal of hoof canker	ISO
Horse 3	Computed tomography	ISO
Horse 4	X-ray of hips	ISO
Horse 5	Removal of 3 sarcoid tumors	ISO
Horse 6	Arthroscopy of the hock	ISO+DET
Horse 7	Removal of the tumor over the coronary band on left front leg	ISO+DET
Horse 8	Arthroscopy of the stifle	ISO+DET
Horse 9	Tooth extraction	ISO+DET
Horse 10	Cryptorchid castration	ISO+DET
Horse 11	Removal of splint bone	ISO+KET
Horse 12	Cryptorchid castration	ISO+KET
Horse 13	Castration	ISO+KET
Horse 14	Arthroscopy	ISO+KET
Horse 15	Removal of proximal sesamoid bone fragment	ISO+KET
Horse 16	Removal of foreign body from fetlock joint	ISO+KET
Horse 17	Castration	ISO+KET
Horse 18	Cryptorchid castration	ISO+KET
Horse 19	Arthroscopy of the fetlock joint	ISO+KET
Horse 20	Removal of the subepiglottical cyst	ISO+KET
Horse 21	Splint bone removal	ISO+KET
Horse 22	Castration	ISO+KET

oral cavity was flushed. Additional clinical examination was performed before the premedication (for heart rate, breaths, capillary refill time, and temperature), and then the catheter was inserted into the right or left jugular vein (B. Braun Braunule BT, 16 G) and stitched to the skin. All the data were recorded on the general anesthesia paper. The patients were assigned to one of the groups according to the anesthetic protocol used during the surgery (the doses and isoflurane-sparing effect were in agreement with (11), (12) and (13)):

– ISO (maintained only with isoflurane (1.3%)) – 5 horses,

– ISO+KET (maintained with inhalant isoflurane (1.0%) and CRI of ketamine (3 mg/kg/h)) – 12 horses,

– ISO+DET (maintained with inhalant isoflurane (1.0%) and CRI of detomidine (0.01 mg/kg/h)) – 5 horses.

Anesthetic protocol. Pre-anesthesia and anesthetic induction. All the patients were premedicated with detomidine (0.02 mg/kg [Domosedan at 10 mg/ml, Orion Pharma]) and butorphanol (0.01 mg/kg [Butomidor at 10 mg/ml, Richter Pharma AG]) administered intravenously through the catheter (IV) for both sedation and analgesia, followed, after 10 minutes, by induction with ketamine (2.2 mg/kg of Bioketan, the concentrion of the drug: 100 mg/ml, manufacturer: Vetoquinol) and diazepam (0.1 mg/kg [Relanium at 5 mg/ml, Polfa] administered IV). If the swallowing reflex was not abolished, a solution of 5% guaiphenesin was administered intravenously to this effect. Guaiphenesin was administered to 3 horses (Patients 3, 7, and 20); no other horse needed any other injectable drugs at the point of induction. The horses were intubated with silicone endotracheal tubes (Kruuse) with diameters appropriate for the sizes of the animals (12 horses were intubated with 26 mm-diameter endotracheal tubes; 3 horses with 28 mm-diameter tubes). Next, the cuff was inflated, and straps were put on the limbs for transporting the horse to the operating table by carrying it with a lift from the recovery box. All of the horses were placed on either the left or right side and then connected via jugular vein catheter to the infusion pump, intravenous fluids, and via endotracheal tube to anesthetic unit for large animals (Stephan, Fritz Stephan Gmbh), allowing the administration of the isoflurane in oxygen to be initiated within 15 minutes after administering the induction agents.

Maintenance of anesthesia prior to surgical incision. The oxygen flow was set at 4 l/min, and the air flow at 1 l/min (29). If the respiratory rate decreased to 4 breaths per minute, the mechanical ventilation was switched to IPPV mode (intermittent positive pressure ventilation), so that the results of pulse oximetry were at least 90% and capnography, no more than 55 mmHg (32). The initial concentration of isoflurane (Aerrane, Baxter) was 5%, set on the vaporizer, and after 10 minutes it was reduced to 1.3% EtAA (end-tidal anesthetic agent) in the ISO group and 1% EtAA in the ISO+KET and ISO+DET group. The end-tidal percentage was measured in the side stream together with capnography with the use of a vital sign monitor. In addition, Ringer's lactate fluids were administered intravenously at a dose of 3 l/h (14). Ketamine was administered in the ISO+KET group by CRI using an infusion syringe pump at a set rate of 3 mg/kg/h; doses were adapted from other publications (5, 30). Detomidine was intravenously administered in the ISO+DET group using an infusion pump (the total dose of detomidine to be administered per hour was dissolved in saline and topped up to 20 ml in a syringe) at a set rate of 0.01 mg kg/h; doses were adapted from other publications (18).

Cardiopulmonary monitoring during surgery. After the attachment of the patient to the anesthetic unit, a vital parameter monitor (Datex Cardiocap S5) was connected and an arterial catheter was placed into the facial artery, with the arterial pressure transducer placed at the level of the heart. The proper depth of anesthesia was maintained during surgery by keeping the horses' vital parameters within the normal ranges: heart rate (ECG), 25-40 beats/min; IBP (invasive mean blood pressure measured on the facial artery) 70-110 mmHg; $EtCO_2$ (sidestream capnography), 35-55 mmHg; respiratory rate, 6-10 breaths/min (according to the results of capnography); pulse oximetry, > 90%.

Records of observations. Provoked palpebral reflexes were elicited by the touch of the finger to the upper eyelid or the medial canthus of the eye and the complete closure of the eye lids after the touch was noted as presence "1", while the lack of closure – absence "0". Spontaneous palpebral reflex was noted as present "1" when the full closure of the eyelid occurred without any interference with the environment (fluids, air, touch). The corneal reflex was checked by flushing the surface of the eye with a small amount of saline. If the horse closed the eyelid after the flushing it was noted as present "1". The eye bulb rotation when it was rotated to the medial canthus of the eye and assessed by the placement of the pupil was noted in the assessment as absent "0" (when the pupil was centered) or present "1". The nystagmus was observed and noted as present "1" when spontaneous movement of the eye bulb from one canthus of the eye to the other was visible.

Observations of the neuro-ophthalmic responses (spontaneous palpebral reflexes, provoked palpebral reflexes, eye bulb rotation to the medial canthus of the eye, corneal reflexes, and nystagmus) were started from the 15th minute of maintenance due to the half-life of ketamine (10-15 minutes) (18), which was given for induction, and the time for the saturation of the lungs with isoflurane (about 10 minutes) (29). The observations were noted on the anesthesia protocol paper, which included all the vital parameters measured routinely every 5 minutes until the end of the surgery. To ensure the comparability of the results, only the first 60 minutes in each patient was considered for further study, resulting in 12 observations per eye sign. The chart had an extra part devoted to the neuro-ophthalmic responses only, which were measured and noted at the same frequency as the rest of the vital parameters.

After finishing the surgery and maintaining the anesthesia, the horse was detached from the vital signs monitor and anesthetic unit and transported to the recovery box, where 0.005 mg/kg of detomidine was administered intravenously to facilitate a smooth, slow recovery. Extubation was performed after the breathing pattern had stabilized and the swallowing reflex had returned.

Statistical methods. For the analysis, all the neuro-ophthalmic responses observations were compared to the expected patterns of reactions described in the literature: the corneal reflex and eye bulb rotation to the medial canthus of the eye should always be present, while provoked, spontaneous palpebral reflexes and nystagmus should be absent in the typical anesthesia protocol (14, 22, 26, 31, 33). All the measurements were recorded by assigning values of 1 for reactions consistent with the baselines suggested by the literature and 0 for reactions that were inconsistent. Subsequently, the values were added up across the 12 measurements collected for each patient and reflex. These indices were used in further steps of the analysis.

The descriptive statistics for all the neuro-ophthalmic responses are presented as the minima, maxima, and medians. A rank-based nonparametric test was used to determine the statistically significant differences between the groups. Comparisons for each of the indices were performed using the Kruskal-Wallis one-way analysis of variance followed by Mann-Whitney U tests for pairwise comparisons. Values of $p < 0.05$ were considered significant. Data analysis was performed using the R programming environment (ver. 4.0.3) (https://www.R-project.org).

Results and discussion

The total duration of the general anesthesia was 75 to 145 minutes. The duration of anesthesia was measured from the time of the patient's connection to and disconnection from the anesthetic unit. All the vital parameters of the patients remained within the previously described norms, which stood for the stable plane of anesthesia. The average time of recovery was 45 minutes. The horses stood without assistance in 17 cases, while 5 horses were assisted by ropes attached to the tail and head halter. All the patients recovery went well over time and without complications. The measurements of the neuro-ophthalmic responses and their descriptive statistics are presented in Table 2.

Group comparisons. The measurements for each of the indices were compared between groups. There were no significant differences in the spontaneous palpebral reflex ($p = 0.788$). However, there were significant differences in the provoked palpebral reflex measurements noted ($p = 0.015$). The observations were almost fully consistent with the literature in the group ISO (11/12), while the consistency was very low in group ISO+DET (4/12). Follow-up post hoc tests showed that the expected reactions were present less often in the ISO+DET than in both the ISO ($p = 0.011$) and ISO+KET ($p = 0.025$) groups. The effects observed for eye bulb rotation proved to be insignificant ($p = 0.057$), although there were mild differences between the patients observed in all the groups, with the group ISO+DET being completely not consistent with the literature. Post hoc tests showed that the reflexes were more consistent in the ISO group than in the ISO+KET patients ($p = 0.048$), while no significant differences were found for the remaining two comparisons (ISO+KET vs. ISO+DET: $p = 0.307$; ISO+DET vs. ISO: $p = 0.071$). Statistical analysis could not be performed for the corneal reflex and nystagmus, as there was no variability in the measurements, and all the indices were at their theoretical maxima.

Tab. 2. Descriptive statistics for all indices and anesthetic protocols. The values represent the numbers of reactions (out of 12 measurements collected for each animal) that were consistent with the observations from literature

Reflex	Expected	Group						p-value
		ISO (n = 5)		ISO+DET (n = 5)		ISO+KET (n = 12)		
		Med	Min-Max	Med	Min-Max	Med	Min-Max	
Spontaneous palpebral reflex	–	12	11-12	12	7-12	12	8-12	0.788
Provoked palpebral reflex	–	11	10-12	4	0-9	10	0-12	0.015
Eye bulb rotation	+	7	3-12	0	0-10	5	4-11	0.057
Corneal reflex	+	12	12-12	12	12-12	12	12-12	NA
Nystagmus	–	12	12-12	12	12-12	12	12-12	NA

The main goal of our study was to systematically compare the validity of neuro-ophthalmic responses in the context of the most commonly used anesthetic protocols. The importance of conducting the research is connected with serious problems that can be met when facing the incorrect assessment of the anesthetic depth in horses. As previously described, observations and interpretations of the occurrence of neuro-ophthalmic responses seem to be an ideal method to directly assess the arousal of the CNS. However, even though nerves connect the eye and the brain directly, the transduction of the signal is not so straight forward. Not only are there other centers of the nervous system that are affected by the drugs (for example the spinal cord, peripheral nerves) but also the transduction can be affected by the drugs used for anesthesia. This can lead to the situation when, misled by the observations, an anesthetist can incorrectly assess the depth – too deep or too short – which can lead to serious subsequent side effects of drug overdose (for example cardiovascular depression) or generating movement in the surgical field and pain sensation with too light anesthesia. Bearing in mind such serious consequences of a mistake in that field and being aware of various influences over the occurrence of neuro-ophthalmic responses, they should be taken under consideration with caution and always with the correlation of other vital parameters (cardiovascular, respiratory etc.).

The obtained results confirm our preliminary hypothesis that the neuro-ophthalmic responses in the ISO group would be more consistent with those reported in the literature than those in the other conditions would (13, 16, 21, 26). These expectations were confirmed, and both comparisons of the ISO group with respect to provoked palpebral reflexes showed significant differences (ISO vs. ISO+KET, $p = 0.048$; ISO vs. ISO+DET, $p = 0.011$). In the case of the ISO+KET group, there were some earlier reports in the literature suggesting a link between ketamine and the occurrence of the neuro-ophthalmic responses (22) (the author's own observations imply that it keeps the spontaneous palpebral reflex active and makes it unrelated to the actual depth of anesthesia). Our observations confirmed that the reactions in that group exhibited less similarity between the horses (to a lesser extent than in the ISO+DET group, however). Interestingly, despite the lack of previous observations on that matter, the lowest consistency was observed in the ISO+DET group, even though alpha-2-agonists were not suspected to have a major influence on the neuro-ophthalmic responses directly. This could be explained by the indirect mechanism of action of alpha-2-agonists, which have a strong analgesic effect, depress the CNS, and alter blood flow (including that in the ocular region). This may, in turn, alter the eye's response to the stimulation. Our results, if confirmed, might have important practical implications.

Nevertheless, it is important to point out the main limitations of our study. The initial analgesic effects of the detomidine preinduction followed by CRI used in this group during surgery are important considerations during clinical anesthesia. It also worth mentioning that – for the purpose of unification – it was assumed that, when the vital parameters remained within the previously described norms (based on the literature), the patient's depth of anesthesia remained stable and sufficient. However, the normal ranges provided were quite wide, and the anesthetics used in those 3 groups probably generated slightly different (but still sufficient) depths. This might have influenced the results.

The protocols for anesthesia used in our groups are typical for maintaining anesthesia in the clinic, and the doses were based on the literature (1, 5, 12). Detomidine was chosen as the representative of alpha-2 agonists, and it is most commonly used in CRI during the maintenance of general anesthesia (24). It must be noted that these groups represent only 3 types of protocols, and the observations during other protocols using different types of anesthetics might differ. However, those 3 chosen for our research reflect the most common methods. Different combinations of drugs are now used at various doses and when needed local anesthetics and analgesics are also administered. Additionally, as mentioned before, different drugs may influence the occurrence of neuro-ophthalmic responses, and while this is known for ketamine (although only for intravenous distribution, without concurrent isoflurane as tested in this study), there is no literature focusing on the influence of other drugs (22). The further study of different combinations is of interest.

Secondly, as our study was observational, our group sizes were unequal, which was related to the profiles of the patients' needs in the clinic. Although the group was not breed-coherent, there were only 3 horses of breeds different than the others, which we assume should not have influenced the overall results. The fact that we did not use experimental horses affected the sample size. It was difficult to include more patients, as we needed to wait for a proper patient anaesthetized in a certain way to qualify it for one of the research groups. Apart from that, the horses underwent different types of procedures (Tab. 1), which is a potential confounding factor, along with differences in nociception and individual reactions to the drugs (the doses were unified). While the vital parameters of the patients remained within acceptable ranges, we assumed that the animals were stable in their depths of anesthesia, but it is not clear whether these attempts were fully successful, as pain perception might not be fully reflected by changes in the vital parameters measured.

Monitoring the quality of anesthetic management requires further studies and assessments of the pain perception. Moreover, the measurement of brain activity could be of great value. The power spectral analysis of the EEG has been used to evaluate brain responses to anesthetic protocols in horses (6-8, 25). Likewise, the bispectral index (BIS) has been used to evaluate brain responses during inhalant anesthesia (34). However, these studies were not designed to verify the validity of neuro-ophthalmic responses in the context of the currently used balanced anesthetic analgesic combinations during equine surgical procedures. This is not a common practice, partly due to the limited availability of the necessary equipment and the logistics of its clinical usage. Expertise in EEG analysis is uncommon in clinical practice, but it has important research value for advancing knowledge of the use of drug combinations in equine anesthesia. However, there are some difficulties with interpretation due to the different influence of the anesthetics on the EEG activity in horses. A good direction in this topic could be a more extensive and better-controlled study, developing the results obtained in our research.

Bearing in mind the limitations discussed previously, the results of our study point towards the variable validity of neuro-ophthalmic responses as a tool for monitoring the depth of balanced anesthesia. Some of the commonly monitored signs (including provoked palpebral reflexes and eye bulb rotation) show significant inconsistencies and differences compared to the expected reactions described in the literature. A take-home message for clinicians is to use the neuro-ophthalmic responses with caution, especially during the administration of ketamine and alpha-2-agonists.

The challenge for the future is to explore new methods that will support the use of vital signs during anesthesia depth assessment to make the overall monitoring more accurate, which will lead to safer surgeries and better outcomes.

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