



Comparison of Caudal Epidural Administration of Lidocaine and Xylazine to Xylazine/Ketamine Combination in Donkey (*Equus asinus*)

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Abstract

Objective- Evaluation of analgesic and sedative characteristics of xylazine/ketamine combination for caudal epidural analgesia in comparison with two routine agents in donkey.

Design- Cross over study.

Animals- Five healthy adult donkeys of both sexes with body weights ranging from 150-200 kg.

Procedures- Three treatments [lidocaine HCl 2% (0.22 mg kg⁻¹), xylazine HCl 2% (0.17 mg kg⁻¹) and xylazine HCl 2% (0.17 mg kg⁻¹) combined with ketamine HCl 10% (1 mg kg⁻¹)] were evaluated and animals received each of treatments randomly at one-week intervals. Cardiopulmonary parameters and rectal temperature were recorded before and every 15 minutes after epidural administration. The onset and duration of analgesia were evaluated every 5 minutes, using noxious stimulus (pin prick and pinch tests) on the skin of tail, perineum, anus and back thigh. Ataxia was assessed qualitatively between onset of anesthesia and return of sensation. The data were analyzed using analysis of variance followed by Dunnett's test; a *P*-value <0.05 was considered significant.

Results- Administration of xylazine along with ketamine resulted in more rapid onset and longer duration of analgesia (*P*<0.05), without any measurable cardiopulmonary side effects in comparison with the other treatments. However, severe ataxia was observed after the injection.

Conclusion and Clinical Relevance- In a clinical point of view, despite early induction and longer duration of analgesia, this combination at these doses is not suitable for standing surgeries of hindquarters in donkey because there was unacceptable likelihood of recumbency.

Key Words- Donkey, Epidural Analgesia, Ketamine, Lidocaine, Xylazine.

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Introduction

Epidural anesthesia is a central neuraxial block technique which is commonly utilized in veterinary medicine to allow diagnostic, obstetrical and surgical intervention in the perineal, sacral, lumbar and caudal parts of the thoracic region.¹ The technique is a convenient method of providing analgesia because it is simple and inexpensive and requires no sophisticated equipment. Caudal epidural anesthesia in the horse was first described in 1925 by Pape and Pitzschk using local anesthetic solution.² The use of epidural analgesia has been reported for pain relief and for various obstetric manipulations and also surgical procedures in the conscious, sedated and standing animal.^{3,4,5,6,7,8} Additionally, caudal epidural anesthesia can be used to provide peri-operative analgesia or relief of inflammatory, traumatic and chronic pain.^{9, 10} The use of various drugs, alone or in combination, has been described for epidural administration. These include local anesthetics such as lidocaine and mepivacaine, alpha-2 agonists such as medetomidine and xylazine, phencyclidine derivatives such as ketamine, and opioids such as morphine.^{8,11,12,13} Ketamine, a potent noncompetitive antagonist at N-methyl-D-aspartate (NMDA) receptors in the spinal cord, has been used as a general anesthetic or analgesic in clinic.¹⁴ Gomez De Segura et al. (1998) reported that epidurally administered ketamine in the horse produces local spinal and central nervous system effects with analgesia and sedation but minimal cardiopulmonary effects.¹³

Although, several workers have studied the effects of various kinds of epidural anesthetics in donkeys^{4,15}, however to the knowledge of the authors no study have been conducted on the analgesic effects of xylazine/ketamine combination in this species. Furthermore, present study was performed to evaluate the clinical analgesic characteristics of a xylazine/ketamine combination injected into the first intercoccygeal (C1-C2) epidural space, in comparison with two standard methods (using local anesthetics and alpha-2 agonists) in standing donkey.

Materials and Methods

The study and experimental design were approved by the clinical sciences committee of Urmia University with reference number 617. Five healthy adult donkeys of both sexes with body weights ranging from 150-200 kg were selected. Health status was determined by physical and hematologic examinations. The animals were maintained under same feeding and other management conditions. Food, but not water, was held for 12 hours before each epidural injection. There were three treatments including lidocaine HCl, 0.22 mg kg⁻¹ (Xylocaine 2%, Pasteur Institute, Tehran, Iran) and xylazine HCl, 0.17 mg kg⁻¹ (Rompun 2%, Bayer, Leverkusen, Germany) and xylazine HCl, 0.17 mg kg⁻¹, combined with ketamine HCl, 1 mg kg⁻¹ (Ketaset 10%,; Alfasan, Woerden, The Netherlands).^{12,16} These preparations were diluted using sterile 0.9% sodium chloride solution (Normal Saline, Shahid Ghazi, Tabriz, Iran) to a total volume of 0.0165 ml.kg⁻¹ and injected into the epidural space at the rate of 0.5 ml. second⁻¹.¹⁷ Each animal received all of these treatments in random order at one-week intervals. For caudal epidural injection, an 18-gauge, 50 mm needle was inserted in the first intercoccygeal space (C1-C2) in the standing donkeys restrained in stocks as described by Faleiros et al (2004).⁴ The intercoccygeal space detection, skin preparation for injection and correct placement of needle, all were done based on clinically approved procedures, as described before.^{4,18} Prior to epidural injections, to check whether the patient feels tenderness or not, the pin prick test or the pinch test

(using 5 inch straight hemostat forceps closed to the first ratchet) on the skin of tail, perineum, anus and back thigh was done and pain responses -based on individual animal sensitivity-including movement, kicking, or contraction of the cutaneous muscles in unmedicated animals were recorded. Cardiopulmonary changes (heart rate and respiratory rate) and rectal temperature were recorded before and every 15 minutes after epidural administration, precisely. After epidural administration of each solution, time to onset and duration of analgesia were assessed and recorded intermittently every 5 minutes. In addition, ataxia was assessed qualitatively between onset of anesthesia and return of sensation. Ataxia was graded as mild (slight stumbling, easily able to continue walking), moderate (marked stumbling, walking but very ataxic), or severe (recumbency).

Effects of anesthetics on vital parameters (heart rate, respiratory rate and rectal temperature) in each group (within subjects measures) and between groups (between subject measures) were evaluated by use of repeated measures analysis of variance. When the overall the test was significant Dunnett's test was used for multiple comparisons between means. Results for the onset and duration of analgesia between groups were compared by use of one way analysis of variance followed by pair-wise comparisons among ketamine/xylazine combination with other groups (lidocaine alone and xylazine alone) by Dunnett's test.

The data were presented as the mean \pm SD. The significance level set at $P < 0.05$.

Results

The mean (\pm SD) value of heart rates (beats/Min), respiratory rates (breaths/Min) and rectal temperatures ($^{\circ}$ C) for all of the animals before the epidural injection and at intervals thereafter are given in Table 1. Heart rate was insignificantly increased after epidural xylazine/ketamine, in comparison with the other injections especially xylazine ($P > 0.05$). Statistical analyses of respiratory rate revealed that there were no significant differences between the base-line values and those recorded at the several intervals (15, 30, 45, 60 minutes) after the injections ($P > 0.05$). No significant difference in rectal temperatures from base value was noticed at different time intervals in all groups ($P > 0.05$) except for a significant fall at 30 and 45 minutes after epidural injection of xylazine/ketamine combination ($P < 0.05$).

No significant differences ($P > 0.05$) were present between administration of lidocaine and xylazine/ketamine combination in onset of analgesia (Table 2). However, the overall results of analysis of variance showed that there is a significant difference ($P < 0.05$) in onset of analgesia among xylazine alone and xylazine/ketamine combination, so that the multiple comparison of the means indicated that epidural injection of xylazine/ketamine combination resulted in a more rapid onset of analgesia in comparison with xylazine ($P < 0.05$). In addition, the duration of analgesia was significantly ($P < 0.05$) longer in xylazine/ketamine combination compared to lidocaine alone, whereas no significant difference was noticed for this variable after epidural administration of xylazine/ketamine combination and xylazine alone ($P > 0.05$) (Table 2). Qualitative parameters including sedative effects such as ear flapping and relaxation of penis were observed in male donkeys after the injections. Severe ataxia was seen in animals received xylazine/ketamine combination among the others. Recumbency developed within 10 minutes after administration of xylazine/ketamine combination in two out of five donkeys lasted up to 45 minutes after injection. Dog-sitting posture was recorded in one of the animals following epidural xylazine/ketamine combination.

Discussion

The results of this study revealed that the epidural administration of xylazine/ketamine combination is as effective as lidocaine and xylazine administration for induction of caudal epidural analgesia. However it should be mentioned that the combination may increase the risk of recumbency in donkeys.

Lidocaine has been shown to be most effective as an epidural analgesic with a rapid onset and almost total pain relief for 60-90 minutes.^{18,19} However, the use of this agent is not without side effects. Hypotension, analgesia of short-lasting duration which may necessitate re-administration of the agent to allow completion of the procedure, and neurotoxicity are some limiting factors with this agent. In addition, local anesthetic agents indiscriminately block motor, sensory, and sympathetic fibers, causing ataxia, hind limb weakness, and occasionally recumbency.²⁰

Xylazine, an alpha-2 agonist, has been used for caudal epidural analgesia in cattle,^{21,22} buffaloes,²³ horses^{8,24} and donkeys.¹⁵ Although xylazine will provide relatively long periods of analgesia, onset of analgesia is generally prolonged (≥ 30 minutes).^{25,26,27} However, bradycardia, respiratory depression and hypothermia have been reported.^{28, 29, 30} In addition, mild to moderate ataxia and recumbency may occur following epidural administration, especially at higher doses, of alpha-2 agonists.^{19,27,31} However, at appropriate doses, xylazine has been reported to be a suitable agent for providing analgesia without excessive ataxia and recumbency.^{14,27}

To overcome the side effects of the drugs, multiple drugs from different pharmacological classes have been used in combination.³² Thus, the side effects of both drugs might be lessened, while simultaneously the desired effects are maintained or improved along with limiting the dose of each drug. There are several reports from different studies about the use of alpha-2 agonists along with other anesthetics for epidural analgesia in different species. However, there seems to be no information available regarding the use of ketamine for enhancing the analgesia produced by xylazine in donkeys. In several studies, ketamine when combined with xylazine increased the depth and duration of analgesia in goats^{33,34,35} and cow calves.³⁶ Another study revealed that co-administration of medetomidine, an alpha-2 agonist, with ketamine resulted in significantly early onset and slightly longer duration of analgesia in buffaloes.¹¹

Cardiopulmonary depression has been reported as the greatest disadvantage of epidural use of xylazine,³⁷ while no significant difference in heart rate and respiratory rate from base-value was noticed at different time intervals in the donkeys after epidural xylazine. Similar results have been reported following epidural administration of xylazine in horse.³⁸ This can be explained by the expected low plasma concentration of the drug after epidural administration, producing no major systemic effects. An insignificant increase in heart rate after epidural xylazine/ketamine may probably be due to the stimulatory effect of ketamine, which is supposed to be as a result of its slow absorption from epidural space to systemic circulation.³⁹

The decrease in rectal temperature might be due to generalized sedation, decrease in basal metabolic rate, muscle relaxation and CNS depression produced by xylazine. Alpha-2 agonists have been reported to induce prolonged depression of thermoregulation⁴⁰ and depress the hypothalamic noradrenergic alpha-2 receptors to cause hypothermia.⁴¹ Hypothermia observed after the administration of ketamine/xylazine combination may be attributed to one of these mechanisms and also to the additive depressant effect of ketamine on thermoregulatory centers in CNS.

In the present study, epidural co-administration of xylazine with ketamine produced significantly early onset and longer duration of analgesia compared to that in animals of the other groups. It has been reported that the onset of analgesia after ketamine administration was rapid and similar with that of lidocaine,^{14,21} while the duration of analgesia was very short.^{11,14} The early onset of analgesia in the xylazine and ketamine group might be due to the local anesthetic action of ketamine at the spinal cord level.^{42,43} Furthermore, in comparison with lidocaine, xylazine caused significant longer duration of analgesia as reported previously.¹⁵ These results suggested an additive or synergistic interaction between xylazine and ketamine. Similar findings have been reported after epidural administration of a combination of ketamine and xylazine in goats,^{35,44} cattle³⁶ and of ketamine combined with medetomidine in dogs.⁴⁵ Higher doses of ketamine may block Na⁺ channels in both sensory and motor nerves, thus produce regional analgesia in a manner similar to local anesthetics.⁴⁶ In the present study, analgesia following epidural xylazine/ketamine, accompanied by motor incoordination, suggested that analgesia could mainly be attributed to blockade of Na⁺ channels by ketamine. It seems severe ataxia observed in the animals of this study might be due to the local anesthetic action of the drug at the spinal cord level, which was also reported in earlier studies.^{33,34,47} In addition, considering that slow systemic absorption of ketamine occurs from the epidural space,³⁹ it is concluded that ataxia in the donkeys after epidural xylazine/ketamine (1 mg kg⁻¹) was also caused by sedative effect of ketamine.

Table 1. Heart rate (HR, beats/Min), respiratory rate (RR, breaths/Min), rectal temperatures (RT, °C) before and after administration of the anesthetics in five donkeys. Values are means ± SD

Anesthetics	Variable	Time (minutes, before or after onset of analgesia)				
		Base-line	15	30	45	60
Lidocaine	HR	43.20 ± 9.55	40.80 ± 11.00	40.40 ± 10.23	42.00 ± 8.94	41.60 ± 8.76
	RR	22.00 ± 6.23	21.60 ± 8.41	20.60 ± 3.84	20.40 ± 4.98	20.60 ± 4.66
	RT	37.34 ± 0.63	36.78 ± 0.93	36.90 ± 1.25	36.66 ± 1.16	36.40 ± 1.14
Xylazine	HR	39.20 ± 4.38	41.60 ± 6.06	41.60 ± 6.06	41.06 ± 6.69	41.60 ± 6.69
	RR	21.60 ± 6.69	21.20 ± 7.43	24.60 ± 5.60	23.20 ± 5.21	21.60 ± 6.06
	RT	37.14 ± 0.60	36.56 ± 0.70	36.64 ± 1.07	36.76 ± 0.98	36.90 ± 0.78
Xylazine + Ketamine	HR	44.80 ± 3.34	48.00 ± 7.48	45.60 ± 3.57	44.80 ± 4.38	44.80 ± 5.21
	RR	21.60 ± 2.19	20.80 ± 3.34	20.80 ± 3.34	21.60 ± 4.56	21.60 ± 6.06
Ketamine	RT	37.36 ± 0.43	37.04 ± 0.39	36.84 ± 0.69*	36.90 ± 0.42*	37.14 ± 0.61

RT values with asterisk differ significantly ($P < 0.05$) in comparison with base-line value
There was no significant difference between anesthetics

Table 2. Comparison of the mean time to the onset and duration of the analgesia after epidural injection of xylazine/ketamine combination with lidocaine and xylazine alone in five donkeys. Values are means ± SD

Anesthetics	Time (minute)	
	Time to the Onset	Duration
Lidocaine	4.80 ± 1.48	75.92 ± 10.33 *
Xylazine	24.20 ± 3.56 *	142.20 ± 13.60
Xylazine + Ketamine	4.20 ± 1.30	144.40 ± 8.17

Values with asterisk differ significantly ($P < 0.05$) in each column in comparison with xylazine/ketamine combination.

The results of present study suggested that the combination of xylazine and ketamine (0.17 mg kg⁻¹ and 1 mg kg⁻¹, respectively) induced analgesia with rapid onset and a longer duration compared to xylazine or lidocaine alone. In spite of the fact that co-administration of xylazine and ketamine did not cause adverse effects on physiological values (HR, RR, and RT); in a clinical point of view, this combination at these doses is not suitable for standing surgeries of hindquarters in donkey because there was unacceptable likelihood of recumbency. Further studies are needed to achieve an optimal combination of these agents providing satisfactory analgesia without any complications.

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مقایسه تجویز خارج سخت‌شامه‌ای لیدوکائین و زایلازین با ترکیب زایلازین و کتامین در الاغ

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هدف- بررسی اثرات ضد دردی و تسکینی ترکیب داروهای زایلازین/کتامین و مقایسه آن با دو داروی متداول در بیحسی خارج سخت‌شامه‌ای الاغ.

طرح مطالعه- مطالعه Cross over.

حیوانات- تعداد ۵ راس الاغ بالغ سالم از هر دو جنس با وزن ۱۵۰ تا ۲۰۰ کیلوگرم.

روش کار- اثرات تسکینی و ضددردی تجویز خارج سخت‌شامه‌ای سه شیوه درمانی متفاوت شامل لیدوکائین هیدروکلراید ۲ درصد (۰/۲۲ میلی‌گرم/کیلوگرم)، زایلازین هیدروکلراید ۲ درصد (۰/۱۷ میلی‌گرم/کیلوگرم) و ترکیب زایلازین هیدروکلراید ۲ درصد (۰/۱۷ میلی‌گرم/کیلوگرم) با کتامین هیدروکلراید ۱۰ درصد (۱ میلی‌گرم/کیلوگرم) بطور تصادفی بفاصله یک هفته در ۵ راس الاغ مورد مطالعه قرار گرفت. تغییرات قلبی-تنفسی و درجه حرارت مقعدی حیوانات مورد مطالعه قبل از تزریق و بفاصله هر ۱۵ دقیقه بعد از تزریق ثبت و مورد مقایسه قرار گرفت. زمان لازم برای ایجاد بیدردی و نیز طول زمان بیدردی با استفاده از تستهای خراش سرسوزن و نیشگون در قسمت خلفی حیوانات مورد مطالعه بفاصله هر ۵ دقیقه بعد از تزریق تعیین و ثبت گردید. میزان بروز و شدت عدم تعادل بعد از ایجاد بیدردی تا برگشت کامل حس ناحیه خلفی مورد توجه قرار گرفت. داده‌های مطالعه با استفاده از روش آماری آنالیز واریانس تست Dunnett's و سطح معنی‌داری $P < 0.05$ مورد مقایسه قرار گرفتند.

نتایج- تجویز ترکیب زایلازین با کتامین بطور معنی‌داری باعث تسریع در ایجاد بیدردی و تداوم زمان بیشتر آن در ناحیه خلفی حیوانات مدل بدون بروز هرگونه تغییر قابل توجه در پارامترهای قلبی-تنفسی گردید ($P < 0.05$). بروز عدم تعادل متعاقب تجویز ترکیب زایلازین با کتامین با شدت بیشتری در مقایسه با سایر شیوه‌های درمانی در حیوانات مدل جلب توجه نمود. نتیجه گیری و کاربرد بالینی- از نقطه نظر درمانگاهی علیرغم تسریع در ایجاد بیدردی و تداوم بیشتر آن، استفاده از ترکیب زایلازین کتامین برای ایجاد بیدردی در قسمت خلفی الاغ بواسطه بروز عدم تعادل گسترده، توصیه نمی‌شود. کلید واژگان- الاغ، بیحسی خارج سخت‌شامه‌ای، زایلازین، کتامین، لیدوکائین.