



Assessment of Analgesic Efficacy of Intra-articular Tramadol Administration Following Arthroscopic Surgery in Horses - A Pilot Study

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Abstract

Objective- The aim of this study was to evaluate the analgesic efficacy of intra-articular administration of tramadol in horses following arthroscopic surgery.

Design- Experimental study.

Animals- Ten Warmblood horses

Procedures- Horses underwent arthroscopic surgery of the tarsocrural joint (TCJ) (8 horses) and metacarpo- metatarsophalangeal joint (MCPJ/MTPJ) (2 horses). Intra-articular tramadol (2 mg/kg) or saline was administered in randomly selected horses (5 in each group; 4x TCJ and 1x MCPJ/MTPJ) under general anesthesia prior to recovery. After the horses were fully recovered and had returned to the stable two observers, blinded to the treatment scored pain independently at 1, 2, 3, 4, 6, 8, 12 and 24 hours based on a composite measure pain scale (CMPS).

Results- Significant difference in pain score ($P < 0.001$) was observed at any individual time-point between the two groups, except at 24 hours post treatment. A significant lower pain score was detected in tramadol treated group ($P < 0.001$), up to the twelfth hour after treatment. No significant difference was seen between various times in the saline group ($P = 0.09$).

Conclusion and Clinical Relevance- Analgesic efficacy of intra-articular tramadol administration was demonstrated by significantly reduced pain scores following arthroscopic surgery in horses. This observation might be useful as basis for a multimodal analgesic protocol; however, more detailed studies are warranted.

Key words - Tramadol, Intra-articular administration, Arthroscopy, Horse.

Introduction

Osteoarthritis is a common cause of reduced performance in the equine athlete. Diagnostic and therapeutic arthroscopy is a procedure frequently performed in relation to this condition. Arthroscopic surgery often includes the manipulation of fragments within the synovial cavity. The joint capsule is incised and synovium and subchondral bone are debrided. Adequate pain management is necessary and important to decrease tissue morbidity and is in the interest of the horse's welfare.

Balanced or multimodal analgesia offers several advantages in the management of postoperative pain. The administration of analgesic drugs in combination and at multiple sites induces analgesia by altering more than one part of the nociceptive process. When multimodal analgesia is used, the dose of individual drugs can be reduced, and the potential for any one drug to induce adverse side effects is decreased.¹ Opioids are not widely used in horses because of their side effects and the fact that regulatory controls make their practical use difficult. After systemic administration opioid-induced sympathetic stimulation, increased locomotion, and CNS excitation, has been described in the horse. Knowledge about the analgesic effects as well side effects of the use of tramadol as a local analgesic agent is limited in the equine patient. Should side effects be limited after local administration, tramadol has the potential to be a useful analgesic in horses.²

Opioid receptors have been identified in synovial cells of human patients with rheumatoid arthritis.^{3,4} Existence of μ -opioid receptors has also been demonstrated in

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synovial membrane of horses using immunohistochemical staining and radioligand binding is demonstrated.⁵ Marked enhance of density of opioid-binding sites in inflamed compared with control joints have been reported in canine articular tissue and in laboratory animals, suggesting that opioid analgesics may be more effective under inflammatory conditions;⁶⁻⁸ however, in synovial membrane samples collected from horses, there has been no significant correlation between the degree of inflammation and the number of opioid receptors.⁵

Tramadol (50 mg) and morphine (5 mg) have been reported to have comparable analgesic effects when used intraarticularly after arthroscopic knee surgery in humans.⁹ Significant reduction in intensity of joint pain has been reported following oral administration of tramadol (50 mg three times a day for 7 days) in patients with knee osteoarthritis. Further reduction of synovial fluid concentrations of substance P and interleukin-6 has been described to be related to a modulatory function of tramadol on inflammatory mediators.¹⁰ Intra-articular tramadol (100 mg) has been shown to provide excellent analgesia in humans after arthroscopic knee surgery; meanwhile it has been shown to have a longer duration of analgesia compared to intravenous injection at the same doses.¹¹ It is therefore suggested that tramadol potentially provides analgesia via a peripheral mechanism when administered intra-articularly.¹¹ Beneficial effects of the use of tramadol as a local anaesthetic agent or for the use in perineural analgesia has also been demonstrated in rats. It has been suggested that lidocaine can be more effective in blocking the Na⁺ channels compared to tramadol whereas tramadol may be more effective on the delayed rectifier K⁺ channels.¹² The aim of the present study was to investigate the analgesic efficacy of the intra-articular administration of tramadol following arthroscopic surgery in horses.

Materials and Methods

Analgesic efficacy of the tramadol was assessed using a composite measure pain scale (CMPS). Ten Warmblood horses that underwent arthroscopic surgery of the tarsocrural joint (TCJ) (8 horses) and metacarpometatarsophalangeal joint (MCPJ/MTPJ) (2 horses) were included in the study (Table 1). Surgery was performed under general anesthesia, the horses were sedated with acepromazine (0.05 mg/kg IV), induced by ketamine (2.2 mg/kg IV) and diazepam (0.05 mg/kg IV). Isoflurane inhalation was used to maintain general anesthesia. Pain-associated behavior was assessed according to the CMPS system described by Pritchett et al.¹³ CMPS has previously been described for the evaluation of analgesic efficacy of intra-articular morphine in experimentally induced radiocarpal synovitis in horses.¹⁴

Two precisely oriented observers scored pain independently at 1, 2, 3, 4, 6, 8, 12 and 24 hours after intra-articular administration of 2 mg/kg tramadol (Ratiopharm 50 mg/ml Injektionslösung; Germany) or saline (volume equivalent to 2 mg/kg tramadol) following arthroscopic surgery in randomly selected cases (4x TCJ and 1x MCPJ/MTPJ). Surgery was performed by the same surgeon in all cases. All horses received the treatment immediately after skin closure. Observers were blinded to the treatment used. Pain scoring started after complete recovery from general anaesthesia and transmission of the horses from the recovery room to their assigned stables.

The CMPS was based on six behavioral categories: gross pain behavior, weight bearing, head position, location in the stall, response to opening of the door, and response to approach from the observer, combined with an overall subjective pain score. For all categories each score was precisely defined to ensure consistency between observers (Tables 2 and 3). At each time point scores for all behavioral categories were summed to yield a final pain score ranging from 0 to 23. At each time point horses were initially observed for 3 minutes without entering the stable. After that, the stable was entered and the horse's socialization behavior was evaluated by opening the stable door and finally by entering the stable.

Statistical analysis was performed using SPSS program for windows (SPSS Inc., Chicago, IL, USA). CMPS of the tramadol and saline group were compared using Mann-Whitney test, and differences of the various evaluation times in each group was compared using Kruskal-Wallis and Duncan tests. Data is reported as means \pm SEM and differences were considered significant at $P \leq 0.05$.

Results

Significant difference in pain score ($P < 0.001$) was observed between treatments (tramadol and saline) at all time points following arthroscopic surgery, except at 24 hours post-injection. No significant differences were seen between various sampling times in the saline treated group ($P = 0.09$), meanwhile it was observed in the tramadol treated group ($P < 0.001$). CMPS scores at 12 and 24 hours showed significantly higher scores in comparison with other time-points in tramadol group. Results of the CMPS scoring are presented in Table 4.

Table 1- Joint lesion, affected limb and affected joint of the horses underwent arthroscopic surgery. RH: right hind; LH: left hind; OCD: osteochondrosis dissecans; P1: proximal of first phalange.

Case number	Affected limb	Affected joint	Joint lesion	IA injection
1	RH	Hock	Avulsion fracture of the medial malleolus of tibia	Tramadol
2	RH	Hock	OCD; intermediate ridge of the distal tibia	Tramadol
3	RH	Hock	OCD; intermediate ridge of the distal tibia	Tramadol
4	LH	Hock	OCD; intermediate ridge of the distal tibia	Tramadol
5	RH	Fetlock	Lateral fragmentation of the proximal palmar eminence of the P1	Tramadol
6	LH	Hock	OCD; intermediate ridge of the distal tibia	Saline
7	RH	Hock	OCD; intermediate ridge of the distal tibia	Saline
8	LH	Hock	OCD; intermediate ridge of the distal tibia	Saline
9	RH	Hock	Avulsion fracture of the medial malleolus of tibia	Saline
10	RH	Fetlock	Medial fragmentation of the proximal palmar eminence of the P1	Saline

Table 2. Definitions of the composite measure pain scale for subjective pain evaluation.¹⁴

Behavior category	Pain score				
	0	1	2	3	4
Gross pain behavior*	none		Occasional		Continuous
Weight bearing	Normal weight bearing or walking	Foot intermittent off the ground/resting more than other thoracic limb		continuously taking foot off the ground and trying to replace it Carpus slightly flexed	No weight bearing; Foot totally off the ground or toe just touching the ground
Head position	Above withers or eating	level of withers	below withers		
Location in stall	At door watching environment	Standing in the middle, facing door	Standing in the middle, facing sides	Standing in the middle, facing back or standing in the back	
Response to open door	Moves to door	Looks at door		No response	
Response to approach	Moves to observer, ears forward	Looks at observer, ears forward	Moves away from observer	Does not move, ears back	
Overall subjective pain score	No apparent pain	Mild discomfort	Slight pain	Moderate pain	Severe orthopedic pain

*Gross pain behavior is defined as tooth-grinding, lip curt, pawing, and sweating.

Table 3. Prepared form of composite measure pain scale for subjective pain evaluation after arthroscopic surgery in each horse.

Option	Time (h)							
	1	2	3	4	6	8	12	24
Gross pain behavior								
Weight bearing								
Head position								
Location in stall								
Response to open door								
Response to approach								
Overall subjective pain score								

Table 4. Results of the overall composite measure pain scale (CMPS) scores in intra-articularly saline and tramadol treated animals following arthroscopic surgery. Higher scores indicate greater pain; maximum pain score at each time point is 23.

		CMPS scores of post-injection time points							
		1	2	3	4	6	8	12	24
Overall CMPS	Tramadol	2±0.73 ^a	3.6±0.99 ^a	4±0.87 ^a	2.8±0.44 ^a	5.6±0.79 ^a	6.4±0.78 ^a	9.3±0.37 ^{*a}	11.5±0.31 [*]
	Saline	13.3±0.86 ^b	14.8±1.16 ^b	16.2±0.63 ^b	16.3±0.84 ^b	17.7±0.58 ^b	18±0.37 ^b	16.7±0.37 ^b	13.9±0.43

*Significant difference with the first score ($P < 0.05$).

^a Significantly different from ^b in the same time between groups

Discussion

Significantly lower pain scores were observed in horses treated with intra-articular tramadol compared to horses in the saline treated group, up to 12 hours post-operatively. Pain management including adequate analgesia is a vital step in any surgical procedure, considering the animal's welfare and improving the outcome.¹⁵ Procedures such as osteochondral fragment removal and subchondral bone debridement of large areas caused by osteochondritis dissecans lesions or lesions like femorocondylar cysts require pain management following arthroscopic surgery.¹⁶

In equine medicine, there is a reluctance to use systemically administered opioids, based on the concern that there may be adverse side effects such as excitation, sedation, and reduced gastrointestinal motility. Therefore, recent clinical investigations are focused on the development of new peripheral opioid agonists as well as on ways to stimulate the endogenous analgesic system in order to induce effective peripheral analgesia with reduced central side effects. Local administration of opioids has been described to be useful for horses with acute inflammatory joint pain and offers possibilities for multimodal analgesic therapies without opioid-related systemic side effects.¹⁷ Minimal effects on cardio-respiratory function and fewer effects on gastrointestinal motility than those of morphine as well as minimal organ toxicity have been described for the use of tramadol in horses. It has been demonstrated that articular synovial membrane μ -opioid receptors are up-regulated in acute equine synovitis, whilst anti-inflammatory treatment will attenuate this response.¹⁸

No gold standard for pain assessment in horses is available to date. Recently, a new approach to pain assessment named "Horse Grimace Scale" (HGS) has been developed. This system has been reported to be effective and reliable to evaluate pain following castration, utilizing the assessment of facial expressions. This score has been correlated positively with the Composite Pain Sale (CPS) score used in this study.¹⁹ Action units relating to pain have been identified and incorporated "grimace scales" were developed as an on-farm pain assessment tool in this method.

Subjective pain scoring using behavioral parameters after arthroscopic surgery in horses has previously been used in several clinical studies.^{20,21} The pain scoring system utilized in the present study has previously been used in order to evaluate the analgesic efficacy of intra-articular morphine in induced synovitis of the radiocarpal joint in eight horses.¹⁴ This method was further modified for the evaluation of orthopedic pain based on the system described by Pritchett et al.¹⁴ From a clinical point of view, CMPS has been less subjective, easier to use, reproducible, and consequently more reliable with good inter-observer agreement.¹⁴ So, it has been suggested to be employed for evaluation of orthopedic pain in equine patients. Shafford et al. compared intra-articular lidocaine plus bupivacaine, in the setting of multimodal pain management, with no injection in control group in sheep underwent stifle arthrotomy. Two observers blinded to the treatment assessed sheep for total pain score using a numeric ranking scale in their stall for 15 minutes including: comfort, movement, and flock behavior. It was concluded that intra-articular lidocaine plus bupivacaine provides 3-7 hours postoperative analgesia for joint surgery.²²

Intravenous tramadol administration in horses does not seem to cause the same side-effects that have been reported for the systemic use of other opioids in horses.² In the current study, no adverse effects were observed after intra-articular tramadol administration in horses, although nausea, confusion, agitation, tremor, and tachycardia are reported in donkeys.²⁴ Recently, a decrease in inflammatory edema and joint effusion in the rat model of knee joint inflammation has been described after intra-articular tramadol administration.²⁵ Since the existence of opioid receptors has been discovered in equine synovium, intra-articular administration of opioid drugs may have analgesic and anti-inflammatory properties in horses similar to those demonstrated in other species.¹⁴ Intra-articular morphine has been suggested to have potent analgesic and anti-inflammatory effects in horses suffering from acute synovitis.¹⁷

Tramadol provides analgesia with a peripheral mechanism when administered intra-articularly in

human surgery.¹¹ The doses of 50 mg of tramadol and 5 mg of morphine have been shown to have comparable analgesic effects when used intra-articularly after arthroscopic knee surgery in humans.⁹

It is also suggested that preemptive intra-articular 100 mg tramadol provides effective and reliable pain control and can be preferred to postoperative administration.²⁶ Similar results were obtained in a further study using preemptive intra-articular tramadol (100 mg) in comparison to the postoperative tramadol group.²⁷

Although, intra-articular 50 mg tramadol was not found to be very efficacious after meniscectomy in one study,²⁸ the authors suggested that it might be resulted from inadequate dosage. In the present study, 2 mg/kg tramadol was used, it equals the systemic dose of tramadol reported to induce analgesia, which is the suggested dose for parenteral administration in horses.²⁹ In tramadol treated horses, the mean CMPS scores were between 2 and 4 until 4 hours after surgery, afterwards it started to increase until the end of evaluation time at 24 hours. Scores were less than 10 before 12 hours after surgery were reached and about 12 at 24 hours. In saline treated group, the mean CMPS score increased until 8 hours post surgery and thereafter showed a decrease until 24 hours. The overall score was not less than 12. In the tramadol treated group, CMPS scores of the 12 and 24 hours were significantly higher than at any other time. This may be related to the duration of analgesic

efficacy of tramadol, which is reduced through the postoperative period.

Epidural administration of tramadol 2 mg/kg has been effective in management of perineal and lumbosacral pain in horse without side effect, and it has been detectable in plasma after 5 minutes up to 8 hours post administration.³⁰ In the present study, the highest CMPS (less pain) has been established between 6-8 hours postoperatively. The main limitations of the present study were inconsistency of the treated joints; however joints were matched between the tramadol treated group and the saline treated group. No behavioral assessment was made for any horse prior to the procedures, which could have enabled horses to act as their own control. These will be considered in further studies with inclusion of a bigger case number. In addition, it should be noted that effects of any surgery and general anesthesia on equine behavior are still not completely understood.³¹

In conclusion, possible clinically observable effects of tramadol as anti-inflammatory, analgesic and local anesthetic besides its limited side effects present this drug as a suitable choice for intra-articular administration after arthroscopic surgery. Therefore, it can be used as a part of multimodal analgesic protocol; however, more detailed studies are warranted.

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چکیده

ارزیابی تاثیر بی دردی تجویز داخل مفصلی ترامادول متعاقب جراحی آرتروسکوپی در اسب: مطالعه اولیه

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هدف- هدف این مطالعه ارزیابی اثر بی دردی تجویز داخل مفصلی ترامادول در اسب متعاقب جراحی آرتروسکوپی بود.

طرح- مطالعه تجربی.

حیوانات- تعداد ۱۰ راس اسب.

روش کار- حیوانات تحت جراحی آرتروسکوپی مفاصل خرگوشی (۸ راس) و فتلاک (۲ راس) قرار گرفتند. تجویز داخل مفصلی ترامادول (۲ میلی گرم بازای هر کیلوگرم وزن بدن) یا مقدار هم‌حجم سالین نرمال در دو گروه ۵ راسی اسب به شکل تصادفی (۴ مفصل خرگوشی و ۱ مفصل فتلاک) در پایان بیهوشی عمومی و پیش از بازگشت از بیهوشی صورت گرفت. پس از بازگشت کامل از بیهوشی و بازگشت به اصطبل، دو ارزیاب بدون اطلاع از نوع تجویز، در زمان های ۱، ۲، ۳، ۴، ۶، ۸، ۱۲ و ۲۴ درد را بر اساس معیار composite measure pain scale (CMPS) ارزیابی و ثبت کردند.

نتایج- تفاوت معنی داری بین گروه ترامادول و سالین در سایر زمانهای ارزیابی به غیر از زمان ۲۴ مشاهده شد. کاهش قابل ملاحظه درد در گروهی که ترامادول دریافت کرده بودند تا ۱۲ ساعت پس از تجویز مشاهده شد. تفاوت معنی داری در زمان های مختلف ارزیابی در گروه سالین مشاهده نشد.

نتیجه گیری و کاربرد بالینی- تاثیر بی دردی تجویز داخل مفصلی ترامادول با کاهش معیار درد پس از جراحی آرتروسکوپی مشاهده شد. این یافته می‌تواند به عنوان پایه ای برای پروتکل بی دردی چندوجهی مد نظر قرار گیرد؛ اگرچه مطالعات دقیق تری نیز مورد نیاز خواهد بود.

کلمات کلیدی- ترامادول، تجویز داخل مفصلی، اسب.