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Effects of Intraarticular Tramadol Administration on Biochemical and Cytological Properties of Equine Synovial Fluid: Comparison with Lidocaine

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Abstract: Problem statement: Diagnostic and therapeutic arthroscopic surgeries are procedures performed quite frequently in equine practice; and are considered to cause some degree of postoperative pain. The aim of the present study was to evaluate the equine synovial fluid biochemical and cytological changes following intra-articular administration of tramadol as a potential analgesic. **Approach:** Six adult healthy donkeys were selected after clinical examination. Synovial fluid samples were taken from both middle carpal joints after routine preparation. Tramadol 2 mg kg^{-1} and 100 mg lidocaine 2% were administered to the right and left joints respectively. Synovial fluid collection from the joints was performed at 12, 24, 48-192 h after medication. Cytological examination, total protein, glucose, specific gravity, Alkaline Phosphates (ALP), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), viscosity and quality of mucin clot were measured. Comparison of treatments was performed by nonparametric sign test and Wilcoxon rank sum test. Significance level was set to $p \leq 0.05$. **Results:** Neither detectable lameness nor special side effect was observed throughout the study. Mucin clot quality test and viscosity, the amount of total nucleated cell count, glucose, ALP and LDH revealed no significant differences between various sampling times between the tramadol and lidocaine groups ($P>0.05$). Neutrophil count, total protein, specific gravity and AST activity were significantly different. **Conclusion/Recommendations:** Despite the slightly different results compared to the lidocaine, it seems that the injection of tramadol into the middle carpal joint has no adverse effects on the synovial fluid composition in this joint and it can be considered a good analgesic after arthroscopic surgery with the lowest side effects in horses.

Key words: Intraarticular tramadol, lidocaine, equine, synovial fluid

INTRODUCTION

Joint injuries are common in horses and about 33% of lameness is considered to have originated from articular injuries (Leme *et al*., 1999). Pathologic conditions that involve the joints of horses cause a decrease in their athletic performance. Diagnostic and therapeutic arthroscopy are procedures performed quite frequently in equine referral practice (Price *et al*., 2003) and are considered to produce a moderate degree of postoperative inflammatory orthopedic pain (Colahan *et al*., 1998), which will inevitably lead to postoperative discomfort despite peri-operative and post-operative analgesia.

In human medicine Intraarticular local anesthetics and/or opioids are often used for the management and prevention of pain after arthroscopic surgeries (Chirwa *et al*., 1989; Dahl *et al*., 1990; Stein *et al*., 1991; Khoury *et al*., 1992; Reuben and Connelly, 1996; Kanbak *et al*., 1997). The addition of opioids to local anesthetics increases the analgesic effect during the postoperative period, which is the rationale of the multimodal analgesia (Allen *et al*., 1993). However, because of the high systemic absorption, the amount of

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local anesthetic drugs is limited when administered intraarticularly (Alagol *et al*., 2004). In equine medicine, there is a reluctance to use systemically administered opioids, based on concern that there may be adverse side effects. Therefore, clinical investigations now focus 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 (Janson and Stein, 2003).

The discovery of opioid receptors in the equine synovial membrane (Sheehy *et al*., 2001) makes it plausible that intraarticular (IA) administration of opioid drugs may have analgesic and anti-inflammatory properties in horses similar to those demonstrated in other species (Lindegaard *et al*., 2010); especially in human. Tramadol, a weak μ agonist, interferes with the neuronal release and reuptake of serotonin and norepinephrine in the descending inhibitory pathways like α_2 adrenoceptor agonists. Recently it has been used intraarticularly in human to manage postoperative pain after arthroscopic knee surgery (Likar *et al*., 1995; Kanbak *et al*., 1997; Kürsad *et al*., 1998; Alagol *et al*., 2004).

Some studies have shown greater analgesic efficacy of the tramadol when administered IA than intravenous injection of the same doses (Kapral *et al*., 1999). Lower side effects and limited absorption of the drug is seen and it is concluded that the mechanism of analgesic effect of intraarticularly administered tramadol is not due to the systemic effects (Alagol *et al*., 2004).

Limited information is available on the effects of tramadol in horses; most of the information comes from studies in human patients and laboratory animals. Minimal effects on cardiorespiratory function and fewer effects on gastrointestinal motility than those of morphine and minimal organ toxicity are suggested for tramadol in equine (Doherty and Valverde 2006). Recently, a decrease in inflammatory edema in the rat model of knee joint inflammation has been suggested after IA tramadol administration (Garlicki *et al*., 2006).

Chemical synovitis, often referred to as joint flare, can also occur in response to the injection of corticosteroids, local anesthetics, HA and polysulfated glycosaminoglycans (Steel, 2008). Laboratory analyses of small amounts of synovial fluid provide a simple and effective method for assessing the state of articulation, including pathological processes (White *et al*., 1989). Despite the recently cited reports of oral, epidural and intravenous effects of tramadol in equine, to the author's knowledge, no study evaluating the effect of tramadol on the synovial fluid properties is available. Although detomidine HCL, lidocaine, mepivacaine and morphine have been used IA in the horse. So, the objective of the present study was to investigate the effect of IA administration of clinically available tramadol on synovial fluid biochemical and cytological properties compared to lidocaine, as one of the most commonly used drugs for joint blocks in horses.

MATERIALS AND METHODS

Six adult healthy native donkeys (Iranian donkey breed), aged 2-3 years, weighing 200-240 kg were used. All donkeys were determined to be clinically healthy based on general physical examination and were lameness-free when examined at the walk and trot on a hard surface, in a straight line and in a circle. Flexion tests of the limbs were negative, too.

The middle carpal joints of both forelimbs were selected for injection of the drugs after routine preparation; 100 mg Lidocaine 2% in the left joint and tramadol 2 mg kg^{-1} in the right joint. An equal injected volume of the drugs was corrected with the addition of normal saline. Synovial fluid samples (1.5 mL) were collected at 0 (immediately before injection of the drugs), 12, 24, 48-192 h after IA administration of the drugs from both middle carpal joints in flexed position. After each arthrocentesis, the affected carpus was placed in a standard wrap. The animals were examined for lameness based on the American Association of Equine Practitioners scale and the joints heat, inflammation and pain were clinically evaluated during study on the days of sampling.

Synovial fluid samples were evaluated for cytological and biochemical properties; total white blood cell count (mononuclear and neutrophil), total protein, glucose, specific gravity, aspartate aminotransferase (AST), Alkaline Phosphates (ALP) and Lactate Dehydrogenase (LDH). The specimen was used to prepare slides for cytological examination; differential cell count was done following Giemsa staining. Viscosity was evaluated subjectively by observing the length of the strand formed by a drop of Synovial Fluid (SF) as it is expelled from the end of the syringe. Mucin clot formation was evaluated by adding 0.5 ml of synovial fluid to 2 ml of 2% acetic acid solution, mixing it rapidly and allowing it to stand for 1 h at room temperature and using the following clot grading: Normal (N), a tight ropy clump in a clear solution; fair (F), a soft mass in a very slightly turbid solution; Poor (P), a small friable mass in a turbid solution; and Very Poor (VP), a few flecks present in a turbid solution.

Total protein (biuret method), glucose, ALP and AST were measured using commercial kits (ZiestChem Diagnostics, Tehran, Iran) with a spectrophotometer.

Table 1: Total white blood cells, neutrophil, mononuclear cells, total protein, glucose, specific gravity, ALP, AST and LDH in synovial fluid of donkeys in various sampling times following intra-articular tramadol and lidocaine administration

	Sampling time									
	0		12		24		48		192	
Parameter	Lidocaine	Tramadol	Lidocaine	Tramadol	Lidocaine	Tramadol	Lidocaine	Tramadol	Lidocaine	Tramadol
Total WBC (cell/μl)	132.5± 52.97	163.83± 149.45	2188.8± 998.26*	2819.5± 1885.51*	3146.5± 474.32*	1889.3± 1121.46*	962.17± 122.32	933.83± 269.06	307.17± 113.92	550.33± 181.06
Neutrophils (cell/μl)	4.33± 2.94 (3.06)	2.83± 1.6 (2.44)	329.66± 149.94 (15.13)	194.5± 139.08 (7.62)	1321.5± 321.41*[a] (42.76)	364± 214.44*[b] (48.49)	395.33± 72.52[a] (40.96)	163± 34.61[b] (11.98)	231.66± 9.02[a] (7.54)	41.83± 15.53[b] (7.68)
Mononuclear (cell/μl) (%)	128.16± 50.46	161± 148.97	1859.1± 854.46*	2625± 1770.66*	1825± 553.72[a]*	1525.3± 907.3[b]*	566.83± 72.6	770.8± 251.4	284± 106.81	508.5± 168.67
Total protein (gr/dl)	1.96± 0.86	3.11± 2.57	5.22±* 1.83	5.04± 1.62	4.39± 1.66*	6.81± 2.65	2.48± 0.86[a]	7.08± 2.87[b]	2.6± 0.57	4.73± 5.36
Glucose (mg/dl)	87.92± 49.31	91.81± 30.94	118.45± 41.31*	118.02± 34.74	92.1± 17.93	88.4± 58.79	83.04± 18.01	72.15± 22	92.13± 44.11	100.75± 29.77
Specific gravity	1.003± 0.002	1.003± 0.001	1.006± 0.002	1.007± 0.001	1.008± 0.002*	1.010± 0.002*	1.005± 0.005[a]	1.011± 0.003*[b]	1.005± 0.001	1.007± 0.002
AST (U/L)	40.5± 11.43	30.16± 13.87	40.5± 4.54	77.16± 34.46*	54.66± 12.87*[a]	121.33± 33.01*[b]	44.33± 9.5[a]	85.16± 63.57[b]*	39.66± 5.88[a]	73.83± 58.28[b]*
ALP (U/L)	82.61± 37.36	83.26± 32.6	141.13± 43.76*	149.12± 49.63*	121.6± 35.95*	159.61± 79.98*	94.62± 17.15	104.34± 43.09	76.83± 33.76	71.5± 18.23
LDH (U/L)	97.47± 9.26	97.4± 8.62	101.38± 8.24	97.65± 12.6	106.26± 7.88	107.3± 8.77*	96.55± 5.66	100.28± 8.46	96.44± 6.11	96.59± 5.27
Joint circumference (cm)	22±1.38	21.83± 1.25	22.58± 1.20	22.58± 1.28	23.83± 0.61*	23± 1.05	24.67± 0.41*	23.47± 1.04*	22.58± 1.16	22.58± 1.46

AST aspartate aminotransferase, ALP alkaline phosphates, LDH lactate dehydrogenase; *Significant difference with day 0 ($P<0.05$); [a]Significantly different from [b] in the same time between groups

Statistical analysis was performed using SPSS program for windows (SPSS Inc., Chicago, IL, USA). The median of the grading data including lameness and mucin clot quality were analyzed using a nonparametric sign test and the rest using Mann-Whitney and Friedman tests. Differences were considered significant at $P\leq0.05$.

RESULTS

There was no detectable lameness throughout the study during the days of arthrocentesis of either carpal joint. Clinical examination of the joints did not reveal any sign of the heat, inflammation or pain. Mucin clot quality tests were uniformly normal in both groups thorough the study and there were no significant differences between the different times of the sampling. Viscosity of the samples at 12, 24, 48-192 h did not change considerably compared to the initial samples in both groups. Cytological examination revealed similar significant differences of the 12-24 sampling times in total white blood cell count and mononuclear cells; and 24 of the neutrophil count in both groups compared to the time 0. The only difference between the tramadol and lidocaine groups was seen for mononuclear cells at the time 24 and neutrophil counts at 24, 48-192 sampling times.

Specific gravity and total protein at time 48 and AST at time 24 showed a significant difference between the two drugs, although glucose, ALP and LDH were not significantly different. AST activity considerably increased in the tramadol group in all sampling times compared to the time 0; although after the most significant increase in time 24, it did start to decrease. In the tramadol group, LDH activity at time 12, specific gravity at time 24-48 and ALP at time 12-24 were significantly different compared with time 0. The results are available in Table 1.

DISCUSSION

Musculoskeletal injuries involving distal limb joints remain the greatest cause of loss of athletic performance and wastage in the racehorse industry (Todhunter and Lust, 1990). Among these, a common presentation is primary synovitis (Palmer and Bertone, 1994), usually located in the carpal and metacarpo/metatarsophalangeal joint of young horses in active training (Adams and Stashak, 1987). Diagnostic and surgical arthroscopy became popular in horses during the 1970s and 1980s (Muttini *et al*., 2003) and nowadays is being done in equine practice as well as human medicine. Effective and adequate postoperative

analgesia is considered to be an essential requirement for day case surgery (El-Hamamsy and Dorgham, 2009). Postoperative analgesic after arthroscopy has also been examined after the intraarticular administration of conventional local anesthetics (Khoury *et al*., 1992). Traditionally, bupivacaine has been injected into the knee joint after arthroscopy to reduce postoperative pain, but the duration of effective analgesia is usually short (Keading *et al*., 1990; Lyons *et al*., 1995). In human medicine, the long duration of analgesic results, lower pain scores and few side effects is reported after intraarticular tramadol (Likar *et al*., 1995; Kürsad *et al*., 1998; Alagol *et al*., 2004).

In veterinary medicine, pharmacokinetic study of tramadol (2.5 mg kg^{-1}) and Its metabolite in donkeys has been done by (Giorgi *et al*., 2010) and the effectiveness of IV administration is concluded. The local anesthetic effects have been shown when administered as an epidural to horses (Natalini and Robinson, 2000). There are no data on the effects of tramadol on the biochemical and cytological properties of the synovial fluid after intra-articular administration in horses to the author's knowledge. Despite the fact that little is known about tramadol in equine, in the present study, 2 mg kg^{-1} was used intraarticularly, which is recommended by (Shilo *et al*., 2008) for parenteral administration in horses.

Lidocaine has used intraarticularly to induce anesthesia/analgesia in human and veterinary medicine (Shafford *et al*., 2004; Ng *et al*., 2009). There are reports on effective intraarticular lidocaine method of analgesia for facilitating the reduction of shoulder dislocations, too (Miller *et al*., 2002; Socransky and Toner, 2005; Fitch and Kuhn, 2008). The use of a contralateral limb as a control in this model, is used by Hawkins *et al*. (1993) and Campebell *et al*. (2004). The volume of 5 ml of 2% lidocaine, which is one of the most commonly used drugs for joint block (Turner 2003), is recommended for intra-articular anesthesia of carpus and is used by White *et al*. (1989) Rose and Frauenfeldre (1982); Todhunter and Lust (1990) and Campebell *et al*. (2004).

Results of synovial fluid analyses at the 0 time indicate the animal's health and proper laboratory techniques. Although Coppo *et al*. (1988) showed that repeated sampling did not change the biochemical findings and cellularity in the synovial fluid; other authors demonstrated that serial arthrocentesis caused synovial fluid alterations. Total white blood cell count and mononuclear cells were not significantly different; although the neutrophil count revealed a difference between the lidocaine and tramadol treated groups, which was greatest at 24 h after medication and is in agreement with the study of (White *et al*., 1989). Mucin clot quality is a representative indication of the viscous property and quality of hyaluronic acid present in synovial fluid (Mcllwraith and Trotter, 1996). In the articular disease process, reduced polymerization of the hyaluronic acid molecule will result in clot of poor quality and variable degree of flocculation appearing in a cloudy solution (Smith *et al*., 2002). In the present study, mucin clot quality test revealed no significant differences between the various sampling times, either in each group or between them.

There is a close correlation between the activities of Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST) and Lactic Dehydrogenase (LDH) in synovial fluids and the clinical severity of joint disease (Van Pelt, 1962). In the tramadol group, AST activity was significantly higher after medication in all sampling times, compared to the lidocaine group. ALP and LDH showed no difference between the two groups. Cartilage has a much lower level of all isoenzymes of LDH and consequently, lesions of the articular cartilage do not make a significant contribution to the overall LDH elevation (Stashak, 2002).

Overall, it seems that the slight differences of the neutrophil count, AST activity total protein and specific gravity between the two drugs and between various sampling times compared to the time 0 have been attributed to the physiological adaptation process of the joint, trauma of the needle insertion and repeated arthrocentesis. There were no signs of discomfort, lameness and inflammation throughout the study. Viscosity and mucin clot quality were normal and no detectable joint distension was seen.

Considerably lower side effects including respiratory, cardiovascular and gastrointestinal are of the main priorities of the tramadol compared to the other opioids, especially morphine, which is a controlled drug. Clinical studies have confirmed the analgesic efficacy of the tramadol after intraarticular administration in human and it is documented that morphine and tramadol, at the doses used, provide similar analgesia when given intraarticularly, so tramadol can be an alternative to morphine for postoperative analgesia after arthroscopic surgery (Akinci *et al*., 2005). Reduced intensity of joint pain and

significant reduction of synovial fluid concentration of substance P (which is involved in joint damage, inflammation and pain) is revealed in tramadol treated patients with knee osteoarthritis by (Bianchia *et al*., 2003).

CONCLUSION

It is concluded that injection of tramadol into the middle carpal joint has no considerable adverse effects on the synovial fluid composition in this joint, also will not cause in lameness. Therefore, it can be considered as a good analgesic with the fewest side effects and could be used after arthroscopic surgery in horses, although further studies of this drug's clinical efficacy for the treatment of articular pain in horses are warranted.

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