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Intra-articular ketamine administration in equine midcarpal joint: clinical, biochemical and cytological evaluations

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Summary

Providing suitable analgesia following diagnostic and therapeutic arthroscopic surgeries, that are considered to cause some degree of postoperative pain, is a necessity in equine practice. The aim of the present study was to evaluate the equine synovial fluid biochemical and cytological changes as well as clinical assessments of the joint following intra-articular administration of ketamine. Six adult healthy donkeys were selected after clinical examination. Synovial fluid samples were taken from both middle carpal joints after routine preparation. Ketamine 2 mg/kg 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 and 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. Joint circumference, flexion test and lameness examination, stimulation of the joint skin area and radiographic examination were performed as clinical evaluations. Comparison of treatments was performed by nonparametric sign test and Wilcoxon rank sum test. Significance level was set to $P \leq 0.05$. In the ketamine group, increased joint circumference, positive flexion test and negative response to the ball-point pressure of the joint skin area were seen, unlike that of lidocaine. Mucin clot quality test and viscosity, the amount of total nucleated cell count (TNCC), mononuclear and neutrophil count, specific gravity, total protein content, ALP, AST and LDH of the ketamine treated joints revealed considerable differences between various sampling times compared to the 0 time and also between the ketamine and lidocaine groups ($P>0.05$). It was concluded that intra-articular ketamine administration in equine carpal joint resulted in acute inflammatory changes, and failed to demonstrate analgesia; therefore, it is not safe to the joint environment and is not recommended as a local analgesic following arthroscopic surgeries.

Key words: Intra-articular ketamine, Lidocaine, Middle carpal joint, Synovial fluid, Equine

Introduction

Ketamine is considered to be a noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist, although effects on opioids, muscarinic receptors, and voltage-sensitive calcium channels have been reported (Kawamata *et al*., 2000). More recently, it has gained popularity in use at subanesthetic doses to produce analgesia.

Ketamine is effective in treating neuropathic and nociceptive pain at subanesthetic doses and causes none of the side effects that have been associated with doses that produce dissociative anesthesia, such as tremors, tonic spasticity, or convulsive seizures (Valverde and Gunkel, 2005). It has been used alone for caudal epidurals in awake horses, producing 30 to 90 min of analgesia, with mild sedation, but non cardiorespiratory changes (Gomezde de Segura *et al*., 1998).

Today ketamine is gaining increased acceptance as an analgesic that can be used in conjunction with other drugs for standing surgical procedures or to provide multimodal analgesia for acute or chronic

pain. In addition, ketamine has been shown to produce local anesthetic and potent anti-inflammatory effects (López-Sanromán *et al*., 2003). Systemic administration of ketamine and many other centrally acting analgesic drugs is unfortunately often accompanied by side effects. Local application of NMDA receptor antagonists could therefore be an alternative (Ayesh *et al*., 2008).

On the other hand, nowadays, diagnostic and therapeutic arthroscopic surgery is becoming highly frequent in equine practice. Based on this fact, providing a suitable analgesia following this procedure, as a cause of moderate degree of postoperative inflammatory orthopedic pain, is a challenge. So, many studies are now focused on finding and introducing a perfect practical protocol that would be safe to the joint environment, too, in addition to its analgesic effect.

Yu *et al*. (1996) have demonstrated NMDA receptor in rat joints. Intra-articular use of ketamine has been reported to be efficacious, especially in arthritic joints, meanwhile, there are other studies which have reported no analgesic efficacy for intra-articular ketamine administration; so it seems to be a controversial issue (Huang *et al*., 2000; Rosseland *et al*., 2003; Batra *et al*., 2005; Montazeri *et al*., 2006; Borner *et al*., 2007; Ayesh *et al*., 2008).

Chemical synovitis, often referred to as joint flare, can occur in response to the injection of corticosteroids, local anesthetics, hyaluronic acid, 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 this, there are few limited studies of intra-articular administration of the ketamine in human medicine, and to the author's knowledge, there is no study evaluating its intra-articular administration in equine; although detomidine HCl, lidocaine, mepivacaine and morphine have been used intra-articularly in the horse. Therefore, the aim of the present study was the evaluation of cytological, biochemical and clinical responses of the joint following intra-articular ketamine administration. These effects were compared to the lidocaine as a control; which is one of the most popularly used drugs for joint blocks in human and veterinary medicine.

Materials and Methods

Six adult healthy native donkeys (Iranian donkey breed), aged 2-3 years, weighing 200 to 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% (Pasteur Institute of Iran) in the left joint and ketamine 10% (Alfasan; Woerden-Holland), 2 mg/kg 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 and 192 h after intra-articular administration of the drugs from both middle carpal joints in flexed position. After each arthrocentesis, the affected carpus was placed in a standard wrap.

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. A blood film for differential cell counts was prepared and then stained using Giemsa. Viscosity was evaluated subjectively by observing the length of the strand formed by a drop of synovial fluid as it is expelled from the end of the syringe. Strands formation more than 2.5 cm long before breaking was considered as normal.

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, a tight ropy clump in a clear solution; fair, a soft mass in a very slightly turbid solution; poor, a small friable mass in a turbid solution; and very poor, 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).

At each sampling time, the joints were evaluated for signs of inflammation, effusion, pain on maximal flexion of the carpus and circumference (cm) at the level of middle carpal joint (distal to the accessory carpal bone) using rope and ruler. Joint skin area was pressed using the tip of a ball-point object to check for any sign of analgesia at all examination times. Animals were evaluated for lameness following one-minute flexion test of the front limbs using a modification of the standard American Association of Equine Practitioners grading system (0 = none, 1 = difficult to observe and inconsistent, 2 = difficult to observe and consistent, 3 = moderately discernible, 4 = obvious lameness with full weight bearing, and 5 = non-weight bearing).

Radiographic examination at the baseline and 2 weeks after injection was performed in dorsopalmar view from both limbs. Radiographs were evaluated for the presence of joint effusion, periarticular osteophytes, enthesiophytes, subchondral irregularities, decreased or asymmetric joint space, bone destruction and extracapsular thickening/swelling.

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 analysed using a nonparametric sign test and the rest using Mann-Whitney and Friedman tests. Differences were considered significant at $P \leq 0.05$.

Results

Clinical examination of the ketamine treated joints showed some signs of inflammation (effusion, heat and pain in flexion) which could be seen the most at 48 h after administration. In this group, comparison of joint circumference over time demonstrated a considerable difference of 24, 48 and 192 h sampling times to the time 0. It was significantly different at 48 and 192 h compared with the lidocaine group.

Flexion test followed by lameness evaluation was done before any synovial fluid sampling; it was negative in all intra-articular ketamine medicated animals at the base line; grade 1 lameness was observed in 1 animal at 12 h (median score, 0; range, 0-1), and at 24 h, five animals had grade 1 and one other had grade 2 (median score, 1; range, 1-2). At time 48, three animals revealed lameness grade 3, and grade 2 was seen in the rest (median score, 2.5; range, 2-3). At the 192 h sampling time, 1 animal showed lameness of grade 3, grade 2 was seen in 3 animals and grade 1 in 2 others (median score, 2; range, 1-3). Pressure with the tip of a ball-point to the joint skin area failed to demonstrate any sign of analgesia and positive reaction to the stimulation could be seen at all examination times (5, 10, 30, 90, 180 and 300 min after intra-articular administration) like time 0 (immediately before medication). In lidocaine treated joints there was neither detectable lameness nor signs of inflammation throughout the study.

Dorsopalmar radiographs of both limbs at 2 weeks after medication revealed thickening of the joint capsule, joint effusion and increased joint space in all ketamine treated carpal joints; meanwhile, not one of the mentioned signs could be seen in the lidocaine group (Fig. 1).

The results of the mucin clot quality test after intra-articular ketamine are presented below:

Time 12; 2 good and 4 fair
Time 24; 5 fair and 1 poor
Time 48; 1 fair and 5 poor
Time 148; 3 fair and 3 good

Mucin clot quality tests were uniformly normal in the lidocaine group throughout the study. Viscosity of the samples in the ketamine group was normal in 6 (all), 4, 3, 1, and 4, at 0, 12, 24, 48 and 192 h sampling times, respectively. In the lidocaine group, there was no considerable change compared to the initial samples.

Total nucleated cell count revealed an increasing pattern from time 0 till 48 h post injection, and a decreased pattern at time 192. It was significantly different from the

lidocaine group at the times 48 and 192, similar to the mononuclear cell count (MNCC). Also, both TNCC and MNCC showed a significant difference at all sampling times (12, 24, 48 and 192) in comparison with the time 0. Neutrophil count revealed a significant difference at 24 and 48 h sampling times compared to the lidocaine group; and it had a considerable difference at times 24 and 48 in comparison with other sampling times.

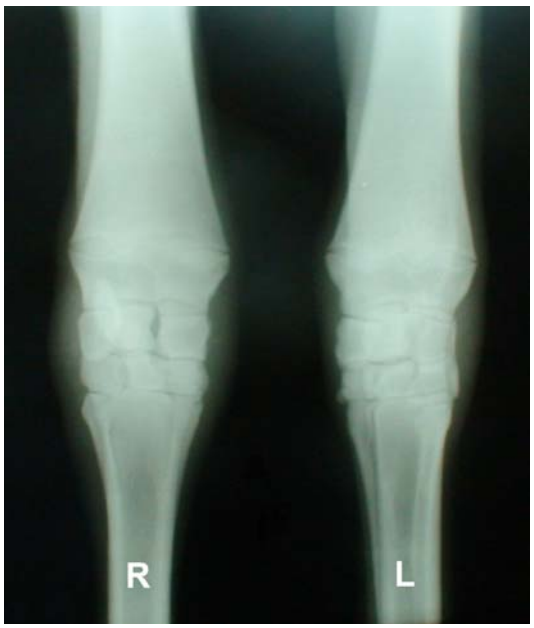

Fig. 1: Dorsopalmar radiographs of the right (R) and left (L) limbs at 2 weeks after intra-articular medications; lidocaine in the left and ketamine in the right middle carpal joint. Thickening of the joint capsule, joint effusion and increased joint space is observed in the ketamine treated joint

Total protein content of the synovial fluid following intra-articular ketamine administration started to decrease till the last sampling time in time 192; and it was significantly different at all times compared to the time 0. In comparison with lidocaine, significant differences were demonstrated at times 24, 48 and 192.

Glucose content decreased slightly following medication and reached the minimum at 24 h sampling time, following a slight increase till 192, although it did not reach the content of the first sampling time. Despite these changes, no significant difference was seen between the different sampling times compared to the 0 time or to the similar times of the lidocaine group.

Significant difference was seen for specific gravity in all sampling times (12, 24, 48 and 192) compared to either the similar sampling times of the lidocaine group or the 0 time of the same group. The highest amount of specific gravity was seen at time 48 and decreased at time 192.

Enzyme activity (LDH, AST and ALP) started to increase following medication and, after reaching the maximum amount at 24 h for LDH and ALP, and 48 for AST, started to decrease. In comparison to the lidocaine group, significant differences were apparent at times 24 and 48 for LDH, 48 and 192 for AST, and 24, 48 and 192 for ALP. In comparison to the time 0 in the same group, ALP and AST activity revealed considerable differences in all sampling times (12, 24, 48 and 192), in which differences were noticed at 12, 24 and 48 for LDH. The results are shown in Table 1.

Discussion

Intra-articular injection of 2 mg/kg ketamine into the equine middle carpal joint resulted in synovitis and also failed to demonstrate analgesia. The presence of ionotropic glutamate receptors, NMDA receptors, on peripheral sensory axons is the basis of peripheral ketamine-induced analgesia (Huang *et al*., 2000). It is demonstrated that abaxial sesamoid block with ketamine produces adequate analgesia in horses, with an onset of action of 2 min and a maximal duration of action of 15 min (López-Sanromán *et al*., 2003).

Controversial results are reported from different studies on analgesic efficacy of the ketamine following intra-articular administration. Despite some reports that confirm the analgesic efficacy (Batra *et al*., 2005; Borner *et al*., 2007), other results failed to demonstrate it (Huang *et al*., 2000; Rosseland *et al*., 2003; Montazeri *et al*., 2006; Ayesh *et al*., 2008); our results are in agreement with the latter.

Lidocaine was used intra-articularly to induce anesthesia/analgesia in human and veterinary medicine (Shafford *et al*., 2004; Ng *et al*., 2009). There are reports on effective intra-articular lidocaine method of analgesia for facilitating the reduction of

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 ketamine and lidocaine administration

Parameter	Sampling time (h)									
	0		12		24		48		192	
	Lidocaine	Ketamine	Lidocaine	Ketamine	Lidocaine	Ketamine	Lidocaine	Ketamine	Lidocaine	Ketamine
Total WBC (cell/µl)	132.5	181.5	2188.8*	1608.2*	3146.5*	3090.2*	962.17^{a}	5742.4^{*b}	307.17^{a}	1867.7^{*b}
Neutrophils (cell/µl) (%)	4.33 (3.06)	8.23 (4.53)	329.66 (15.13)	163.16 (14.4)	1321.5* (42.76)	1531.1* (49.11)	395.33^{a} (40.96)	3098.6^{*b} (53.01)	231.66^{a} (7.54)	422.5^{b} (22.8)
Mononuclear (cell/µl)	128.16	173.27	1859.1*	1445*	1825*	1559*	566.83^{a}	2643.5^{*b}	284^{a}	1445.1^{*b}
Total protein (gr/dl)	1.96	2.17	5.22*	4.13*	4.39^{*a}	6.64^{*b}	2.48^{a}	7.77^{*b}	2.6^{a}	7.91^{*b}
Glucose (mg/dl)	87.92	89.5	118.45*	85.45	92.1	65.45	83.04	65.68	92.13	68.43
Specific gravity	1.003	1.005	1.006^{a}	1.011^{*b}	1.008^{*a}	1.013^{*b}	1.005^{a}	1.022^{*b}	1.005^{a}	1.010^{*b}
AST (U/l)	40.5	44.32	40.5	91.16*	54.66*	101.83*	44.33^{a}	126.5^{*b}	39.66^{a}	96.66^{*b}
ALP (U/l)	82.61	101.3	141.13*	199.67*	121.6^{*a}	320.77^{*b}	94.62^{a}	319.19^{*b}	76.83^{a}	234.32^{*b}
LDH (U/l)	97.47	103.45	101.38	104.89*	106.26^{a}	118.94^{*b}	96.55^{a}	106.4^{*b}	96.44	96.08
Joint circumference (cm)	22	22.55	22.58	23.25	23.83*	24.42*	24.67^{*a}	27.5^{*b}	22.58^{a}	25.75^{*b}

AST aspartate aminotransferase, ALP alkaline phosphates, LDH lactate dehydrogenase. * Significant difference with day 0 ($P<0.05$). ^{a} Significant difference with ^{b} in the same time between groups

shoulder dislocations, too (Miller *et al*., 2002; Socransky and Toner, 2005; Fitch and Kuhn, 2008). Lidocaine and mepivacaine are the most commonly used drugs for joint blocks in horses (Turner, 2003).

The use of a contralateral limb as a control in this study, is used by Campebell *et al*. (2004) and Kawack and McIlwraith (2011). 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 has been used by Rose and Frauenfeldre (1982), White *et al*. (1989), Todhunter and Lust, (1990) and Campebell *et al*. (2004). No clear differences have been identified between synovial fluid responses to the intra-articular lidocaine and mepivacaine in equine carpal joint (White *et al*., 1989).

Synovial fluid should be the best for characterization of events occurring in a specific joint, especially in order to evaluate the safety of a drug to the joint environment. Results of synovial fluid analyses at the 0 time indicate the animal's health and proper laboratory techniques. Synovial fluids can be categorized into non-inflammatory, inflammatory, purulent and hemorrhagic types (Duncan *et al*., 1994). Gross and cytological analysis of synovial fluids can aid in the diagnosis of a variety of joint diseases, including ligaments damage, trauma, neoplasia, infectious and non-infectious synovitis and arthritis, osteoarthritis and immune-mediated polyarthritis (Baniadam and Razi Jalali, 2005).

In the present study, the greatest change of total white blood cell count was seen at 24 and 48 h for lidocaine (which is in agreement with the study of White *et al*. (1989) and ketamine, respectively. After these times, it decreased during latter sampling time(s). A primary synovitis in ketamine treated joints can be concluded from the cytological results.

The normal total protein value for synovial fluid is considered to be below 20 g/liter (Van Pelt, 1974) whilst values above 40 g/liter indicate severe inflammation (McIlwraith, 1987). In ketamine treated joints, unlike glucose content that started to decrease non-significantly during the sampling times, total protein revealed a rise until the end of the study and it was significantly different compared to the lidocaine group at 24, 48 and 192 sampling time. Total protein concentration in the synovial fluid increases in inflammatory and infectious arthritis and synovitis (Duncan *et al*., 1994).

Mucin clot quality is a representative indication of the viscous property and quality of hyaluronic acid present in synovial fluid (McIlwraith, 1996). In our study, mucin clot quality test of the ketamine treated joints revealed

considerable differences between the various sampling times compared to the 0 time and also to the lidocaine group. Similar results were seen for the viscosity of the synovial fluid samples. Released lysozyme into the inflamed joint by polymorphonuclear cells, monocytes, synoviocytes and chondrocytes is capable of degrading the hyaluronic acid (Palmer and AL, 1994). 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).

There is a close correlation between the activities of ALP, AST, and LDH in synovial fluids and the clinical severity of joint disease (Van Pelt, 1974). In the ketamine group, except for LDH activity at 198 h sampling time, all enzymes showed significantly different activity to the pre-treatment time; meanwhile the lidocaine group revealed no considerable difference. The maximum activity of the enzymes was seen at 48 sampling time for ALP and AST; and 24 sampling time for LDH, after these sampling times, a decrease was observed till the end of the study. It has been suggested that the main part of the LDH activity known to be increased in diseased synovial fluid is derived from disruption of leucocytes, abundantly present in the fluid of diseased joint (Ng *et al*., 2009).

Clinical and radiographic evaluations of the joints were in agreement with biochemical and cytological results. Signs of inflammation (effusion, heat and pain in flexion), lameness following flexion test and joint circumference were seen most at 48 h sampling time. Overall, different biochemical, physical and cytological results of the synovial fluid and also clinical evaluations in ketamine treated joints showed a considerable acute inflammatory process of the joint, although the severity of the synovitis showed some signs of improvements at 192 h following intra-articular medication and synovia seemed to start to return to the base line to some extent. These changes take place following increased vascularization, edema, inflammatory cell infiltration, increased synoviocyte numbers, and villous hypertrophy in inflamed synovial membrane and mechanical disruption of blood-synovial barrier. Joint effusion and increased joint space could be seen in dorsopalmar radiographs of the carpal joint of ketamine medicated limb and confirmed the inflammatory processes after 2 weeks. In diseased synovial structures, the synovial fluid volume often increases as a result of inflammatory infiltrate (Viitanen *et al*., 2001).

In the lidocaine group, slight observed variations of the measured factors between various sampling times compared to the time 0 can be 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 in this group. Viscosity and mucin clot quality were normal and no detectable joint distension was seen.

It is concluded that intra-articular injection of 2 mg/kg ketamine, which is the recommended dose for the systemic administration, into the equine middle carpal joint will result in synovitis and arthritis with considerable adverse effects on the synovial fluid composition and also clinical assessments of this joint; intra-articular dosage of the ketamine in equine has not been defined. It also failed to demonstrate analgesia; therefore, it is not safe to the joint environment and is not recommended as a local analgesic following arthroscopic surgeries.

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