Correlation of post-operative pain and levels of creatin phosphokinase enzyme following ovariohysterectomy in cats

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Abstract:

BACKGROUND: Recognition of pain is challenging in veterinary medicine due to lack of verbal communication and universal pain assessment system. Increase in biochemical parameters have been shown to have direct correlation with level of postoperative pain. **OBJECTIVES:** The purpose of the present study is to evaluate the serum levels of CPK and investigate any correlation in serum levels of CPK and postoperative pain following ovariohysterectomy in feline. **METHODS:** Conventional midline ovariohysterectomy was performed in 24 healthy female queens. Serum levels of cortisol, CPK and glucose were measured prior to surgery and at 1 and 3 and 24 hours after the surgery. Also, VAS was used to assess level of post-operative pain. Data was analyzed using repeated measure ANOVA. Spearman's rank correlation coefficient was used to identify any correlation between level of pain and CPK after the surgery. **RESULTS:** The score of pain significantly increased at 1 and 3 hours after the surgery in all of the cats ($p=0.001$). The concentration of cortisol and CPK significantly increased after the surgery in comparison to the values prior to surgery ($p<0.001$). Also, the concentrations increased significantly at 3 hours after the surgery compared to the values at 1 hour after the surgery ($p<0.001$). In 24 hours after the surgery results revealed that serum level of cortisol returned to its normal values but CPK was still higher compared to the values prior to surgery. Significant correlation was detected between the level of pain and CPK after surgery ($p<0.05$). **CONCLUSIONS:** It is concluded that there is a correlation with VAS score of pain and serum levels of Cortisol and CPK at early hours after the surgery. CPK might be used as an indicator of pain in early hours after the surgery in feline. However, the assessment of pain in cats is not possible based on its values alone.

Introduction

Pain is a result of tissue damage following surgery that is associated with decreased gastrointestional motility, tachycardia, respiratory depression, decreased food intake, and even delayed wound healing. Therefore, recognition of pain in patients is very valuable in pain management in veterinary medicine since it results in earlier recovery of the patient and,

consequently, earlier return to normal conditions (Minto et al., 2013; Johnson, 1991; Taylor, 2000). Because of the lack of verbal communication, pain assessment in small animals seems challenging. Many pain scales and indicators of pain like visual analogue scale, numerical rating scale, simple descriptive scale, and behavioral and physiological response rating scales have been introduced in veterinary medicine but there is no universal or self-sufficient pain assessment system (Firth and Haldane, 1999; Holton, 1998; Mathews, 2000; Mich and Helleyr, 2008). Most of the developed scales are subjective and rely on many external factors. Due to the lack of a certain subjective assessment of pain in animals, a multimodal approach is considered accurate and appropriate (Maticic et al., 2010; Mich and Hellyer, 2008). Therefore, if there is a measurable quantitative indicator of pain to be proved to have a correlation with the level of pain, assessment of pain will be very precise, easy, and reliable.

The visual analogue scale is proved to be a sensitive and reliable behavioral scale to assess pain and has been successfully applied in many studies (Pascoe, 2000; Conzemius et al., 1996; Budsburg et al., 2002). However, the subjectivity of the scale and the difference among observers is still an issue (Grant, 2006; Maticic et al., 2010). In addition, biochemical parameters have been shown to be indicators of pain and stress in veterinary medicine. Serum levels of cortisol and blood glucose were used as a marker to interpret post-operative pain (Smith, 1996). Serum cortisol concentration is recognized as one of the most objective criteria for pain assessment in animals and found to have a direct relation with post-operative pain in dogs (Grisneaux et al., 1999; Feldsien et al., 2010). Also, another marker of muscle injury is Creatin phosphokinase enzyme (CPK) that has been used in the assessment of pain in veterinary medicine (Hancock et al., 2005). It is shown that the serum level of the enzyme increases after the surgery and there is a correlation with its activity and the histologic changes of the back muscles (Kawaguchi et al., 1997; Arts et al., 2011). Since pain makes the animal reluctant to move and also the severity of pain is related to the invasiveness of the surgery, inflammation, and muscle injury (Maticic et al., 2010; Hancock et al., 2005), we hypothesized that if CPK has a correlation with scores of post-operative pain, it might be used as a biochemical indicator of pain. Therefore, this study was conducted to evaluate the serum levels of CPK and investigate any correlation in serum levels of CPK and post-operative pain following ovariohysterectomy in cats.

Materials and Methods

After approval was received from the University Research Committee, 24 healthy DSH queens were selected for the study. Their body weights ranged from 3.1 to 4.4 kg, and they were aged 6 months to 3.4 years with a mean of 1.1±0.6 years. The cats were maintained at the same place and lighting conditions a few days prior to surgery. A control blood sample was taken from all the cats to measure the biochemical parameters including serum levels of glucose, cortisol, and CPK prior to surgery. The blood samples for the biochemical parameters analysis were collected from the cephalic vein at the same time. General anesthesia was performed with the administration of a combination of ketamin (Ketalar®, 10%, Alfasan, Woerden, Holland) 6.5 mg/kg and diazepam (Valium®, 10mg/2mL, Razi, Iran) 0.27 mg/kg, intravenously and continued by 1.5-2.2% isoflurane (Forane, Abbott Laboratories Ltd, UK) in oxygen following the intubation of the cats. A single dose of cefazolin (Ancef; Kefzol®, 1gr, Razi, Iran) 20 mg/kg/IV was administered as prophylaxis immediately prior to surgery. Also, all the cats received 0.5 mg/kg/ IV meloxicam (Metacam®, 7.5 mg/ml, Boehringer- Ingelheim, Germany) at the time

of induction of anesthesia. Aseptic preparation of the patients' abdomen was performed in dorsal recumbency similarly. A midline skin incision was started from the umbilicus and extended 3-4 cm caudally. Following the identification of the more accessible ovary, the suspensory ligament and mesovarium were transected. Then, two simple ligatures using 3-0 polygalactin 910 were placed around the ovarian pedicle, and the ovary was transected and removed. The uterine artery and vein were ligated and severed 0.5 cm above the cervix. The stump was checked for hemorrhage and released to the abdomen. Finally, the incision was closed in a routine three-layer manner. The same surgeon performed all the surgeries.

Serum level of cortisol, CPK, and glucose were measured prior to surgery and at 1, 3, and 24 hours after the surgery. For cortisol, the blood samples were taken in the EDTA tubes and the samples were analyzed by a Dia Plus Immunoanlayser kit and using Roche Cobas e 411. For CPK and glucose, blood was taken in 1.5 mL microvettes and tested on an Idexx VetLab. In order to assess the level of pain, a trained observer recorded the score of pain in all the cats just before the surgery and at 1, 3, and 24 hours after the surgery using the Visual analogue scale (VAS) used by Conzemius et al. (1997) and Slingsby et al. (2000). The scale used subjective criteria including behavior, movements, mental status, temper, etc. An analysis of repeated measures with 95% Confidence Interval was carried out by the General Linear Model (GLM) procedure of the SPSS version 16.0. A p-value of less than 0.05 was statistically considered significant. A spearman's rank correlation coefficient was used to relate VAS scores to serum Cortisol, CPK, and glucose. Data were presented as Mean±SEM. A value of $p<0.05$ was considered significant.

Results

Mean pain score measured by Visual Analogue Scale was 2.3±0.22 and 2.8±0.29 and at 1 and 3 hours following the surgery respectively. The score of pain significantly increased at 1 and 3 hours after the surgery in all of the cats ($p=0.001$). Although 3 hours after the surgery Mean±SEM of pain score was higher compared to 1 hour after the surgery, the difference was insignificant ($p>0.05$). The cats did not seem to have any pains 24 hours after the surgery. The concentration of blood glucose was significantly increased one hour after the surgery ($p=0.0013$). However, the increase was insignificant in cats at 3 hours following the surgery ($p>0.05$). Results regarding serum levels of cortisol and CPK indicated that the concentration of cortisol and CPK significantly increased after the surgery in all the cats comparing to the values prior to the surgery ($p<0.001$). Moreover, the concentrations increased significantly at 3 hours after the surgery compared to the values at 1 hour after the surgery ($p<0.001$). 24 hours after the surgery, the results revealed that serum level of cortisol returned to its normal values but CPK still was higher compared to the values prior to surgery. Values of blood concentration of glucose, cortisol, and CPK are illustrated in Table 1. There was a strong correlation between the VAS pain scores and serum cortisol. Also, a significant correlation was detected between the VAS pain scores and CPK at 1 and 3 hours

Table 1. Serum levels of glucose (mg/dl), cortisol (µg/dl), CPK (IU/l), and score of pain (Mean±SEM) prior, 1, and 3 hours following ovariohysterectomy in cats. [abc] Values within rows with different superscripts differ ($p<0.05$).

	Prior to surgery	1 hr after the surgery	3 hr after the surgery	24 hr after the surgery
Glucose (mg/dl)	129±21.21[a]	323.2±47.05[b]	256±74.9 [a]	198±48.3 [a]
Cortisol (µg/dl)	3.21±0.32 [a]	6.93±0.76 [b]	9.00±0.96 [c]	4.33±0.83 [a]
CPK (IU/l)	670.18±130.33 [a]	2752.18±358.27 [b]	3332.27±481.88 [c]	3248.23±544.33 [c]

after the surgery ($p<0.05$; Table 1).

Discussion

Successful pain management requires a valid and reliable assessment of the degree of pain. Because of the inability of animals to describe the level of pain they suffer, it is believed that the accurate recognition of pain needs a multimodal approach and the application of multiple parameters (Maticic et al., 2010). Thus, in this research we used VAS that has been successfully used to evaluate pain in dogs and cats to evaluate post-operative pain (Conzemius et al., 1997; Slingsby et al., 2000). In addition, because biochemical parameters have been used as markers of pain in veterinary medicine (Maticic et al., 2010), the alteration of serum concentration of cortisol, CPK, and glucose were assessed to investigate any correlation with pain.

Ovariohysterectomy produces mild to moderate post-operative pain and is used as a standard surgery to assess pain in animals (Genta and Fee, 1992). The score of pain significantly increased at the early hours after the surgery and decreased a day following the surgery. The concentration of cortisol significantly increased at 1 and 3 hours after the surgery and was very close to its normal values 24 hours after the surgery. The dynamic of changes of serum cortisol was very similar to VAS pain scores and a significant correlation was identified between these two parameters ($p<0.05$). Serum cortisol concentration is recognized as one of the most objective criteria for pain assessment in animals and found to have a direct relation with post-operative pain (Smith et al., 1996; Feldsien et al., 2010). Secretion of cortisol together with glucose typically increase during stress, so they are not specific indicators of pain (Maticic et al., 2010). Both the duration and extent of trauma during the surgery will result in an increase in the serum levels of cortisol. However, because the condition, duration, and type of the surgery were similar to the patients, the increase in cortisol was mainly due to pain in this study. The changes in blood glucose did not correlate to the VAS score of pain. Therefore, the blood level of glucose was not a reliable marker of pain in the present study because it decreased at three hours after the surgery, the time that cats had the highest pain score and were greatly suffering. Glucose has been used as an indicator of pain in newborns and animals (Smith et al., 1996). Similar results were obtained in cranial cruciate rupture surgery in dogs by Maticic et al. (2010).

In the present study, CPK increased significantly at early hours following the surgery and remained high a day after the surgery. It was during the time VAS scores of pain indicated that the cats did not suffer from pain generally. The highest reported pain score was between 3 to 6 hours after ovariohysterectomy, and the use of analgesic medications is not essential after 24 hours following the procedure (Slingsby et al., 2000, Carpenter et al., 2004). There was a correlation between VAS scores of pain and CPK changes at 1 and 3 hours after the surgery. The values of CPK stayed above the normal values, while VAS scores and cortisol indicated that the cats did not experience pain 24 hours after the operation. Different results have been reported in the literature in this regard. Kawaguchi et al. in 1997 reported that the serum level of CPK reaches a maximal value 1 day after the surgery. However, Shin et al. indicated that no significant difference in the serum levels of CPK occurred 24 hours after the surgery compared with the pre-operative condition (Shin et al., 2008) .

Creatin phosphokinase has been reported to be an indicator of muscle damage and operative trauma (Hancock et al., 2005). The increase in creatinine phosphokinase has been shown to occur in response to anesthesia with halothane and propofol, as well as with intramuscular injections (Aktas et al., 1997; Mat-

icic et al., 2010). None of the injections prior and during the procedure were intramuscular, so other sources of pain were eliminated for interpreting CPK values. Pain causes the animal to be reluctant to move after the operation. The recumbency following the surgery in addition to intra-operative trauma leads to muscle injury. This might lead to an increase in the values of CPK. Although CPK increases with skeletal muscle injury and recumbency, it has not been reported as a reliable indicator for pain in dogs (Austin et al., 2003; Hancock et al. 2005).

Conclusion: The results of our study indicated the concordance of the dynamics of pain measured by the VAS with cortisol and CPK at the early hours after the surgery. These findings demonstrated that CPK is a good indicator of pain in cats a few hours after the operation when the highest score of pain is expected. However, it is not recommended for assessing pain in cats based on its values alone. In addition, glucose was not a reliable indicator of pain.

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بررسي وجود ارتباط بين درد پس از عمل جراحي برداشت رحم و تخمدان و سطوح سرمي آنزيم كراتين فسفوكيناز در گربه

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چكيده

زمينه مطالعه: ارزيابي درد در دام‌هاي كوچک به دليل عدم توانايي در بيان درد و فقدان وجود سيستم واحد جهاني سنجش درد همواره با چالش همراه بوده است. مشخص شده است كه بين افزايش برخي از پارامترهاي بيوشيميايي خون و ميزان درد پس از عمل جراحي رابطه مستقيم وجود دارد. **هدف:** هدف از اين مطالعه ارزيابي تغييرات ميزان آنزيم كراتين فسفوكيناز سرم و همچنين احتمال وجود رابطه آماري بين تغييرات اين آنزيم و درد پس از عمل جراحي در گربه‌ها بود. **روش كار:** برداشت رحم و تخمدان به روش معمول جراحي از خط وسط در ۲۴ گربه ماده سالم انجام شد. سطوح سرمي هورمون كورتيزول، آنزيم كراتين فسفوكيناز و گلوكز، در پيش از جراحي و ۱، ۳ و ۲۴ ساعت پس از جراحي اندازه‌گيري شد. همچنين ميزان درد پس از عمل جراحي با استفاده از مقياس سنجش درد بصري VAS در ۱ ، ۳ و ۲۴ ساعت پس از جراحي ثبت شد. داده‌ها به كمک آزمون آناليز داده‌هاي تكراري و همچنين استفاده از ضريب اسپيرمن براي بررسي احتمال وجود رابطه بين ميزان آنزيم كراتين فسفوكيناز و درد پس از عمل جراحي آناليز شد. **نتايج:** ميزان درد به صورت معني‌داري در تمامي گربه‌ها در ۱ و ۳ ساعت پس از جراحي افزايش يافت ($p=۰/۰۰۱$). ميزان هورمون كورتيزول و آنزيم كراتين فسفوكيناز پس از جراحي به صورت معني‌داري نسبت به مقادير پيش از جراحي افزايش يافت ($p<۰/۰۰۱$). نتايج نشان داد كه در ۲۴ ساعت پس از جراحي ميزان آنزيم كراتين فسفوكيناز همچنان نسبت به ميزان پيش از جراحي به صورت معني‌داري بالاتر بود. رابطه مستقيم معني‌داري بين ميزان درد پس از عمل و ميزان آنزيم كراتين فسفوكيناز مشخص شد ($p<۰/۰۵$). **نتيجه‌گيري نهايي:** رابطه مستقيم معني‌داري بين ميزان درد پس از عمل جراحي و سطوح سرمي هورمون كورتيزول و آنزيم كراتين فسفوكيناز در ساعات اوليه پس از جراحي مشاهده شد. آنزيم كراتين فسفوكيناز مي‌تواند به عنوان شاخصي در سنجش درد در ساعات اوليه پس از عمل در گربه‌ها كه درد در ميزان حداكثر مي‌باشد استفاده شود.

واژه هاي كليدي: كورتيزول، آنزيم كراتين فسفوكيناز، گربه، درد پس از عمل جراحي

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