An evaluation of changes over time in serum creatine kinase activity and C-reactive protein concentration in dogs undergoing hemilaminectomy or ovariohysterectomy

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ABSTRACT
The extent of trauma in a patient can be difficult for a clinician to quantify. A prospective study was performed on 2 groups of dogs undergoing either ovariohysterectomy or hemilaminectomy. The serum activity of creatine kinase and serum concentration of C-reactive protein were evaluated preoperatively and then at 4, 6, 8, 12, 24 and 48 hours postoperatively in both groups. The results were compared statistically both within and between the 2 groups. A wide range of results was found at each time point for both analytes although there were no significant differences for either analyte between the 2 surgical groups preoperatively. Thereafter there were significant differences in creatine kinase activity levels between the 2 groups. C-reactive protein concentration results were very similar in the 2 groups with no statistical difference at any time point. The results of this study suggest that the evaluation of CK and CRP at any one time point in a traumatised animal is of limited value. However, the evaluation of the trend of these 2 analytes, even over a relatively short time period, may allow for useful prognostication in clinical cases.

Keywords: C-reactive protein, creatine kinase, hemilaminectomy, ovariohysterectomy, trauma.

INTRODUCTION
Trauma of diverse origins is a common reason for presentation of pets for treatment. It is often difficult clinically to objectively quantify the severity of any trauma suffered by an animal. One approach is to measure changes in the various serum constituents that are known to alter in response to trauma or inflammation. Creatine kinase (CK) is an enzyme found predominantly in skeletal muscle and significantly elevated serum activity is largely associated with muscle damage. It is an extremely sensitive indicator of muscle damage, but is not specific as to cause. Serum elevations in dogs are associated with cell membrane leakage and will therefore be seen in any condition associated with muscular inflammation, necrosis or degeneration. Peak serum activity is expected between 3 and 12 hours after muscular insult and the elevation is roughly proportional to the amount of muscle tissue involved. It is also possible to quantify the mass of muscle damage if the changes in CK values over time after a particular insult are plotted.

C-reactive protein (CRP) is a member of a large group of plasma proteins called acute phase proteins (APPs) which show elevated serum concentrations in response to a broad range of inflammatory stimuli. These proteins are integral to the acute phase response, which is the body’s rapid initial systemic inflammatory reaction to any non-specific tissue injury. Examples of other acute phase proteins are fibrinogen, serum amyloid A, haptoglobin and ceruloplasmin. Most of the APPs, including CRP, are positive in that they increase in serum concentration in response to inflammation. Others are negative, that is they show a decreased serum concentration in response to inflammation. A well known negative APP is the plasma protein albumin. The synthesis of positive APPs is stimulated by various proinflammatory cytokines in response to tissue injury or infection. The main stimulatory cytokines are interleukin-1, interleukin-6 and tumour necrosis factor alpha. The exact functions of the APPs are not completely understood, but it is known that they regulate and coordinate the body’s response to tissue injury. The functions of CRP include suppressing microbial growth, clearance of damaged tissues and regulation of the inflammatory response.

Thoracolumbar disc disease is commonly seen in small animal practice. This is a degenerative condition of the intervertebral discs, often leading to disc extrusion. Most of the dogs seen are chondrodystrophic breeds, in particular Dachshunds. At the Onderstepoort Veterinary Academic Hospital (OVAH), decompression of a thoracolumbar disc extrusion is achieved surgically by means of a hemilaminectomy or pediculectomy over the affected intervertebral space. The surgical approach involves extensive elevation and retraction of the epaxial musculature over the affected disc space resulting in surgical trauma primarily to skeletal muscle. Ovariohysterectomies are performed routinely at the OVAH, generally on healthy pets under a year of age. The standard method of ovariohysterectomy is by means of a midline coeliotomy through the linea alba, with removal of the ovaries and uterus up to the cervix. The linea alba is a midline tendinous aponeurosis of the abdominal muscles. As such there is minimal skeletal muscle damage during the procedure, with surgical trauma confined to the genital tract.

Many parameters are used as measures of trauma. In humans, both CRP and CK have been employed in attempts to quantitatively compare the degree of tissue trauma between different surgical techniques. CK has also been used to evaluate the extent and cause of muscle damage resulting from lumbar back surgery.

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of the spay group. Although the median CK activity on presentation was greater in the spine group, in both spay and spine groups the medians were greater than the upper limit of the OVAH reference interval (49-146 U/l). A dog in the spay group had the highest CK activity of all the dogs in the study. The overall range of CRP concentration was similar in both groups and the medians both fell within the normal reference range of the OVAH (<35 mg/l). A dog in the spay group had the highest CRP concentration.

Figure 3 shows the mean CK values for each time point for both spay and spine groups. Both groups had a similar basic trend of postoperative peak and subsequent decline. It is clear that the spine group had a greater and more sustained increase in activity compared with the spay group, with all postoperative time points being significantly different between the 2 groups (P < 0.05). Within the spay group, only the 4 hour postoperative mean was significantly elevated from the preoperative mean (P = 0.015). Within the spine group, all postoperative time point means were significantly elevated over the preoperative mean (P = 0.015). Median time to maximum CK activity was significantly greater in the spine group (12 h) than in the spay group (4 h) (P < 0.001). Adjusted for sex and body mass, the area under the curve for the spine group was significantly greater than that of the spay group (P < 0.001). Figure 4 shows the mean CK values for each time point for both spay and spine groups. The results appear broadly similar in the 2 groups with an immediate postopera-
tive elevation, although the spay group tended to peak earlier. Median time to maximum CRP concentration was 12 hours in the spay group vs 24 hours in the spine group ($P = 0.066$). However, no significant differences were found between the 2 groups at any time point. All time points, except the immediate postoperative one, were found to be significantly different from the preoperative mean in both the spay and spine groups ($P < 0.05$).

DISCUSSION

The stated hypotheses were found to be supported with 2 exceptions. CK activity in dogs admitted for ovariohysterectomy was found to be greater at presentation than the upper limit of the OVAH reference interval and CRP concentration was not elevated in the spine group on presentation.

The high CK median obtained for the spay group on presentation was unexpected. This study comprised of a group of clinically normal animals and a median more in line with other reference values was expected. Individual animals may have been exposed to potentially confounding preanalytical events not ascertained by the history such as exercise, injections or trauma which may have influenced the results. The same was of course also potentially true for the spine group. Adult levels of CK are reportedly reached in dogs by the age of 7 months. However, other studies have found that dogs between 6 and 12 months of age had a significantly higher mean CK activity level (73 ± 6 SD 27 U/l) compared with dogs over 1 year of age (46 ± 6 SD 22 U/l). This may at least partially account for the high CK level on presentation in the spay group as they were on the whole much younger than the spine group, with 50% of the spay group less than 1 year of age. Although the CK levels in both the spay and spine groups displayed a postoperative rise to peak and subsequent decline, it is interesting that in the spay group, only the 4 hour mean was significantly elevated from the preoperative levels. This suggests that the degree of muscle trauma in the spay group was not only relatively minor but also not sustained. The reason for this is probably that the surgical approach was made through the linea alba with minimal trauma to striated muscle. In addition, it is known that the soft tissues and smooth muscle in the genital tract contain very little CK.

The higher median CK seen in the spine group on presentation was in line with expectations, although statistically there was no significant difference between preoperative spine and spay group activity. The spine group showed an immediate postoperative rise and was significantly elevated over preoperative levels at all time points. The maximum CK activity levels were found at about 12 hours postoperatively. These were perhaps somewhat lower than might have been anticipated when one considers the nature of the surgical procedure, in particular the approach. The greatest CK value in the spine group was below 10000 U/l and only 4 results at any of the time points were over 5000 U/l, with 3 of those from 1 dog. This should be considered against reports that a single intramuscular injection of chloramphenicol can result in CK elevations of greater than 60 times normal values and that in racing sled dogs, for instance, CK activity levels of less than 5000 U/l have been regarded as not significant. These events are of course not directly comparable, but should perhaps make clinicians question the value of isolated CK measurements. A study evaluating CK in dogs undergoing laparoscopic ovariohysterectomy supported this view, concluding that CK was not useful as a measure of surgical stress as the postoperative increases of CK in their patients differed widely, despite their undergoing a uniform procedure. Other authors have further suggested that when utilizing CK as a measure of

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Fig. 1: CK preoperative results for the spay and spine groups. The dashed line represents the upper limit of the OVAH reference interval.

Fig. 2: CRP preoperative results for the spay and spine groups. The dashed line represents the upper limit of the OVAH reference interval.
trauma, isolated measurements of CK activity are of little use. The aim should rather be to obtain a more complete profile of CK activity over time so as to accurately estimate the Area Under the Curve (AUC). This calculation has been used to accurately quantify and compare muscle damage in dogs under various circumstances. This approach perhaps improves CK as a tool, but it necessitates many more CK measurements over time and may be too cumbersome to apply in a clinical environment.

Both spay and spine groups exhibited a wide range in the CRP results on presentation. Although the CRP median for the spine group was higher than that of the spay group, for both groups it fell well within the normal OVAH laboratory range. This makes sense for the spay group where there were no anticipated reasons for increased levels. It is, however, more difficult to explain why the spine group’s preoperative values were not more elevated. It may be that the insult experienced by the body is very localised and therefore that the actual trauma is comparatively minor, despite having potentially severe consequences. The wide range of preoperative values in this study suggests that, as for CK, single CRP measurements, even if elevated, need to be interpreted with caution. The highest preoperative CRP value was found in a clinically healthy dog from the spay group. However, the peak in mean postoperative CRP concentration was at a point between 12 and 24 hours for both groups as it was for CK in the spine group. This time period may thus be the most informative interval in which to monitor both CK and CRP levels in traumatised animals.

The similarity of the postoperative CRP results between the 2 groups was perhaps a little surprising (Fig. 4). In a recent review of acute phase proteins, the authors stated that postoperative CRP increases are approximately proportional to the intensity of surgical trauma. Macroscopically, it seems that the surgical procedure for spinal decompression is much more traumatic than an ovariohysterectomy and that this should be reflected by higher CRP concentrations. CRP values were found to increase much more in orthopaedic surgery compared with ovariohysterectomy in 1 study, and the authors concluded that the rise in CRP was indeed proportional to the intensity of surgical trauma. Another, larger study found the opposite, with the median CRP concentration 24 hours postoperatively being higher in dogs undergoing ovariohysterectomy than in dogs undergoing orthopaedic procedures. In human studies, no correlation has been found between serum CRP concentration and severity of injury or survival. In other words CRP appears to be a sensitive indicator of trauma but cannot be used as a reliable quantitative measure of trauma. Single time point values are, however, probably more applicable to CRP than to CK. CRP is used as an indicator of inflammation in human medicine and clinically relevant cut-off points have been used routinely for various conditions. This has not yet reached the same level of sophistication in veterinary medicine, although the relatively rapid production and clearance of CRP should make it a relevant indication of the clinical situation in an animal at any given time, or at least provide proof of the presence or otherwise of an inflammatory process. The same should be true for any traumatic process. CRP levels may thus be most applicable in the monitoring of cases where a particular inflammatory or trau-
matic condition is already known to be present. CRP cut off points could then be used prognostically, or the CRP trend used to monitor progress and efficacy of treatment.\cite{10,11}

The ability to quantitatively measure the degree of trauma in an injured animal would be useful therapeutically and prognostically. CRP and CK have both been used previously as measures of trauma and were thus evaluated and compared in this study. A wide range of results was obtained for each time point for both CRP and CK, although as groups they followed a predictable pattern over time after trauma. The results of this study suggest that measuring the serum levels of CK and CRP in a traumatised dog at a single time point, for instance on presentation, is of limited value. Establishing the maximal CK and/or CRP levels is similar of little clinical use. The information gained does not necessarily accurately reflect the degree or severity of trauma suffered by the animal. The time interval 12–24 hours post-trauma is potentially the most informative for both analytes, especially if a baseline value is available for comparison. The trend over time, even a relatively short time period of 48 hours, will provide the most meaningful information.

REFERENCES


