

Szent István University
Postgraduate School of Veterinary Science

Prognostic and therapeutic possibilities of canine pancreatitis

Theses of PhD dissertation

Kinga Pápa, DVM

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Supervisor and board members:

Prof. Károly Vörös, DVM, DSc

Department and Clinic of Internal Medicine, Faculty of Veterinary Science

Szent István University

supervisor

Prof. Tibor Gaál, DVM, CSc

Pathology Department, Faculty of Health Sciences

Murdoch University, School of Veterinary and Biomedical Sciences

board member

Prof. Péter Gálfi, DVM, DSc

Department of Pharmacology and Toxicology, Faculty of Veterinary Science

Szent István University

board member

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Kinga Pápa, DVM

INTRODUCTION AND OBJECTIVES

During our studies we examined canine pancreatitis and we investigated the possibilities of a more accurate diagnosis and prognosis. Furthermore, we were looking for more effective ways of therapy.

The course of pancreatitis is very diverse in dogs. Severity is changing from a mild, self-limiting disease to a very severe and even fatal form with systemic complications and concurrent disorders (Steiner, 2010). Detection of complications is extremely important for the precise prognosis, and for the early, specific therapy (Cook et al., 1993, Ruaux and Atwell, 1998*a*, Hess et al., 1999). To facilitate the assessment of the severity, several research teams have developed clinical classification schemes with analyzing clinical and laboratory markers (Ruaux and Atwell, 1998*b*, Mansfield et al., 2008). However, to date, no readily available blood test can predict the severity of the disease.

The aim of our first and second study was to supplement the classification schemes of these earlier researches. At first, we performed a retrospective study. The goal of our work was to investigate the occurrence, the clinical characteristics and outcome of pancreatitis.

In our second study we paid our attention to such laboratory markers that are relatively simple and inexpensive to determine, and are good prognostic indicators in human pancreatitis (Ignjatovic et al., 2004, De Sola et al., 1998). The prognostic value of C-reactive protein (CRP) was described only in few studies including small study groups (Spillmann et al., 2002, Holm et al., 2004, Mansfield et al., 2008), while the prognostic role of thyroxine was not described previously at all in canine pancreatitis.

In our third research we investigated the possibilities of enteral nutrition in dogs. Our study was inspired by the widely accepted theory that prevention of severe complications with early enteral nutrition in acute pancreatitis is even more important than to detect them when they are already present (Qin et al., 2002).

By the adaptation of a human endoscopic technique (Pap et al., 1995), we developed a new endoscopic method of nasojejunal tube placement in dogs. It might become an essential part of the clinical nutrition of dogs with pancreatitis in the future. We also studied chyme sampling through the nasojejunal tube. Chyme analysis is important in obtaining relevant information on enzymatic mechanisms and microflora of the intestines (Harmoinen et al., 2001). Our method may offer a minimally invasive alternative for chyme withdrawal and examination.

OCCURRENCE, CLINICAL FEATURES AND OUTCOME OF CANINE PANCREATITIS (80 CASES)

Publications related to the chapter:

Pápa, K., Máthé, Á., Abonyi-Tóth, Zs., Sterczer, Á., Psáder, R., Hetyey, Cs., Vajdovich, P., Vörös, K. (2011): Occurrence, clinical features and outcome of canine pancreatitis (80 cases). *Acta Vet Hung*, **59**, 37–52.

Pápa, K., Vajdovich, P., Sterczer, Á., Psáder, R., Vörös, K. (2012): A kutyák heveny hasnyálmirigygyulladásának korszerű gyógykezelése. *Magyar Állatorv. Lapja*, **134**, 221–231.

Materials and methods

Our retrospective study involved 80 dogs diagnosed with acute pancreatitis at the Small Animal Hospital of the Department and Clinic of Internal Medicine between 2000 and 2003. Cases were selected based on complex criteria including clinical, laboratory and morphological alterations. To provide a more balanced and reliable evaluation of canine pancreatitis, our study included a large group of dogs with both surviving and fatal cases. We studied correlations between the data of signalment (breed, age, gender, nutritional condition) and the occurrence as well as the severity of acute pancreatitis. We also reviewed the characteristics of co-existing disorders and complications. Furthermore, we assessed the prognostic value of the routine laboratory parameters (hematology, biochemistry, acid-base status).

Results and discussion

We found that in addition to previously mentioned predisposed breeds, Dachshunds and sled dogs (Alaskan Malamute and Laika) are also predisposed to pancreatitis in the Hungarian canine population. The general state on admission of the patients showed no significant correlation with the outcome. Neutered dogs of both sexes appeared to have increased risk for developing acute pancreatitis ($p = 0.0005$). In the study group the incidence of pancreatitis was significantly higher in dogs older than ten years ($p < 0.0001$), and was significantly lower in dogs younger than five years ($p < 0.0001$). Breed, age, gender, neutering and nutritional condition did not influence the outcome of the disease significantly.

Most dogs (70%) were diagnosed as having concurrent diseases, diabetes mellitus (36%) being the most common disorder. Other frequent co-existing disorders were: hepatopathy, hyperadrenocorticism, babesiosis, endocardiosis, gastrointestinal disorders and

hypothyroidism. Local complications, like pancreatic abscess and extrahepatic biliary tract obstruction were rarely observed, whereas systemic complications such as systemic inflammatory response syndrome (SIRS), disseminated intravascular coagulation (DIC), and multiple organ dysfunction syndrome (MODS) were more commonly detected. Dogs having hypothermia ($p = 0.0413$) and metabolic acidosis ($p = 0.0063$) had significantly worse chance to survive pancreatitis. No significant differences were found between the improved and worsened groups regarding the biochemistry parameters and hematology. Nevertheless, measurement of alanine aminotransferase (ALT) and creatinine might have prognostic value, as a marked elevation of these parameters (8-fold increase of ALT and 4.5-fold increase of creatinine) indicated that likelihood of death was more than 75%.

Abdominal ultrasonography is an essential and reliable tool for the diagnosis of pancreatitis. According to our findings, the sensitivity of abdominal ultrasonography is up to 87%. In our study, abdominal ultrasonography had an important role in the detection of morphologic changes of other organs (hepatomegaly, hyperechoic liver and renal cortex, cholestasis, peritonitis, adrenal gland hypertrophy, and splenomegaly) possibly related to pancreatitis.

Conclusions

We concluded that hypothermia and metabolic acidosis are valuable factors for severity assessment in canine acute pancreatitis, and can be involved in the clinical severity index established previously by Mansfield et al. (2008). Our survey might fill in a gap in the veterinary literature, because in the previous studies, evidence of pancreatitis was not based on such strict criteria as described here or mostly fatal cases or small group of dogs were evaluated (Cook et al., 1993, Hess et al., 1999).

THE PROGNOSTIC VALUE OF C-REACTIVE PROTEIN AND THYROXINE IN CANINE ACUTE PANCREATITIS

Oral presentation related to the chapter:

Pápa, K., Máthé, Á., Psáder, R., Abonyi-Tóth, Zs., Szenes, K., Vörös, K., Sterczer, Á. (2010): C-reactive protein és a thyroxin prognosztikai értéke akut pancreatitisben megbetegedett kutyákban. *MTA Állatorvos-tudományi Bizottsága, Akadémiai beszámoló, Klinikumok, gyógyszerstan*

In our retrospective study we found that the simple markers, such as general state and routine laboratory parameters often do not correlate with disease severity. Since we considered the previous clinical classification schemes too difficult and time consuming, we turned our attention to such laboratory markers that are relatively simple and inexpensive to determine, and are good prognostic indicators in human pancreatitis or in canine diseases other than pancreatitis. The purpose of our study was to investigate the prognostic value of CRP and thyroxine.

Materials and methods

The data of 19 dogs with acute pancreatitis admitted to the Department of Internal Medicine and Clinic (Faculty of Veterinary Science, Szent István University, Budapest) between 2007 and 2010 was reviewed. Diagnosis of pancreatitis was confirmed with canine pancreas-specific lipase test (Spec cPL) in each of the dogs. Spec cPL is a commercial test thought to be the most sensitive and specific for canine pancreatitis.

Results and discussion

We did not find significant correlation between the Spec cPL concentration and the outcome ($p = 0.1488$).

The CRP values of most patients (89%) were greater than the upper limit of the reference range in our survey. All dogs but one had concurrent (partly inflammatory or neoplastic) disorders as well, which might have contributed to the elevation of CRP concentration. Although the mean CRP concentration for nonsurvivors was higher than the value for survivors, the difference was not significant ($p = 0.07131$).

In conclusion, CRP concentration in patients with severe acute pancreatitis was similarly high for 3–5 days following the onset of clinical signs in the surviving and in the nonsurviving groups as well, thus it is not possible to predict the outcome from the CRP value. However, sequential measurements may be useful in monitoring clinical progression

and response to treatment. In our study we determined a cut-off value of CRP (34.3 mg/l). Above this value the likelihood of survival was less than 50%.

Alterations in thyroid hormone concentrations in response to non-thyroidal illness (NTI) are well recognized (Lechan, 2008, Aytug et al., 2011). Among thyroid hormones, decrease of thyroxine concentration was observed most often in dogs (Kantrowitz et al., 2001, Mooney et al., 2008).

In our study the thyroxine concentration was significantly lower in the nonsurviving group ($p = 0.01631$) compared to the surviving group. We determined a cut-off value of thyroxine (9.92 nmol/l), under this value the likelihood of survival is less than 50%.

Conclusions

Severe pancreatitis is often accompanied with complications. The concurrent disorders and complications may strongly influence both thyroxine and CRP concentration. Thyroxine and CRP are sensitive but not specific prognostic indicators in canine pancreatitis, therefore their sole application in the prognostic assessment is not suggested.

Further studies with a larger number of cases more diverse in severity are warranted to evaluate the usefulness of CRP and thyroxine as predictors of severity in canine pancreatitis.

A NOVEL POSSIBILITY OF ENTERAL NUTRITION IN DOGS WITH SPECIAL REGARD TO THE THERAPY OF PANCREATITIS

Publications related to the chapter:

Pápa, K., Psáder, R., Sterczer, Á., Pap, Á., Rinkinen, M., Spillmann, T. (2009): Endoscopically guided nasojejunal tube placement in dogs for short-term post-duodenal feeding. *J Vet Emerg Crit Care*, **19**, 554–63.

Pápa, K., Vajdovich, P., Sterczer, Á., Psáder, R., Vörös, K. (2012): A kutyák heveny hasnyálmirigygyulladásának korszerű gyógykezelése. *Magyar Állatorv. Lapja*, **134**, 221–231.

In the third part of our research we investigated the possibilities of enteral nutrition in dogs. Enteral feeding has an indisputable role in the management of pancreatitis. Jejunal feeding via feeding tube is the only possibility to keep the pancreas „in rest” and to administer enteral nutrition simultaneously in pancreatitis. To avoid the risk of infection and sepsis, noninvasive enteral feeding methods should be strongly considered in critically ill patients. Satisfactory clinical results are achieved by nasojejunal feeding tube placement using endoscopic guidance in human beings with pancreatitis. The aim of our study was to develop a rapid, minimally invasive, and inexpensive method of nasojejunal tube placement in purpose-bred research dogs. The procedure, which uses only endoscopy, was adapted from nasojejunal tube placement techniques in humans and has not been described in the veterinary literature at the time of the study.

Materials and methods

The survey was done in the Teaching Hospital of the University of Helsinki. Three healthy 3-year-old male Beagles with permanent intestinal fistulas were utilized as study subjects.

Endoscopically guided nasojejunal tube placement was performed using a flexible endoscope. The dogs were positioned in left lateral recumbency. The endoscope was inserted into the mouth and introduced into the transverse duodenum via the esophagus and stomach. A Seldinger guide wire was passed through the working channel deep into the jejunum. The polyvinyl chloride (PVC) tube was advanced into the jejunum over the guide wire (in the endoscope) and through the working channel of the endoscope.

The distal tip of the tube was positioned at three different distances caudal to the pylorus. In dog 1, the tube was inserted over the duodenojejunal flexure at an estimated length of 25 cm distal from the pylorus. In dogs 2 and 3, the tube was marked at the distal end at 20

cm intervals with a waterproof marker to allow more precise endoscopic control of the tube length positioned into the jejunum.

During removal of the endoscope the PVC tube and the guide wire were held in the jejunum. The endoscope was then reinserted into the stomach to control the correct placement of the tube with the assistance of the pen markings. Under visual control the excess length of the tube located in the stomach was pulled backwards to place it near the angular notch of the stomach to avoid loop formation and subsequent displacement.

At the end of the endoscopic procedure fluoroscopy was used as a reference technique to check the placement of the nasojejunal tube. In each dog, the Seldinger guide wire was removed when the tube was in place. The oral end of the feeding tube was marked using a waterproof pen at the distance of the tip of the nose. Finally, a lidocaine-lubricated red rubber catheter was inserted through the nostril of all dogs via the ventral nasal meatus into the nasopharynx and oral cavity. The proximal end of the feeding tube located in the oral cavity was firmly attached to the rubber catheter and pulled retrograde through the nasopharynx until the marking reached the outer nares. The tube was sutured to the skin just lateral to the external nares, to the skin on the dorsal nasal midline, and to the skin of the forehead. To prevent self-removal of the feeding tube, an Elizabethan collar was placed on each dog after they regained consciousness.

After endoscopic tube placement, appropriate tube positioning was confirmed and documented by performing ventrodorsal radiographs in each dog. Furthermore, radiographs were taken on days 2 and 3 of jejunal feeding and before tube removal to document the position of the tubes and assess the degree of proximal displacement. To confirm the correct endoscopically estimated length of the intrainstestinal portion of the tube, the distance from the pylorus to the distal tip of the tube was measured on the radiographs using a computer program.

Results and discussion

Fluoroscopic and radiographic examination confirmed the correct intestinal placement of the tube with endoscopic guidance. Pen markings on the tube made the procedure more accurate.

Since some proximal displacement of the nasojejunal tube (3–9 cm) was observed in radiographic images in our study, it seems beneficial to place the distal tip of the tube at least 40–60 cm distal from the pylorus. This may avoid marked proximal displacement, leading to intraduodenal or gastric feeding.

We also noted hardening of the PVC tubes at the time of tube removal. Increasing stiffness of the PVC tube within the stomach and small intestine may have foreign body-like adverse effects if tube feeding is continued for longer than the time assessed in our study (4–5 days). We conclude that PVC tubes may only be usable for short-term enteral nutritional support (less than 1 week). Whether tubes made of other material, such as Teflon, silicone, or polyurethane would be superior for long-term nasojejunal feeding remains to be studied.

In all dogs, nasojejunal feeding was carried out for 4 consecutive days. In our small study, we showed that in healthy active dogs the placement of an Elizabethan collar was sufficient to avoid inadvertent self-removal of the feeding tube, even during periods without continuous surveillance. However, kinking of the tube commonly occurred. Since this problem can influence the usability of the tube, regular checking is advisable.

The nasojejunal tube is small in diameter (2.6 mm). The tube diameter determines which type of liquid diet is possible to feed. We observed that only a well-homogenized, concentrated, commercial liquid diet could be used. Regular flushing of the tube with 20 mL of drinking water before and after the feeding period was sufficient to avoid occlusion of the tube.

Using a nasojejunal tube enabled us to administer the calculated daily caloric requirements as a liquid diet. However, we recorded in all dogs a weight loss of approximately 2.6% without significant alteration in the body condition score (BCS), which may be related to the special feeding protocol with gradually increasing volume and energy.

Repeated laboratory examinations revealed no abnormalities, however, temporary CRP elevation was observed after carrying out the tube insertion procedure. This mild and temporary elevation may have been due to the anesthesia, endoscopic procedure, or nasal manipulation during tube placement.

As acute pancreatitis is one of the major indications for jejunal feeding, the activities of pancreatic serum enzymes such as amylase and lipase, and the Spec cPL concentration were monitored in all dogs throughout the study. These parameters did not change considerably during the course of the study. Thus, intrajejunal feeding probably does not influence the monitoring of acute pancreatitis by serum parameters. This confirms the findings of other studies finding no stimulation of pancreatic secretory function during jejunal feeding.

Conclusions

To our knowledge, there are no previous experimental or clinical studies on jejunal feeding in dogs using nasojejunal tube placement with endoscopic guidance alone. We concluded that endoscopically assisted nasojejunal tube placement is a minimally invasive, well-tolerated method for short-term jejunal feeding in healthy dogs. To perform correct jejunal intubation in larger dogs, we strongly suggest that the distal tip of the tube should be placed at least 40–60 cm caudal to the pylorus. Radiographic confirmation of jejunal tube placement is essential due to individual differences.

In our study, we were able to gain jejunal chyme via the nasojejunal tube. Nasojejunal tube placement may offer a minimally invasive alternative for chyme sampling, compared to the current experimental model of surgically placed, irreversible, lifelong jejunal fistulas.

Our study population is not representative of all dog types and sizes with different clinical conditions. To assess the usefulness of nasojejunal tube placement in canine patients, further studies are required in larger group of clinically ill dogs.

NEW SCIENTIFIC RESULTS

1. We established that hypothermia and metabolic acidosis show significant correlation with the outcome of canine acute pancreatitis.
2. We determined a cut-off value of CRP-concentration (34.3 mg/l; reference range: 0–10 mg/l). Above this value the likelihood of death is more than 50% in canine pancreatitis.
3. We firstly described the strong relationship between the serum thyroxin concentration and the severity of pancreatitis. There is a negative correlation between low thyroxine level and survival. We determined a cut-off value of thyroxine (9.92 nmol/l, reference range: 17–54 nmol/l), under this value the probability of death exceeds 50%.
4. We firstly described in the literature the technique of nasojejunal tube placement with endoscopic guidance in dogs. We established that endoscopically assisted nasojejunal tube placement is a minimally invasive, well-tolerated method for short-term jejunal feeding in healthy dogs. We used successfully the nasojejunal tube for jejunal chyme sampling.

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PUBLICATIONS

Publications related to the dissertation

Pápa, K., Psáder, R., Sterczer, Á., Pap, Á., Rinkinen, M., Spillmann, T. (2009): Endoscopically guided nasojejunal tube placement in dogs for short-term post-duodenal feeding. *J Vet Emerg Crit Care*, **19**, 554–63.

Pápa, K., Máthé, Á., Abonyi-Tóth, Zs., Sterczer, Á., Psáder, R., Hetey, Cs., Vajdovich, P., Vörös, K. (2011): Occurrence, clinical features and outcome of canine pancreatitis (80 cases). *Acta Vet Hung*, **59**, 37–52.

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Posters and oral presentations related to the dissertation

Pápa, K., Sterczer, Á., Psáder, R., Vörös, K., Burai, M., Pap, Á. (2005): Nasojejunális tápszonda levezetése endoszkóp segítségével kutyában. *MTA Állatorvos-tudományi Bizottsága, Akadémiai beszámoló, Klinikumok, gyógyszerstan*

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Pápa, K., Máthé, Á., Psáder, R., Abonyi-Tóth, Zs., Szenes, K., Vörös, K., Sterczer, Á. (2010): C-reactive protein és a thyroxin prognosztikai értéke akut pancreatitisben megbetegedett kutyákban. *MTA Állatorvos-tudományi Bizottsága, Akadémiai beszámoló, Klinikumok, gyógyszerstan*