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Research Article

Evaluation of Survivability Predictors in Acute Kidney Injury-Affected dogs Managed with Continuous Renal Replacement Therapy

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Abstract

Several survivability predictors have been identified in acute kidney injury (AKI) affected humans managed with continuous renal replacement therapy (CRRT). The aim of this study was to evaluate various blood and urine parameters as survivability predictors in AKI affected dogs managed with CRRT. Twenty dogs that presented with AKI to a veterinary hospital were managed with CRRT. Physical examination, urinalysis, arterial/venous blood gas analysis, and ELISA for analysis of Kidney Injury Molecule-1 (KIM-1) and Cystatin-C (Cys-C) were performed on the first day of presentation (Pre-CRRT).

Survivability evaluated on day 21 post-CRRT indicated 12 survivors and 8 non-survivors. Pre-CRRT parameters were compared between survivors and non-survivors using independent t-tests. Of the various parameters analyzed, KIM-1 concentrations and anion gap (AG) were significantly different between survivors and non-survivors. Other parameters such as APACHE III score, Cys-C, renal failure index (RFI), and fractional excretion of sodium (FENa) were not significantly different between survivors and non- survivors. Results of this study suggest that KIM-1 and AG could be employed as survivability predictors in AKI affected dogs managed with CRRT.

Key Words: acute kidney injury; canine; crrt; kim-1; prognosis

1.Introduction

In human nephrology, Acute Kidney Injury (AKI) is defined as an abrupt decrease in kidney function generally documented in hospitalised patients with substantial morbidity and mortality (Mehta et al., 2007). However, animals most commonly develop community acquired AKI and, consequently, the magnitude of changes of several parameters, including urine quantification and time of occurrence, is rarely quantitated (IRIS, 2013). Different pathogenetic factors such as ischemia, infectious diseases, nephrotoxic drug exposure, and toxins contribute to the development of AKI (Segev, 2011). Identifying and reversing these pathophysiological factors are important in the early phase of AKI to prevent its establishment (Ross, 2011). The aim of early diagnosis of renal failure in dogs is to support and guide appropriate application of therapeutics that may reduce or prevent disease advancement. Successful renal replacement therapy (RRT) such as with continuous renal replacement therapy (CRRT) is the only potentially effective treatment for most patients with AKI.

Despite advances in the management of AKI, mortality rates associated with this condition are as high as 50–60% (Thoen and Kerl, 2011). Factors associated with the high mortality rates are multiple, including insensitive diagnostic tests in the early stages, late presentation to a veterinarian and the rapid progression of the disease. Serum creatinine is the most commonly used biomarker for renal function.

However, due to the lack of sensitivity and specificity, it cannot be employed as a diagnostic tool, especially in the early stages of renal injury. An ideal biomarker should be able to identify an early damage, detect the extent of injury, check the progression of the disease, and predict the prognosis accurately. Kidney Injury Molecule-1 (KIM-1) is one of the various promising biomarkers. It is a membrane protein normally found in healthy proximal convoluted tubular cells and shed into the urine at low concentrations (Pressler, 2013). Production of KIM-1 is rapidly increased by tubular epithelium after kidney injury. Earlier studies for urinary KIM-1 on humans, cats and rodents have reported diagnostic importance in AKI (Han et al., 2002; Vaidya and Bonventre, 2006; Bland et al., 2014). However, there are no reports on plasma KIM-1 in dogs with AKI. Similarly, another biomarker Cystatin C (Cys-C) is produced by all nucleated cells in the body.

Once produced, Cys-C is released into the circulation and is freely filtered(greater than 99percentage) by the glomeruli and catabolised by proximal tubular cells with insignificant concentration being lost in urine of healthy animals. Among various renal indices, fractional excretion of sodium (FENa) and renal failure index (RFI) have specifically been used to distinguish between prerenal azotemia and acute tubular necrosis. A FENa calculation in oliguric or anuric patients is more sensitive and even more predictive when used in conjunction with other renal parameters (Waldrop, 2008).Severity or predictive scores can be utilised as a tool for baseline assessment at admission especially in critically ill patients. Scores calculated for a specific patient are taken as outcome predictions score (Hayes et al., 2010). In a clinical setting, scores can be useful as complementary tool for patient evaluation, in addition to clinical assessment. One such baseline assessment method in humans, referred as APACHE (Acute Physiology, Age, Chronic Health Evaluation) was developed to precisely predict hospital mortality risk for critically ill hospitalised patients (Knaus et al., 1991). Zimmerman et al. (1998) concluded that APACHE III scoring accurately predicted aggregate hospital mortality in an independent population of ICU admissions. However, this scoring system has not been evaluated yet in AKI affected dogs. In dogs, a scoring system based on CBC, serum biochemistry profile, and urinalysis at admission has been developed and validated in acute kidney injury affected patients managed by hemodialysis (Segev et al., 2008; Segev et al., 2016).

To date, several retrospective and prospective studies have been done to evaluate various parameters for prognosis in dogs with AKI (Lee et al., 2011). One study evaluated mode of treatment as a factor for survivability in dogs with AKI (Eatroff et al., 2012). Other studies have evaluated survivability based on the type of etiology (Eubig et al., 2005; Morrow et al., 2005; Goldstein et al., 2006; Segev et al., 2008).

However, the information about various survivability predictors in dogs is scarce and there is need for in- depth evaluation of several other novel parameters to improve knowledge about prognosis in AKI affected dogs. Therefore, the present study was conducted with the objective of evaluating various survivability indicators in dogs with AKI.

Materials and Methods

The experimental protocol was approved by the institutional animal care and use committee. Before the start of the procedure or treatment, a written consent from the owners was taken. During the study period, dogs that presented with clinical signs suggestive of AKI were subjected to physical examination, urinalysis, arterial/venous blood gas analysis, ELISA for analysis of Canine KIM-1 and Canine Cys-C as biomarkers of early kidney injury.

Twenty clinical cases confirmed as suffering from AKI, based on International Renal Interest Society classification (IRIS, 2013), were subjected to CRRT. A criterion of inclusion of AKI patients for CRRT was based on IRIS Stage IV (creatinine $\geq$ 5.0, n = 5) and V (creatinine $\geq$ 10.0, n = 15). Survivability was determined on day 21 post CRRT. Of the 20 dogs treated, 12 dogs survived, and 8 dogs died. Pre-CRRT data was analyzed between the survivors (n = 12) and the non-survivors (n = 8).

Serum Biochemistry and Electrolyte Analysis

About 2 mL blood was collected from saphenous or cephalic vein in a vacutainer with no additive for biochemical study.

ELISA for Canine KIM-1 and Canine Cys-C: About 1.5 mL of blood was collected in heparinised vial. The plasma was separated from heparinised blood using standard aseptic procedures and the samples were stored at – 20 ºC until used. For determining the concentration of KIM-1 (ng/mL) in the plasma, commercially available Dog KIM-1 ELISA Kit (Immunology Consultants Laboratory, Inc. Portland, USA) was used as per the manufacturers recommended protocol. Similarly, for the analysis of concentration of Cys-C (µg/mL), Dog Cys-C ELISA Kit (MyBiosource, USA) was used as per the manufacturer's protocol.

Blood Gas Analysis

About 1mL of arterial blood was collected from femoral artery in heparinized syringes and fed in an automated Blood gas analyzer for analysis.

Apache Iii Score

The APACHE (Acute Physiology, Age, Chronic Health Evaluation) methodology was developed to precisely predict hospital mortality risk for critically ill hospitalised patients in humans (Knaus et al., 1991). From the APACHE III prognostic system, we utilized the APACHE III scoring method, and evaluated the pre-CRRT data between Live and Dead at day 21 post-CRRT. The score was calculated as per Knaus et al. (1991) with minor modification for dog years.

Urinalysis

Urine samples were collected in sterilized containers by catheterization in both male and female dogs. Urine sodium, chloride, and creatinine were analyzed in addition to routine urinalysis. Advanced renal function tests, such as FENa and RFI were calculated as per Waldrop (2008).

Statistical Analysis

Statistical analysis of data was performed using SPSS statistics 17.0 software (SPSS Inc., Chicago, IL). Data were evaluated for normality by inspection of Q-Q plots and application of the Shapiro-Wilk test.

Differences in the mean values of pre-CRRT data on the various parameters between survivors and non- survivors were evaluated for statistical significance using 'independent samples t test'. Differences with P-values of less than 0.05 were considered to be statistically significant. Results are presented as Mean ± Standard Error of Mean (Mean ± SEM).

Results

Survivability evaluated on day 21 post-CRRT indicated 12 survivors and 8 non-survivors (60% survivability and 40% mortality). Results of the pre-CRRT data analysis are presented in Table 1.

Parameter	Survivors (n=12)	Non-survivors (n=8)	P-value
KIM-1 (ng/mL)	2.47±0.12	3.49±0.04	<0.001
Cys-C (µg/mL)	165.85±48.66	219.99±22.79	0.33
APACHE III	51.42±2.51	61.25±14.09	0.11
FENa			
With outliers[a]	11.54±3.19	21.72±11.70	0.43
Without outliers	8.53±1.17	10.11±1.71	0.46
RFI			
With outliers[a]	16.54±4.61	31.45±16.96	0.42
Without outliers	12.20±1.75	14.64±2.51	0.44
Anion gap (mmol/L)	26.84±1.25[a]	34.67±2.22	0.03

Table-1 Survivability predictors (Mean±SEM) in acute kidney injury affected dogs managed with continuous renal replacement therapy (CRRT)

KIM-1: Kidney injury molecule-1, Cys-C: Cystatin-C, APACHE III: Acute physiologic assessment and chronic health evaluation III score, FENa: Fractional excretion of sodium, RFI: Renal failure index

aVisual inspection of data distribution and statistical analysis indicated presence of one outlier observation each in the survivor and non-survivor groups. Results of the statistical analyses with and without the outliers are presented. Among the various pre-CRRT parameters evaluated, KIM-1 concentration and anion gap were significantly lower in survivors than in non-survivors. Other parameters such as APACHE-III score, Cys-C, FENa and RFI were not significantly different between survivors and non-survivors.

Discussion

The survival rate in this study was higher than reported previously in studies involving medical management and hemodialysis (Vaden et al., 1997; Francey and Cowgill, 2002; Segev et al., 2008). This could be due to multiple reasons, including early initiation of CRRT and selection of cases with no concurrent diseases in our study. Evaluation of the various pre-CRRT parameters identified some potential survivability indicators that may have prognostic value in the diagnosis and management of dogs with AKI.

In the present study, the concentration of KIM-1 was significantly different between survivors and non- survivors. These levels indicate that KIM-1 increases with severity of AKI. KIM-1 concentrations appear to reflect variable degrees of tubular injury (Bagshaw and Bellomo, 2010). Until now, there are reports of urinary assay for KIM-1 in laboratory animals and to the authors' knowledge, there are no reports of Canine specific plasma KIM-1 in AKI patients. We analysed AKI affected dogs for plasma KIM-1 instead of urinary KIM-1. There are potential reasons to believe that KIM-1 may be released into the circulation after the kidney damage is initiated. Contributing factors such as lost in cell polarity and backleak phenomenon are the major ones (Ross, 2011). Moreover, urine assays of renal clearance are more laborious to perform because they require collection of urine produced in a 24-hour period. Since large population of AKI affected dogs are oliguric, it is difficult to collect urine in the clinical setting.

Furthermore, assays for plasma clearance are closely corresponded to renal clearance, such that in the emergency setting urine sampling is not necessary (Van Hoek et al., 2007; Von Hendy and Pressler, 2011). This study revealed that measurement of canine plasma KIM-1 appears to be novel biomarker for AKI with ability to predict survivability. Therefore, our data will provide a new insight into the plasma KIM-1 data in dogs with AKI.

Canine specific Plasma Cys-C evaluation in dogs with AKI is scarce. Earlier reports in animal medicine suggested that Cys-C had a better sensitivity as compared to creatinine for documenting decreased GFR (Wehner et al., 2008). In this study we analysed canine specific plasma Cys-C concentration among dogs with AKI with respect to he outcome as survivor or non-survivor. Although, the concentration of Cys-C was not significant between survivors and non-survivors, but the concentration was higher in survivors than non-survivors. Our study indicates that plasma Cys-C is a good biomarker for the prediction of AKI but the ability to predict survival is questionable. Our findings agree with several reports suggesting excellent diagnostic performance (Haase-Fielitz et al., 2009; Nejat et al., 2010), but disagree with theconclusion of Bagshaw and Bellomo (2010) who stated reasonable predictive ability for death by Cys-C in humans with AKI. Several factors may explain the conflicting results, including low number of cases in the present study and the reason for starting CRRT. In our study, the selection criteria for the initiation of CRRT were IRIS stage VI and V, whereas in other studies selection criteria was either oliguria or low GFR (Royakkers et al., 2011). Moreover, some of the studies do not report how many patients received RRT (Nejat et al., 2010).

In our study, the levels for FENa and RFI between the survivors and non-survivors were non-significantly elevated. FENa documented in AKI cases was very high than established range (< 1%) indicating severe renal tubular damage. Moreover, following individual assessment of the cases, higher levels corresponded to the mortality indicating association between FENa and severity. Data analysis from a systematic review in humans indicated that the FENa was highly variable in AKI patients (Bagshaw and Bellomo, 2010). In other similar studies, the FENa was partially dependent on the timing of measures adopted from onset of AKI with many transforming progressively from FENa < 1 to > 1%. Furthermore, in humans AKI is generally recognized in hospitalized patients with majority diagnosed early and many patients falling under lower stages of AKI. However, in our study, all the AKI cases were community acquired and lately presented falling under IRIS stage IV and V indicating more severity. Moreover, cases with concurrent diseases were excluded from our study. In contrast, among various studies in humans where FENa was evaluated, AKI patients with concurrent diseases were included which could have influenced and masked the true analysis of FENa in specific AKI patients. In humans, FENa and RFI have been evaluated in large populations as compared to our study which might be a limiting factor. Therefore, our study depicts FENa and RFI as very promising urinary indices to diagnose Acute Tubular Injury (ATI) and need further evaluation in a larger population of dogs with AKI.

Recently, validation of a scoring system for outcome prediction in AKI affected dogs was reported by Segev et al. (2016). The authors concluded that the scoring system was easy to apply, and outcome prediction was closer to the actual outcome depicting a valuable prognostication tool. In this study, we analysed the patient's chances of survival to hospital discharge based on the mean of APACHE-III score between survivors and non-survivors. There was no significant difference observed between survivors and non-survivors. However, the mean value of APACHE-III score was higher in survivors as compared to non-survivors demonstrating an inclination as a predictive tool for risk stratification in critically ill patients. Knowledge of the risk faced by a patient on the day of ICU admission could provide basis for quality

assurance and utilization activities. So far APACHE III scoring has been developed and utilised in a large human population size as compared to our study population (Knaus et al., 1991; Nematifard et al., 2018). Small study population might be the major limiting factor in our study. APACHE III score could prove a significant risk stratification tool if analysed in a large canine population with AKI. Therefore, APACHE III score needs to be evaluated in a large study population to precisely predict and validate its role as a tool for risk stratification.

Based on blood gas analysis (BGA), a diagnosis of metabolic acidosis was confirmed. Under this study, significantly higher level of AG was found in non-survivors than survivors. Moreover, in this study, hyperphosphatemia was documented as a major anion contributing to the high anion gap, hence, confirming hyperphosphatemic acidosis or high AG acidosis. Renal failure is one of the predominant causes for high AG metabolic acidosis (Kaae and Morais, 2008) which corroborated with the findings of this study. Therefore, AG could be useful in predicting survivability in dogs with AKI. Furthermore, lower pH has been reported to be correlated with survival of critically ill patients in human medicine (Maciel and Park, 2009; Hopper and Epstein, 2012). Moreover, several other BGA parameters have been evaluated in veterinary patients (Hayes et al., 2011). However, there are several parameters including anion gap which have influence on the blood pH. As a result, pH alone cannot be used to determine the severity or nature of an acid base disorder. Therefore, to recognize and differentiate disorders of metabolic acidosis, increased AG can be utilised as a valuable tool (Kaae and Morais, 2008) for prognostication.

Conclusions

This study demonstrated that canine plasma KIM-1 is a promising biomarker with ability to predict survivability in dogs with AKI. Similarly, AG could be a useful prognostic indicator. However, the results need to be confirmed in future studies involving larger sample sizes to effectively validate the role of these parameters in risk stratification.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

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