A Pilot Study of Effect of Methylprednisolone Sodium Succinate for Mitral Valve Repair During Cardiopulmonary Bypass in Dogs

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ABSTRACT

Objective: To investigate whether methylprednisolone sodium succinate (MPSS) benefits anti-inflammation of dogs undergoing cardiac surgery with cardiopulmonary bypass (CPB).

Animals: Fifty-seven client-owned dogs.

Methods: Medical records of dogs diagnosed with myxomatous mitral valve disease that underwent mitral valve repair surgery using CPB between November 2016 and March 2017 were reviewed. This period included a period which MPSS was used for every dog (MP group) and a period which MPSS wasn't used (non-MP group). Signalment, blood test results, intra-operative events, postoperative complications, and 30-day mortality were compared between the groups.

Results: There were 24 dogs in the MP group and 26 dogs in the non-MP group. Seven dogs were excluded in this study. No significant differences were observed between the MP and non-MP groups for all parameters evaluated. Of note, the three dogs that died within 30 days of surgery all exhibited postoperative acute respiratory failure and belonged to the MP group. The cause of acute respiratory failure was unilateral diaphragmatic paralysis, suspected acute respiratory distress syndromes, and pulmonary edema for each case.

Conclusion: The validity of using MPSS during CPB in mitral valve repair for dogs could not be verified in this study. Further studies are necessary to evaluate its relation with postoperative complications.

INTRODUCTION

Myxomatous mitral valve disease (MMVD) is one of the most common cardiac diseases in dogs, accounting for 75–80% of cardiac

diseases.[1,2] Mitral valve repair (MVR) is an open-heart surgery that uses cardiopulmonary bypass (CPB). It is known to be an effective therapy for severe mitral valve regurgitation (MR) in dogs.[3] Reduction in MR can improve symptoms and extends survival time.[3] Another major advantage of this procedure is that it can reduce the number of medications and dosages.[4] Based on the study done in stage C MMVD dogs, the median survival period with medical therapy was 267 days,[4] while 93.3% of cases that underwent MVR were still alive 38 months postoperatively.[3]

In humans, MVR surgery with CPB causes a generalized inflammatory response that is characterized by both cell and protein activation[5, 6] with release of inflammatory mediators into systemic circulation.[7, 8] Platelets, neutrophils, monocytes, macrophages, coagulation, fibrinolytic, and kallikrein cascades all take part in a process that results in increased endothelial permeability, vascular, and parenchymal damage.[9, 10] These inflammatory process in CPB have been studied intensively in human medicine, because it is associated with postoperative outcome; in particular: complications such as myocardial, respiratory, renal, liver, neurological dysfunction, excessive bleeding, and multiple organ failure or death.[6,11]

To abrogate the inflammation associated with CPB, several immunomodulatory strategies have been attempted.[10,12] In studies of steroid intervention trials, most studies use one of the following three drugs: methylprednisolone sodium succinate (MPSS), dexamethasone, or hydrocortisone. Steroids inhibit inflammation through a variety of different mechanisms, and several regimens of steroid therapies have been used ostensibly to attenuate the postoperative inflammatory processes associated with CPB.[10, 12]

Although perioperative steroid prophylaxis for CPB is still controversial, many studies have proposed its beneficial possibility of reducing the risk of systemic inflammation and subsequent organ injury that affects the human patients' mobility and mortality. In dogs undergoing MVR with CPB, MPSS has been used conventionally based on these human studies. However, details on the role of steroids during cardiac surgery with CPB have not yet been studied as thoroughly as in human medicine and its effect is still questionable. Therefore, we aimed to investigate whether MPSS benefits the postoperative conditions of dogs undergoing MVR with CPB.

MATERIALS AND METHODS

Study Population

Medical records of dogs diagnosed with MMVD that underwent MVR using CPB at the JASMINE Veterinary Cardiovascular Medical Center between November 2016 and March 2017 were reviewed. During November 2016 to January 2017, dogs received 10 mg/kg MPSS at two points during the surgical procedure; at initiation of CPB and right after weaning from CPB (MP group). During the rest of the period (February to March 2017), MPSS was not used because questions arose for the effect of steroids. Dogs were excluded from the study if they had been medicated with steroids during the previous month of MVR, if medical records were missing or subsequent follow-up information could not be obtained after hospital discharge.

Review of Medical Records

All dogs included in this study underwent physical examination, pre- and postoperative blood tests, and radiographic and echocardiographic evaluation. Demographic information (age in months, weight in kilograms [kg], sex, and heart failure classification based on American College of Veterinary Internal Medicine [ACVIM][13]) at the time of surgery was obtained from the medical records. White blood cell (WBC) counts including neutrophils and lymphocytes, and plasma C-reactive protein (CRP) results, were used for assessment of inflammation. Plasma concentrations of CRP were analyzed using an enzyme immunoassay test.[a] The WBC counts were determined from blood mixed with ethylenediaminetetraacetic acid by an automated cell counter.[b] Data

for intubation time, CPB time (defined as the period from the beginning of CPB to weaning from CPB), and aortic cross-clamp time (defined as the period from aortic clamping to aortic clamp releasing) were collected as intra-operative information. In addition, postoperative data including complications, period of hospitalization, and survival were recorded.

Technique of Mitral Valve Repair Surgery and Anesthesia

Details of the anesthetic protocol and procedure of MVR surgery are as previously described.[3] A modified anesthesia method and MVR was performed in the same manner for each dog in this study.[3] Briefly, preanesthetic medications included glycopyrrolate (0.011 mg/kg subcutaneously), midazolam (0.3 mg/kg IV), fentanyl (5 µg/kg IV), cefazolin sodium (20 mg/kg IV), and famotidine (1mg/kg IV). Each dog was then oxygenated with 100% oxygen, followed by induction with ketamine (5.0 mg/kg IV) and intubation with an endotracheal tube (internal diameter, 4–8 mm). All dogs received CRI of fentanyl (0.4 µg/kg/min IV) and injection of vecuronium (0.08 mg/kg IV). Intravenous infusion of 0.08 mg/kg vecuronium was added when severe respiratory muscle reflexes occurred. The dogs were mechanically ventilated with oxygen and received 2.0–3.0% end-tidal isoflurane anesthesia. The oxygen flow rate was 2.0 L/min.

After induction of cardiac arrest, a mitral annuloplasty was performed, and the chordae tendineae were replaced with expanded polytetrafluoroethylene chordal prostheses. After closure of the left atrium and declamping to restart the heart, the thorax was closed.

After MVR surgery, patients were housed in an oxygen cage maintained at an FiO2 of 21–50%. In all patients, low molecular weight heparin (100–150 IU/kg, subcutaneously, q8hr), and clopidogrel (2–4 mg/kg, PO, q24hr) were administered during hospitalization as antithrombotic treatment. Furthermore, cefazolin (20 mg/kg, IV or PO, q12hr) was administered until discharge.

Statistical Analysis

Statistical analysis was performed with a commercial statistical software.[c] Continuous variables were tested for normality by using a Shapiro-Wilk test. Non-normally distributed variables were summarized as median (minimum - maximum) and compared between the MP group and non-MP group by using Mann-Whitney U test in demographics, pre- and postoperative WBC counts, CRP concentration, intra-operative intubation time, CPB time, aortic cross-clamp time, and postoperative days spent in the hospital. Categorical data were described with frequencies and percentages. Fisher's exact test was used to assess differences in demographics, defibrillation, temporary cardiac pacing, postoperative complications, and 30-day mortality. Furthermore, the Wilcoxon signed rank test for paired data were used to compare pre- and postoperative values. For all analyses, significance was set at $p < 0.05$.

RESULTS

A total of 57 dogs underwent MVR surgery between November 2016 and March 2017. No dogs had a history of steroid use during the prior month to surgery. Of these dogs, six were excluded from this study because of incomplete data, and one was excluded due to re-operation. Of the 50 dogs that met the inclusion criteria, 24 were from the period with MPSS administration during CPB (MP group), and 26 were from the period without any steroid administration during CPB (non-MP group). The MP group consisted of 11 Chihuahuas, 3 Pomeranians, 3 mix breed dogs of terrier types, 2 Cavalier King Charles Spaniels, and 1 each of Maltese, Miniature Dachshund, Shih Tzu, Toy Poodle, and Yorkshire terrier. The non-MP group consisted of 11 Chihuahuas, 5 Cavalier King Charles Spaniels, 3 Toy Poodles, 2 mix breed dogs of terrier types, and 1 each of Maltese, Miniature Dachshund, Pomeranian, Jack Russell Terrier, and Mongrel. Characteristics of both groups are shown in Table 1. No significant differences in age, body weight, sex, ACVIM classification

were observed between the two groups.

Blood Cell Counts and CRP Concentrations

White blood cell counts and CRP concentrations are summarized in Table 2. White blood cell > 17,000μL and CRP > 0.7 mg/dL were set as the upper limit of the normal range based on the manufacture's standards. White blood cell and neutrophil counts on postoperative day 1 were significantly high in both groups compared to each preoperative data ($p < 0.001$). A remarkable increase was observed in the CRP concentrations on postoperative day 1 in both groups ($p < 0.001$).

Postoperative Complications

Postoperative complication occurred in 10 dogs (20%) included in this study. Complications observed in the MP group were three acute respiratory failures, and one each of persistent ventricular tachycardia (VT), acute kidney injury, and peripheral circulatory failure. The cause of acute respiratory failure was unilateral diaphragmatic paralysis, suspected acute respiratory distress syndromes, and pulmonary edema for each case. The complications in the non-MP group were three persistent VT and one thromboembolism.

Period of Hospitalization and Survival Analysis

No significant difference was observed in the period of hospitalization between the MP and non-MP groups ($p = 0.076$; Table 3). The three dogs that had acute respiratory failure, all of which were from the MP group, deceased by 30 days after MVR (all-cause mortality). In the MP group, no characteristics were seen in postoperative WBC counts and CRP concentrations between dogs with and without acute respiratory failure. All dogs in the non-MP group survived during the same period. However, there was no difference in 30 days mortality between the MP and non-MP groups ($p = 0.137$; Table 3).

DISCUSSION

In dogs undergoing MVR with CPB, administration of perioperative MPSS did not reduce inflammation in terms of WBC counts or CRP concentrations, along with the risk of death or postoperative complications.

Previous trials of human patients undergoing CPB[14] and clinical studies of dogs treated secondary spinal cord injury by intervertebral disk herniation[15, 16] conducted that MPSS dose was 30 mg/kg or more. The SIRS pilot study showed that lower dose was effectively abolished the inflammatory response to CPB across a broad array of measured mediators.[14, 17] This suggests that higher doses of steroids might be associated with adverse outcomes. There is no study regarding this matter in veterinary medicine and high dose MPSS (more 30mg/kg) causes gastrointestinal tract ulcers and hemorrhage in dogs.[18] Hence, we decided to applied 20 mg/kg MPSS from those study.

In humans, 20 mg/kg dosage of MPSS intravenously before and after CPB significantly diminished CRP concentrations, although WBC counts was high on postoperative day 1. They concluded that total 40 mg/kg of MPSS suppressed T cell function, and changed immunological reactions.[19] Another study reported a significant increase in WBC counts after 6 hours, and an increased in CRP concentrations after 24 hours from CPB, than preoperative values.[20] This report is consistent with present study, WBC counts, and CRP concentrations significantly increased postoperative day 1 in both the MP and non-MP groups. These changes are thought to be caused by the inflammatory response of surgical trauma. However, this surgical inflammatory response was not attenuated with 10 mg/kg dosage of MPSS before and after CPB.

Pulmonary complications after cardiac surgery with CPB are common in human medicine, as lungs are especially vulnerable to the inflammatory effects ascribed to the use of CPB and extracorporeal circulation.[21] Several trials[22, 23, 24] and review[25] were discussing the impact of steroids on the inflammatory response and outcomes after use of extracorporeal circulation. Their discussions

Table 1. *Demographic data of dogs enrolled into the study*

Parameter	MP (n = 24)	non-MP (n = 26)	P value
Age at surgery (months)	118.0 ± 18.6	127.8 ± 18.8	0.71
Body weight (kg)	4.04 (2.30–11.20)	4.06 (2.10–9.88)	0.534
Sex (MN / FS)	15 / 9	14 / 12	0.578
ACVIM classification (stage B2 / C / D)	4 / 11 / 9	6 / 10 / 10	0.932
VHS	11.6 (10.0–13.8)	11.8 (10.1–13.9)	0.884
LA/Ao	1.96 (1.28–2.74)	2.28 (1.37–3.01)	0.285
LVIDDN	2.18 (1.36–2.67)	2.18 (1.51–2.77)	0.607

Data presented as mean ± standard error for age and median (minimum – maximum) for body weight, VHS, LA/Ao, LVIDDN.
Abbreviations: ACVIM, American College of Veterinary Internal Medicine; clamping, aortic cross-clamping; FS, female spayed; LA/Ao, left atrial-to-aortic root diameter ratio; LVIDDN, normalized left ventricular internal diameter in diastole; MN, male neutered; MP, methylprednisolone sodium succinate; VHS, vertebral heart size

Table 2. *Pre- and postoperative day 1 comparisons of body weight, WBC counts, and CRP concentrations*

		MP (n = 24)	non-MP (n = 26)	*P* value
WBC (μL)	Pre	9000 (4200–29800)	9000 (4500–16700)	0.869
	Post	21750 (11400–57300)*	19000 (10100–42500)*	0.180
Neutrophil	Pre	6050 (3100–25900)	6250 (3200–12200)	0.756
	Post	18650 (7400–53000)*	16800 (7900–40000)*	0.210
Lymphocyte	Pre	1700 (500–5400)	2000 (1000–3900)	0.371
	Post	1450 (400–8800)	1900 (400–12800)	0.915
CRP (mg/dL)	Pre	0.7 (0.3–5.0)	0.7 (0.3–1.8)	1.000
	Post	10.1 (0.4–19.2)*	11.40 (5.1–20.1)*	0.099

Data presented as median (minimum–maximum).
*Abbreviations: CRP, c-reactive protein; MP, methylprednisolone sodium succinate; Pre, preoperative; Post, postoperative day 1; WBC, white blood cell; *significant difference compared to preoperative value ($p < 0.001$)*

Table 3. *Operation and postoperative information of dogs enrolled into the study*

Parameter	MP (n = 24)	non-MP (n = 26)	P value
Anesthesia time (min)	313 (243–463)	309 (263–456)	0.838
CPB time (min)	95 (76–134)	95 (72–150)	0.593
Clamping time (min)	57 (34–76)	56 (46–86)	0.515
Hospitalization (day)	6 (3–12)	5 (3–7)	0.076
30-day mortality	3 / 24	0 / 26	0.137

Data presented as median (minimum – maximum).
Abbreviations: Clamping, aortic cross-clamping; CPB, cardiopulmonary bypass; MP, methylprednisolone sodium succinate

were controversial and not reach final conclusion. The systematic review concluded that steroid administration during CPB has no effect on pulmonary complications.[25] There was no acute respiratory failure in the non-MP group, although MP group showed acute respiratory failure in three dogs. This result may be consistent with useless of steroids to reduce pulmonary complications in humans.

Recent investigations have demonstrated that respiratory disorder was related to high mortality during hospitalization after MVR in dogs.[26] In the present study, all dogs that developed acute respiratory failure died during the same period. This data was consistent with the previous study. Acute respiratory distress syndromes are related to lung damage caused by the postoperative systemic inflammatory response,[27] and its risk can be reduced by suppressing the excessive inflammation. In the present study, there was no obvious anti-inflammatory effect of MPSS based on postoperative WBC counts and CRP concentrations. In human medicine, WBC migration inhibitors have been reported to be effective therapeutic agents for acute lung injury.[28] Therefore, if the relation between respiratory impairment and WBC increase after CPB in dogs become apparent in the future, drugs that suppress WBC activation may have the potential to suppress pulmonary complications after cardiac surgery with CPB in dogs.

In human medicine, administration of MPSS 1 hour before aortic cross-clamp significantly reduces myocardial damage during reperfusion[29] and cTnI levels after CPB.[30] In animal studies, the blunting of apoptosis was associated with improved recovery of left ventricular systolic function after CPB and circulatory arrest in glucocorticoid-treated neonatal animals.[31] Although these reports support the potential of steroids for protecting postoperative myocardial damage, persistent VT was observed in both groups in the present study. There were no significant differences between the MP and the non-MP group for the hospitalization period or 30-day postoperative mortality. This result is consistent with previous studies in human medicine.[17, 25, 32] Our dosage of MPSS may not affect protection of myocardial damage which caused ventricular tachycardia, and term of hospitalization.

There were several limitations in this study. A limited case number caused low statistical power, as the minimum of 100 cases required for each group could not be obtained. Also, this study was based on a retrospective design, and ideally, MPSS should be administered double blindly based on the cohort study manner. The evaluation of inflammation was limited to the results of only WBC counts and CRP concentration from medical records. Because there are multiple indices for inflammatory reactions, other markers such as cytokine levels are required to discuss a thorough evaluation of inflammation in MVR using CPB.

CONCLUSION

In conclusion, MPSS cumulative 20 mg/kg did not affect suppressing WBC counts and CRP concentrations after MVR. This dosage of MPSS may useless in supression of inflammatory reaction. Further dose comparison and other inflammatory indices study are needed.

FOOTNOTES

a FUJI DRI-CHEM 4000V, Fujifilm, Co, Ltd., Japan

b Celltac Alpha MEK-6450, Nihon Kohden, Co, Ltd., Japan

c SPSS® Statistics Grad Pack Version 25.0, IBM Japan, Japan

Conflict of Interest

The authors declare no conflicts of interest related to this report.

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