

## The Effect of Sodium Carboxymethylcellulose on Prevention of Post-operative Pleural and Pericardial Adhesions in Dogs

Dongkyu Jung, Jongtae Cheong<sup>1</sup>, Kyungkap Lee, Heeseok Kim, Minjoo Choi\*,  
Seongchan Yeon\*\* and Kangmoon Seo\*\*\*  
College of Agriculture, Cheju National University, \*College of Medicine, Cheju National University,  
\*\*College of Veterinary Medicine, Gyeongsang National University,  
\*\*\*College of Animal Husbandry, Kangwon National University

### 개에서 Sodium Carboxymethylcellulose의 흉막 및 심낭에 대한 유착방지효과

정동규 · 정종태<sup>1</sup> · 이경갑 · 김희석 · 최민주\* · 연심찬\*\* · 서강문\*\*\*  
제주대학교 농과대학, \*제주대학교 의과대학, \*경상대학교 수의과대학, \*\*\*강원대학교 축산대학

**요 약** : 개의 개흉술이나 개심술 후에 주요 합병증인 유착에 대한 sodium carboxymethylcellulose (SCMC)의 효과를 평가하기 위하여 1% SCMC 용액을 흉막 및 심낭에 적용하였다. 10두의 개를 SCMC 투여 군과 생리식염수 투여 군으로 각각 5두씩 배치하고, 개흉 후 4번째에서 6번째 늑골의 늑연골 연접부 부위에 찰과상을 유도하였고 심낭 절개 후 심낭의 내측 및 맞닿는 심근에 각각 2×2 cm 크기로 찰과상을 유발하였다. 찰과상 유발 후 생리식염수 투여 군은 평균 생리식염수를 3.5 ml/kg을, SCMC 투여 군은 같은 용량의 1% SCMC를 흉강 및 심낭 내에 각각 도포 하였다. 수술 전후에 CBC와 혈장 plasminogen치를 측정하였다. 유착 정도는 수술 30일 후에 0-4로 점수화하여 판정하였다. 심장과 심낭의 평균 유착치는 SCMC 투여 군이 2.4±0.8, 생리식염수 투여군이 3.7±0.9로 나타나 SCMC 투여군에서 유착 발생이 유의성 있게 낮았다(p<0.01). 폐엽과 흉막간의 평균 유착치는 SCMC 투여군이 1.7±0.2이었고, saline 투여군은 3.5±0.8로 SCMC 투여 군에서 유착 발생이 유의성 있게 낮았다(p<0.01). Saline 투여군의 혈중 plasminogen 농도는 술 후 1일에 28.2±5.6%로 감소하였고, 술 후 7일에 47±1.4%로 증가하였다(p<0.05). SCMC 투여군에서는 실험적 수술 1일 후 27.1±10.3%로 감소하였고 7일 후에는 30.8±21.6%로 증가(p<0.01)하였으나 두 군간의 유의적인 차이는 없었다. 이상의 결과로 볼 때 개흉술 및 개심술 시 1% SCMC를 투여하여 흉강 내의 유착을 방지함으로써 제수술이 필요한 경우에 수술의 어려움과 조직손상의 위험을 감소시킬 것으로 사료된다.

**Key words** : dog, pleurum, pericardium, adhesion, SCMC

### Introduction

Adhesions across the pericardial space are a common complication of cardiac operation<sup>3</sup>. Although the previous formation of dense adhesions between the heart and the surrounding tissues does not result in immediate or obvious morbidity, repeated cardiac surgical procedures are associated with increased technical difficulty to surgeon and risk because of the

adhesions. Also, these complications may to cause serious secondary complications and diseases such as atelectasis and torsion of lung lobe<sup>2,3,4,9</sup>.

Suspected causes of the pleural adhesions are concurrent appearances of spilled blood<sup>10</sup>, mesothelial injuries such as drying of pleural membrane, and inflammatory response activation by spilled blood<sup>2,3</sup>. Currently, so many experiments and studies have been performed to prevent thoracic and pericardial adhesions. The pharmacological basis for adhesion prophylaxis includes agent that decrease the inflam-

<sup>1</sup>Corresponding author.

matory reaction<sup>1,12</sup>, prevent blood coagulation and fibrin deposition<sup>22</sup>, promote fibrinolysis<sup>8,24</sup>, mechanically separate the injured tissues<sup>11,14,17,18,26</sup> and closure of pericardium with loose suture and insertion of chest tubes<sup>4,15</sup>.

Sodium carboxymethylcellulose (SCMC) is a high molecular weight polysaccharide polymer that is water soluble, biocompatible and viscous<sup>5</sup>. It is believed that these substances act through a mechanical flotation method separating viscera by a physical barrier<sup>6,20</sup>.

The purposes of this study are to evaluate the efficacy of 1% SCMC to prevent postoperative pleural and pericardial adhesions and to find common adhesive structure after intra-thoracic operation in the dog.

## Materials and Methods

### 1. Experimental animal:

Ten mongrel dogs weighing between 5 to 10 kg were assigned to two groups at random. Each group consisted of 5 dogs. Food and water were available *ad libitum*. To determine previous diseases of the dogs, physical examinations and complete blood counts (CBC) were performed. The SCMC was prepared as 1% by weight per volume of distilled water, and sterilized in 121°C for 30 minutes

### 2. Experimental procedure:

**Preparing and Premedication:** CBC and plasminogen concentrations were evaluated three days before experimental operation. Broad spectrum antibiotics were given to the dogs two hours before surgical procedure intramuscularly and atropine sulfate (0.05 mg/kg of body weight) was injected intramuscularly before the operation.

**Anesthesia:** General anesthesia was induced with intravenous thiopental sodium (Pentothal®, 10-15 mg/kg of body weight). After the animal was anesthetized, endotracheal intubation was immediately done and inhalation of oxygen was allowed for 35 minutes to provide the sufficient oxygenation and "lung wash-out". Draping in a sterile fashion was performed during anesthesia. After the animal had general anesthesia, a combination of N<sub>2</sub>O (120 ml/kg/min)

and oxygen (200 ml/kg/min) was inhaled in the semi-open circuit system. Stage III surgical anesthesia was maintained with nitrous oxide, oxygen, and enflurane. Ancillary respiratory support (PEEP) was performed during the operation.

**Operative procedure:** Thoracotomy was performed by median sternotomy. After opening the thorax, the costal pleurum between the 4th and 6th intercostal spaces at the costochondral junction was then abraded bilaterally with dry gauze sponge. After making the two pleural abrasions (right and left pleurum), the pericardium was incised longitudinally from the apex to the base of heart about 1 cm anterior to the left phrenic nerve. An Abrasion between visceral pericardium and myocardium by rubbing with a dry gauze sponge was made in the middle part of myocardium. The size of each abrasion was 2×2 cm. Instillation of 0.9% sterilized normal saline (3.5 ml/kg) into the pleural and pericardial space then done in saline-treated group, but irrigation of sterilized 1% SCMC (3.5 ml/kg) was performed into the thoracic cavity in SCMC-treated group. Then, the thorax was closed without closing the opened pericardium.

**Evaluation of CBC and plasma plasminogen concentration:** CBC was evaluated every 3 days after surgery for 30 days, but plasminogen concentration was determined on the 1st, 3rd, 5th day after the operation. Blood samples were obtained from cephalic vein in the dogs. Fibrinogen and total protein were evaluated with a refractometer. RBC counts, WBC counts were determined manually with a hemocytometer. PCV value was evaluated by microhematocrit method. Plasma plasminogen concentration was evaluated using chromogenic plasminogen kit (Accucolor, Sigma, USA).

**Evaluation of adhesions:** All dogs were sacrificed on the 30th day after the operation. Two veterinarians who were unaware of the operation schedule and application evaluated severity of the adhesions. Evaluation was performed by scoring 0 to 4 point according to severity of the adhesions (Table 1). In addition, predominant adhesion sites of the thoracic organs were classified and determined.

**Statistical analyses:** Scores from each group were compared using *t*-test and ANOVA. Hematological

**Table 1.** Classification of Adhesion Scores

Pericardial/pleural adhesion score	Observation
0	No adhesions
1	Filmy adhesions with easily identifiable plane
2	Mild adhesions with freely identifiable plane
3	Moderate adhesions with difficult plane of dissection
4	Dense adhesions with no plane of dissection

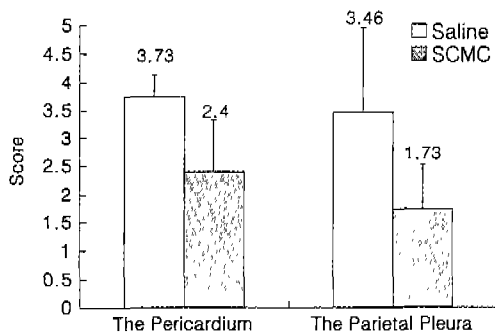
- Derived from "Prevention of pericardial adhesions using tissue protective solutions" by Seeger et al.<sup>21</sup>.

values were analyzed using *t*-test. Determination of common adhesion formation structure analyzed using ANOVA.

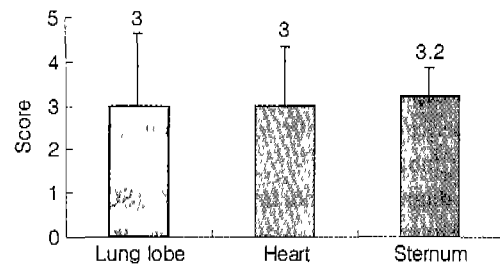
**Results**

The adhesions were formed in all dogs in saline-treated group, whereas they are formed in 3 dogs in SCMC-treated group. Mean adhesion scores in saline-treated group, and SCMC-treated group are shown in the Fig 1. Mean adhesion score in saline-treated group (3.7) was much higher than that in SCMC-treated group (2.4) in the pericardium. Mean adhesion score of saline-treated group (3.5) in the parietal pleura was also significantly higher than that of SCMC-treated group (1.7).

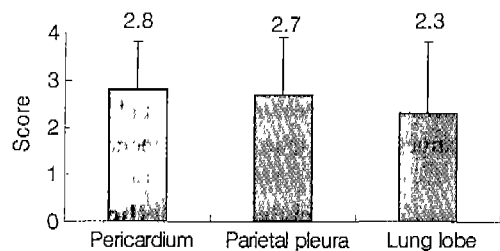
Fig 2 and 3 show the predominant adhesions formation areas in the pleural cavity. Mean adhesion



**Fig 1.** Mean adhesion scores of saline-treated group were significantly higher than that of SCMC-treated group in the pericardium and the parietal pleura ( $p < 0.01$ ).



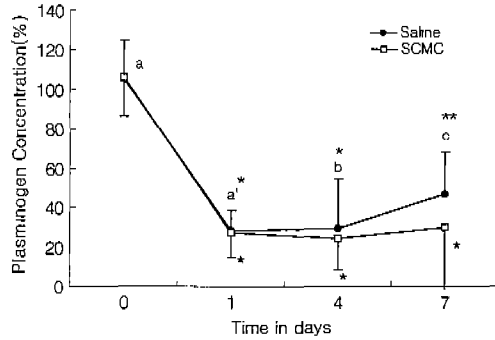
**Fig 2.** The sternum was the most common adhesion structure to the pericardium ( $p < 0.05$ ).



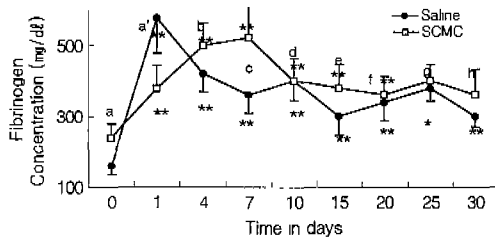
**Fig 3.** The pericardium was the most adhesive structure on the parietal pleura ( $p < 0.05$ ).

scores in the lung lobes and hearts were 3.0 but mean adhesion score between the pericardium and the sternum was 3.2. In addition, 33% of adhesions formed between the lung lobes and pericardium, or between the pericardium and the heart. Whereas, 34% of adhesions formed in the sternum. Retro-sternal pericardial adhesions occurred most often. Mean adhesion scores in the lung lobes are shown in Fig 3. Mean adhesions scores in the pericardium and in the parietal pleurum were 2.8 (36%) and 2.7 (35%). Mean adhesion score among the lung lobes was 2.3 (29%). The pericardium was the most significant adhesion formation area in the pleural cavity ( $p < 0.05$ ).

The variances of plasminogen concentration in the control and SCMC-treated group are shown in the Fig 4. Mean plasminogen concentration on the 3rd day before the operation was 105.6% in saline-treated group and 105.9% in SCMC-treated group. On the first day after the operation mean plasminogen concentrations in saline-treated group and SCMC-treated group decreased to 28.2% and 27.1%, respectively. From the 4th day after the operation, mean plasminogen concentration in saline-treated group increased to 29.5% but it decreased further to 24.4% in SCMC-



**Fig 4.** Mean plasminogen concentrations of saline-treated and SCMC-treated groups were similar 3 days before the operation, but difference between two groups appeared on the first day after the operation. a:a, a:b, a:c; significantly differential pairs (\* $p < 0.01$ , \*\* $p < 0.05$ ).

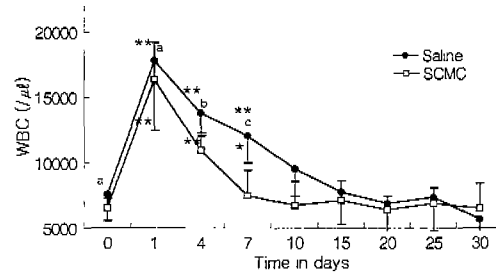


**Fig 5.** Mean fibrinogen concentration variation in saline-treated group significantly increased on the first day after the operation. a:a, a:b, a:c, a:d, a:e, a:f, a:g, a:h, a:i; significantly differential pairs (\* $p < 0.01$ , \*\* $p < 0.05$ ).

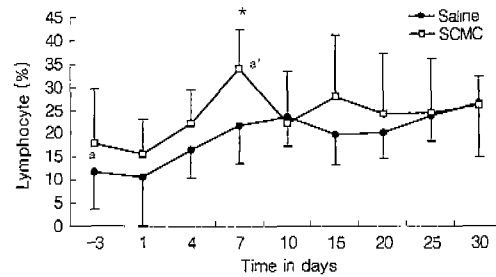
treated group.

Mean variation of fibrinogen concentration in blood is shown in Fig 5. Mean fibrinogen concentration in saline-treated group increased significantly to 580 mg/dl on the 1st day after the operation, but that of saline-treated group increased to 520 mg/dl on the 7th day after the operation. It decreased on the 4th day after the operation and gradually decreased to 300 mg/dl in saline-treated group but increased slowly up to the 7th day and decreased on the 10th day after the operation in SCMC-treated group.

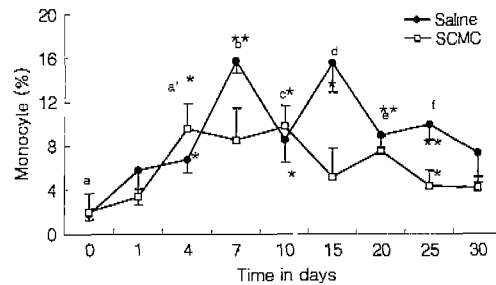
Mean numbers of white blood cells (WBC) had no significant difference between saline-treated group and SCMC-treated group (Fig 6). Mean WBC counts of saline-treated group and SCMC-treated group were significantly increased on the 1st day and decreased gradually upto the 7th day after the operation. In addition, mean WBC counts of SCMC-treated group were



**Fig 6.** WBC values in SCMC-treated group were lower than those in saline-treated group. a:a, a:b, a:c; significantly differential pairs (\* $p < 0.01$ , \*\* $p < 0.05$ ).



**Fig 7.** Mean values of lymphocyte counts significantly increased on the 7th day after the operation in SCMC-treated group. a:a; significantly differential pairs (\* $p < 0.01$ ).



**Fig 8.** Mean monocyte counts of saline-treated group were higher than those of SCMC-treated group. The peak point of them achieved on the 7th day in saline-treated group but was achieved on the 10th day after the operation in SCMC-treated group. a:a, a:b, a:c, a:d, a:e, a:f; significantly differential pairs (\* $p < 0.01$ , \*\* $p < 0.05$ ).

lower than those of saline-treated group.

Mean values of the lymphocyte and monocyte counts are shown on Fig 7 and 8. Mean value of the lymphocyte of SCMC-treated group was significantly increased on the 7th day after the operation (34.0%) but that of saline-treated group did not increase significantly. Mean values of the monocytes of saline-

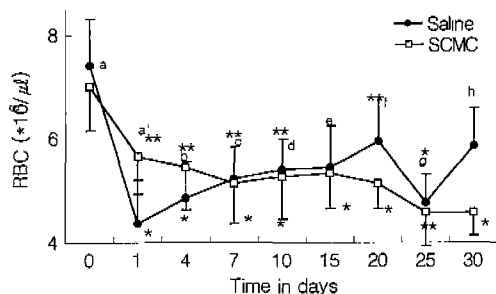
treated group (6.8%) and SCMC-treated group (9.6%) significantly increased on the 4th day after the operation. In addition, mean values of the monocytes of saline-treated group (15.8%) much increased on the 7th day after the operation and those of SCMC-treated group (9.8%) also increased. In saline-treated group, they increased to the peak point (15.8%) on the 7th day after the operation. The peak point of SCMC-treated group (9.8%) was achieved on the 10th day after the operation.

Mean variation tendencies of RBC counts are shown on Fig 9. Mean RBC counts of saline-treated group (4.4106/ $\mu$ l) and SCMC-treated group (5.1106/ $\mu$ l) decreased after the operation. RBC counts of SCMC-treated group decreased significantly on the 1st day after the operation and recovered slowly during the one month time span.

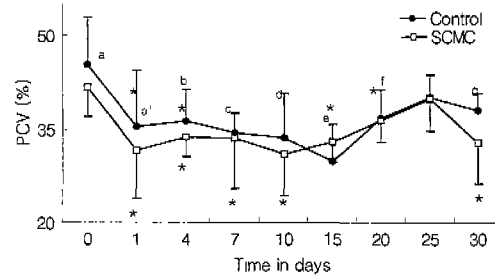
Mean packed cell volume (PCV) is shown in Fig 10. PCV decreased on the 1st day in control and SCMC-treated group and gradually increased during the one month time span.

## Discussion

Mean adhesion score of SCMC-treated group was lower than that of saline-treated group. Seeger et al.<sup>21</sup> demonstrated that SCMC is six times more effective than saline, but it had dramatic effects in this study. The increased adhesion scores in this study, compared with previous studies, may have been due to more vigorous and severe abrasions, which were inflicted



**Fig 9.** Mean RBC values in saline-treated group decreased on the 1st day after the operation and slowly increased during 30 days. Whereas, those in SCMC-treated group slowly decreased in all trials. a:a, a:b, a:c, a:d, a:e, a:f, a:g, a:h; significantly differential pairs (\* $p$ <0.01, \*\* $p$ <0.05).



**Fig 10.** Mean packed cell volume variations decreased to 35.6% in saline-treated group and 31.8% in SCMC-treated group on the 1st day after the operation. a:a, a:b, a:c, a:d, a:e, a:f, a:g; significantly differential pairs (\* $p$ <0.01, \*\* $p$ <0.05).

in the animals, compared with those of the previous studies. The mechanism of SCMC have not been defined clearly, but it is suggested that separation of serosal surface because of its lubricating and floating action. Normal saline is reabsorbed quickly, but SCMC may be done more slowly. The fact may explain the positive result of this experiment.

This study found that pericardium commonly formed retrosternal adhesion. Moreover, the pericardium adheres to lung lobe most commonly. Therefore, it was suggested that the pericardium most easily forms adhesions among pleural structures. Previous study of Okuyama et al.<sup>16</sup> supported this result.

Plasma plasminogen concentrations were at the lowest point on the first day after the operation but it increased slowly in saline-treated group. In the SCMC-treated group, plasminogen concentration did not increase in comparison with saline-treated group. Trent and Bailey<sup>23</sup> demonstrated plasminogen variation after trauma. They suggested that activity of plasminogen activator initially decreases precipitously below base-line activity, then increase to well above base line values by 5 days after trauma, gradually decreasing to base-line values during the following weeks and months. In this experiment, plasminogen concentration decreased on the 1st day after the operation and increased a little on the 4th day after the operation. On the 7th day, mean plasminogen concentration increased more, but there was no significant difference between saline-treated group and SCMC-treated group. Mean plasminogen concentration of SCMC-treated group increased more slowly

than that of saline-treated group. It may be suggested that fibrinolytic activity would be prolonged in SCMC-treated group. In addition, it may be explained that more acute and severe non-infectious inflammatory response presented in saline-treated group than SCMC-treated group. It also demonstrated that migration of plasminogen from tissue to blood was interrupted by SCMC in SCMC-treated group. More recent speculation by Ryan and Sax<sup>20</sup> suggested that polymer coatings of SCMC prevent removal of plasminogen from traumatized surfaces, thereby increasing its availability for activation. In saline-treated group, mean fibrinogen concentration was increased to peak point on the first day after the operation. But in SCMC-treated group, the fibrinogen concentration increased on the 7th day after the operation to peak point. These results may suggest that fibrosis was disturbed and slowly formed in SCMC-treated group. Good et al.<sup>7</sup> demonstrated the fibrinogen concentration variation in a model of pleural adhesions. The peak fibrinogen concentration presented 24 hours after the induction of adhesion and progressively decreased over time. In this experiment, mean fibrinogen concentration of saline-treated group reached peak point on the 1st day after the experimental operation and decreased gradually for 30 days. The peak point of mean fibrinogen concentration in SCMC-treated group, however, was achieved on the 7th day after the operation. It may be explained preventive efficacy of SCMC in pleural cavity.

Good et al.<sup>7</sup> also suggested leukocyte values of pleural fluid. WBC counts in pleural fluid peaked at 24 hours and progressively decreased over 30 days. Mean WBC counts of this study also demonstrates the variance of the leukocyte in pleural adhesion animal model. Mean WBC counts peaked on the 1st day after the operation in saline-treated group and decreased gradually. Although mean WBC counts of SCMC-treated group were much less than those of saline-treated group, similar variation tendency was observed.

Mean lymphocyte and monocyte counts were determined in this study. Activated macrophages and T-lymphocytes are known that they play an important role in postoperative wound healing and adhesion for-

mation. Mean lymphocyte counts of saline-treated group peaked on the 7th day after the operation but mean lymphocyte counts of SCMC-treated group peaked on the 10th day after the operation. Leak et al.<sup>12</sup> suggested that fibroblasts and macrophages increased but small numbers of lymphocytes were found on the 3rd day and fibroblasts, macrophages and small numbers of lymphocytes were found on the 8th day after adhesion induction. This study found that lymphocytes of blood increased on the 7th day and then decreased on the 15th day after the operation in the pleural and pericardial adhesion animal model. Mean monocyte counts increased on the 4th day after the operation. Rein and Hill<sup>17</sup> suggested that macrophages might further contribute to postoperative adhesion formation by stimulating angiogenesis and secreting plasminogen activators. Therefore, mean monocyte counts in this experiment re-demonstrate the suggestion of Rein and Hill<sup>17</sup>. Mean lymphocyte and monocyte counts of SCMC-treated group were lower than those of saline-treated group. Moreover, the changing tendency of them in SCMC-treated group was significantly different from those in saline-treated group and slow variation tendency was observed. These results can explain the adhesion prevention effect of SCMC.

In order to accelerate diffusion of SCMC, the incised pericardium was left open. Usually the pericardium has been left open following the operation to permit drainage into the pleural spaces or mediastinum<sup>4</sup>. Moreover, additional reason was that attempting the closure of the pericardium often visibly constricted the heart, with impairment of function. Cunningham Jr. et al.<sup>4</sup> and Nandi et al.<sup>15</sup> described the result from closure of pericardium after open-heart surgery. They demonstrated that closure of pericardium could reduce adhesion formation of the heart to the median sternum and cardiac tamponade. In this study, closure of pericardium was hazardous because it would inhibit diffusion of SCMC into the pericardial space. Moreover, if there were over-tension in pericardium, it might cause cardiac tamponade and fatal results. Malm et al.<sup>13</sup> and Okuyama et al.<sup>16</sup> suggested that cardiac tamponade occurs more often after pericardial closure. Pericardium adheres to the middle

or caudal lung lobes most commonly in this study but there was no evidence of hypoventilation or exercise intolerance among the affected dogs. Except for pericardial adhesions to lung lobes, there were no additional adhesions in the thoracic cavity. Therefore, resection of the incised pericardium or closure of pericardium may be a sensible choice in surgical procedure. Kerstetter et al.<sup>10</sup> reported the results of pericardiectomy in dogs. They suggested that the surgical procedure (subtotal vs. total pericardiectomy) was not significantly associated with survival time of dogs. This fact further supported that suggestion in this study.

The determination of the dose of 1% SCMC in thoracic surgery was the main problem in this study. In general abdominal and pelvic surgical procedures, 7 ml/kg of body weight of 1% SCMC have been used in veterinary surgical procedures until now but it may make artificial ascites (float action) which can interrupt normal movement of organs. The heart or the lung lobes are life-threatening organs. Seeger et al.<sup>21</sup> experimented with SCMC to prevent postoperative pericardial adhesions. They used 25 ml of 1% SCMC solution in weighing 15-20 kg dogs but in this study, the dose of 1% SCMC was a half of general abdominal or pelvic the operation (3.5 ml/kg of body weight). As a mechanism of SCMC, artificial pericardial effusion probably was induced. Good et al.<sup>7</sup> and Ik heimo et al.<sup>9</sup> suggested that pericardial effusion can reduce cardiac tamponade and pleural fluid has not evident effect of adhesion formation. At necropsy which was performed one month after experimental operation, there was no residual exudate or SCMC solution.

### Conclusion

The sodium carboxymethylcellulose (SCMC) have been shown to be effective in the prevention of both pleural and pericardial adhesions. In addition, more adhesive structure of pleural cavity was found to the pericardium in this experiment. The adhesions formed more commonly between the pericardium and the sternum. This study suggests that the dosage of 1% SCMC (3.5 ml/kg of body weight) could prevent postoperative pleural and pericardial adhesions with-

out any complications.

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