Triple-combination surgery with thoracic duct ligation, partial pericardectomy, and cisterna chyli ablation for treatment of canine idiopathic chylothorax

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Running head: SURGERY FOR CANINE CHYLOTHORAX
Abstract

This study aimed to evaluate the outcomes and complications of triple-combination surgery consisting of thoracic duct ligation (TDL), partial pericardiectomy (PPC), and cisterna chyli ablation (CCA) for the treatment of idiopathic chylothorax in dogs. Eleven privately owned dogs with idiopathic chylothorax underwent the triple-combination surgery: TDL and PPC were performed in left recumbency, followed by CCA in dorsal recumbency. Of the 11 dogs, seven were Shiba, two were Afghan hounds, and one each was Borzoi and mixed-breed. TDL and PPC required two intercostal thoracotomies in five dogs, whereas they were performed through a single intercostal incision in the other dogs. None of the dogs showed major intraoperative complications. The median operation time was 190 min (range, 151–234 min). Nine dogs showed no pleural effusion after surgery without medical management. Another dog showed the disappearance of chylous effusion, followed by the pleural accumulation of modified transudate. However, the residual one dog in whom chylothorax did not improve postoperatively died 4 months after the combination surgery. The mortality rate at the conclusion of this study was 9.1%. Although the triple-combination surgery with TDL, PPC, and CCA was complex and required a prolonged operation time, the success rate of resolving chylothorax in our study was comparable to that of open surgery as previously reported. Therefore, this study suggests that such triple-combination surgery can become one of the therapeutic options for the management of canine idiopathic chylothorax.

Keywords: cisterna chyli ablation, dog, idiopathic chylothorax, partial pericardiectomy, thoracic duct ligation
INTRODUCTION

Chylothorax refers to the collection of chyle in the pleural space [7,13], and is categorized into primary and secondary types: primary chylothorax is the so-called idiopathic form, while the pathogenesis of secondary chylothorax includes cardiomyopathy, mediastinal masses (e.g., lymphosarcoma, thymoma), dirofilariasis, cranial caval thrombosis, diaphragmatic hernia, congenital cardiac diseases (e.g., tetralogy of Fallot, tricuspid dysplasia, cor triatriatum dexter), pericardial effusion associated with lung lobe torsion, and congenital anomalies [7, 13]. Idiopathic chylothorax is more common in dogs as compared to secondary chylothorax. In canine idiopathic chylothorax, medical treatment includes low-fat diet feeding, chylous drainage by a thoracic tube or thoracocentesis, and rutin, predonisolone and/or octreotide administration [7]. However, medical treatment often fails to alleviate chyle accumulation in dogs.

Surgery is warranted for the treatment of canine idiopathic chylothorax for which medical management has become impractical or ineffective [7]. Thoracic duct ligation (TDL) is the conventional surgical treatment in such cases; however, the clinical resolution rate for a single TDL procedure has been reported to be 50–59% in dogs with idiopathic chylothorax [2, 16]. Several surgical techniques have been proposed for the treatment of canine idiopathic chylothorax [7, 14, 16]. Surgical ligation of the thoracic duct in combination with cisterna chyli ablation (CCA) [9, 13] or partial pericardiectomy (PPC) [4, 6, 8] has been reported to show the highest curative rates among several surgical procedures.

We hypothesized that the combination of these three techniques (TDL, PPC, and CCA) could improve the success rate for the treatment of canine idiopathic chylothorax. The purpose of this clinical study was to evaluate the outcomes and complications of a triple-combination surgery (TDL, PPC, and CCA) in dogs with idiopathic chylothorax.
MATERIALS AND METHODS

Animals

Eleven dogs were referred to the Animal Medical Center of Nihon University with a suspicion of idiopathic chylothorax. All dogs were diagnosed as an idiopathic chylothorax by physical examination, complete blood count, serum chemistry, radiography, ultrasonography, and pleural effusion analysis following thoracocentesis. At the initial evaluation, the clinical signs and amount of pleural effusion removed by thoracocentesis were recorded in all dogs. Each dog underwent a combination surgery consisting of TDL, PPC, and CCA after showing little response to medical management, including rutin and prednisolone administration.

Surgery

Oral administration of corn oil (1.0 mL/kg) was performed in each dog 4, 3, and 2 hr before the operation. Before general anesthesia, subcutaneous injections of 1.0 mg/kg prednisolone (Kyoritsu Seiyaku Co., Tokyo, Japan), 1.0 mg/kg famotidine (LTL Pharma Co., Tokyo, Japan), and 1.0 mg/kg maropitant citrate (Cerenia®; Zoetis, Parsippany, NJ, USA) were administered. Subcutaneous injection of 0.04 mg/kg atropine (Mitsubishi Tanabe Pharma Co., Osaka, Japan), followed by intravenous injection of 0.1 mg/kg midazolam (Dormicum; Astellas Pharma Inc., Tokyo, Japan) and 5.0 µg/kg fentanyl–0.25 mg/kg droperidol (Thalamonal; Daiichi-Sankyo Propharma Co., Ltd., Tokyo, Japan) were performed as a premedication. General anesthesia was induced with propofol (Mylan; Mylan Seiyaku Ltd., Tokyo, Japan). After endotracheal intubation, each dog was mechanically ventilated with an isoflurane (IsoFlo; Zoetis) and oxygen mixture. For analgesia, intra- and postoperative continuous drip infusions of remifentanil (5–40 µg/kg/hr) (Ultiva; Janssen Pharmaceutical K.K., Tokyo, Japan) and pre- and postoperative intramuscular injections of morphine (0.3 mg/kg each dose) (Takeda Pharmaceutical Co. Ltd., Osaka, Japan) were administered.
Each dog was positioned in left lateral recumbency under general anesthesia. Right eighth, ninth, or tenth intercostal thoracotomy was routinely performed to drain the chyle and confirm the thoracic duct. After the paracostal abdominal incision, placement of a 26G over-the-needle catheter in the lymph duct was attempted. Successful placement was followed by lymphangiography and 0.5 mg/kg injection of indocyanine green (ICG; Daiichi-Sankyo Propharma Co., Ltd.) into the lymph duct for the confirmation of the thoracic ducts. In the case of unsuccessful catheter placement, fractionated injections of ICG (total 0.5 mg/kg) were performed into the mesenteric lymph nodes. Two to four ligations of the thoracic duct with 4-0 polypropylene suture material (Prolene®, Johnson & Johnson, New Brunswick, NJ, USA) were performed in all dogs. After the TDL, PPC under the phrenic nerves was performed by a monopolar electrocautery and vessel sealing system (Force Triad™; Medtronic, Minneapolis, MN, USA) via the same intercostal incision in some cases. In the presence of severe intrathoracic adhesion, PPC under the phrenic nerves was achieved via another intercostal incision in other cases. In cases showing simultaneous lobar torsion, lung lobectomy was subsequently performed by surgical ligation of each vessel with 3-0 polydioxanone sutures (PDS II®, Johnson & Johnson). All the obtained specimens including the pericardium were submitted for histopathological examination. One or two intercostal incisions and paracostal abdominal incisions were routinely closed following chest tube placement. Each dog was repositioned in dorsal recumbency. After median celiotomy, cisterna chyli was identified via dissection around the aorta between the left adrenal gland and the bifurcation of the left renal artery, followed by CCA with monopolar and bipolar electrocauterities to confirm the adequate leakage of chyle. The abdominal incision was routinely closed.

*Histopathological examination*

The obtained tissue samples were immersed in 10% neutral buffered formalin for 48 hr and then embedded in paraffin. The sections were then deparaffinized with xylene and immersed in
ethanol. The slides were stained with hematoxylin and eosin and subjected to histopathological diagnosis.

Postoperative management

Postoperatively, the amount of pleural fluid and air leakage were investigated while the dogs were hospitalized. Postoperative outcome was determined as excellent (chylous effusion disappeared with no medical management and the patient's quality of life [QOL] improved), good (chylous effusion disappeared and the patient's QOL improved, but medical management was needed for major complications), and poor (chylous effusion continued and the patient's QOL did not improve) by surveying the medical records or by interviewing the referring veterinarians or dog owners.
RESULTS

The signalment and outcomes of 11 dogs with idiopathic chylothorax are summarized in Table 1. Of the 11 dogs, seven were Shiba, two were Afghan hounds, and one each was Borzoi and mixed-breed. The median age was 4.6 years old (range, 3.5–12.2 years old). There were 6 males (including 3 neutered) and 5 females (including 1 spayed). The median body weight was 9.4 kg (range, 6.7–32.1 kg).

The clinical symptoms identified in the initial evaluation were tachypnea in nine cases (81.8%), anorexia in five cases (45.5%), lethargy in three cases (27.3%), cough in two cases (18.2%), and nausea, weight loss and exercise intolerance in one each case (9.1%). Initial radiographic examinations showed pleural effusion in all cases. The median amount of pleural effusion removed in the initial evaluation was 47.7 mL/kg (range, 14.5–159 mL/kg) in all dogs. The median rate of accumulating pleural fluid was 10.8 mL/kg/day (range, 5.6–17.6 mL/kg/day) in all dogs except for one dog that could not be calculated due to the missing data. The median period from clinical manifestation to initial evaluation at our hospital was 32 days (range, 5–568 days), whereas the median period from initial evaluation to surgery in our hospital was 13 days (range, 1–33 days).

The median operation time was 188 min (range, 151–234 min). Of the 11 dogs, five underwent two intercostal thoracotomies for TDL. None of the dogs showed major intraoperative complications. Each dog was monitored in the oxygen room for a few days after the operation. For perioperative analgesia, continuous intravenous infusion of remifentanil was used from the start of operation to 3 days after the operation. In addition, perioperative morphine and meloxicam were subcutaneously administered.

Histopathological examination of the pericardium showed mesothelial proliferation and thickening in seven cases and lymphocytic infiltration in six cases. Among the two cases showing torsion of the lung lobes, the lungs showed intralobar hemorrhage in one case and necrosis in the second case.
The median postoperative follow-up period was 1,640 days (range, 117–3,275 days). During the follow-up period, ten (90.9%) showed resolution of chylous effusion. Of these ten dogs, nine showed an excellent prognosis with no recurrence of pleural effusion during the follow-up period. While the residual one dog showed the postoperative disappearance of chyle, but a small amount of modified transudate slowly accumulated in the thorax. This dog did not show respiratory distress on any follow-up examination but required thoracocentesis every 3 to 4 months to check for recurrence of chylothorax and remove pleural transudate. Thus, her QOL was improved postoperatively, and her prognosis was good. Of the nine patients with excellent prognosis, one dog died of unknown causes: however, this patient showed no recurrence of chylous effusion on the day of death.

In the dog with a poor prognosis, the respiratory status did not improve even after pleural effusion was adequately removed by thoracentesis, and rapid re-accumulation of chylous fluid was observed. The intraoperative gross findings in this dog showed severe proliferation of parietal and visceral pleural membranes and insufficient inflation of the lungs. Because of the repeated postoperative retention of pleural chyle, the dog underwent surgical implantation of a Denver pleuroperitoneal shunt tube on postoperative day 87; however, it died of potential respiratory failure 117 days after the triple-combination surgery. Thus, the mortality rate in this clinical study was 9.1%.
DISCUSSION

Since TDL alone has an unsatisfactory cure rate, various methods such as omentalization [3, 19], CCA [9, 13], PPC [4, 6, 8, 13], and shunt tube placement [17] have been combined with TDL. However, the optimal combination of surgical techniques is still being debated. A previous systematic review did not arrive at favorable conclusions for the effectiveness of any surgical method in dogs and cats, nor did they find any evidence to support continued medical treatment [14]. However, CCA and PPC are promising surgical methods for combination with TDL. A prospective comparative study of CCA and PPC in addition to TDL showed that TDL-CCA (83%) had a higher cure rate than PC-TDL (60%) [13]. However, in our study, the triple combination of TDL with CCA and PPC resulted in a 90.9% success rate of resolving chylothorax, yielding comparable outcomes as compared with other open surgeries previously reported [13, 14]. Therefore, a surgical approach that combines the three surgical methods is suggested to become an alternative therapeutic option for canine idiopathic chylothorax.

The rationales for adjunctive CCA are to prevent the development of hypertension within the cisterna chyli and secondary collateral lymphatic vessels developing around the ligation site, and to promote formation of new lymphaticovenous connections outside of the thorax [9, 13, 15, 16]. A previous experimental study demonstrated that CCA combined with TDL was successful in creating alternate lymphaticovenous connections in healthy dogs [15]. On the other hand, the effectiveness of adjunctive PPC is based on the hypothesis that the development of a thickened pericardium secondary to chylothorax may lead to increased right-sided venous pressure that could in turn impede chyle drainage through new lymphaticovenous connections formed as a result of TDL [8, 13, 16]. In the previous study, the salvage procedures including PPC caused the resolution of chylothorax in 1 of 2 dogs with treatment failure after a combination surgery of TDL and CCA, and salvage CCA procedure resolved chylothorax in 1 of 2 dogs with treatment failure after a combination surgery of TDL and PPC [13]. Therefore, the triple combination surgery of TDL, CCA, and PPC potentially has
clinical usefulness based on both adjunctive procedures' rationales. However, the previous study on comparison of TDL and PPC versus TDL and PPC plus CCA in 22 cats with idiopathic chylothorax reported the additional CCA produced no better outcome than TDL and PPC alone [20]. Further large-scaled clinical studies on the triple-combination surgery are warranted to evaluate its superiority in canine idiopathic chylothorax.

In our study, intercostal thoracotomy in the left lateral recumbency was chosen as a surgical approach for TDL and PPC. In the previous study, the surgical approach for TDL and PPC was median sternotomy and cranial midline celiotomy in the dorsal recumbency [6, 13]. Considering the triple-combination surgery, such surgical approach is thought to have the advantage that TDL, PPC and CCA can be achieved via one skin incision without change in the patient's position. In addition, PPC under the median sternotomy and cranial midline celiotomy might be more easily performed than that under the lateral intercostal thoracotomy. However, the thoracic ducts generally run in the dorsal aspect of aorta and are behind the aorta, hidden from view from the ventral side via the surgical approach of combined median sternotomy and cranial midline celiotomy. We considered that thorough ligations of thoracic ducts should be difficult under median sternotomy and cranial midline celiotomy: however, a previous study has described that TDL was feasible via such surgical approach in 10 of 11 dogs [6]. Further investigations on comparison of the surgical approaches are required for the triple-combination surgery in canine idiopathic chylothorax.

The pre- and intraoperative identification of thoracic ducts are essential for the complete surgical ligation of the thoracic ducts. A few previous studies have shown that computed tomographic (CT) lymphangiography is useful for preoperatively identifying the thoracic ducts in dogs with chylothorax [10, 11]. This novel technique has the potential for visualization of lymphatic vessels in the thoracic and abdominal cavities without laparotomy and thus, might help in understanding the anatomical patterns of thoracic duct variations. Therefore, preoperative CT lymphangiography might facilitate the complete ligation of thoracic ducts. Recently, near-infrared fluorescent imaging using
ICG was reported to be feasible for thoracic duct identification under thoracoscopy [18]. During the TDL, this technique might serve as a guide for the identification of thoracic ducts. Therefore, both imaging techniques of CT lymphangiography and ICG fluorescent imaging may improve the success rate in resolving chylothorax for the triple-combination surgery in dogs.

The major drawbacks of using TDL, PPC, and CCA together are as follows: (1) the need for intraoperative repositioning, (2) increased surgical invasion due to an increase in incisions, and (3) extension of the surgery time because of the need to perform three procedures. In some cases, severe pleural thickening and adhesions necessitated two intercostal incisions, requiring more careful analgesic management. However, in our study, the extension of surgery time did not increase the incidence of perioperative complications, although methodological improvement to shorten the surgery time might be required. Endoscopic surgery [1, 12] and thoracic duct glue embolization [5] can eliminate these shortcomings in terms of increased surgical invasion and extended surgical time. However, these treatments require a high level of surgeon skill, and the facilities where these procedures can be performed are still limited; thus, the superiority of the treatment method is not definitive. Further clinical studies of these procedures on spontaneous cases of canine idiopathic chylothorax are needed to clarify these issues.

In our study, one dog with severe pleuritis observed intraoperatively had a poor prognosis after undergoing triple-combination surgery. In animals with severe pleuritis, complete ligation of the thoracic duct may technically fail because it is difficult to visualize the ducts [7]. In addition, in cases with pleural proliferation of the lung, respiratory failure due to restriction of pulmonary compliance may continue postoperatively. An objective grading system for severity of pleuritis has not been established to date; therefore, its establishment is required to clarify the association between the severity of pleuritis and surgical outcome. We considered that a longer duration and higher volume of intrapleural chylous fluid accumulation could lead to more severe pleuritis, resulting in a poor prognosis. However, the period from clinical manifestation to surgery and the amount of transudate
removed preoperatively were not associated with the surgical outcome in our study. The time of onset of the patient's clinical manifestations depended on the owners. Additionally, the amount of preoperative chylous fluid removed would depend on the referring hospital. Therefore, further investigations are required to clarify the relationship between chylous fluid retention and the severity of pleuritis.

The limitations of this study included a small sample size and a bias in dog breeds. Notably, the treatment method in this study was limited to open surgery including thoracotomy and laparotomy surgery and excluded endoscopic surgery or interventional radiology.

In conclusion, the success rate in resolving chylothorax in our study was comparable with to open surgery as previously reported, although the triple-combination surgery with TDL, PPC, and CCA was complex and required a prolonged operation time. Therefore, this study suggests that such triple-combination surgery may become one of the therapeutic options for canine idiopathic chylothorax.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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REFERENCES


Table 1. Outcome of surgical treatment of idiopathic chylothorax in 11 dogs.

<table>
<thead>
<tr>
<th>No.</th>
<th>Breed</th>
<th>Age (y-o)</th>
<th>Gender</th>
<th>BW (kg)</th>
<th>Clinical signs</th>
<th>Removed pleural fluid</th>
<th>Period (days)</th>
<th>Op time (min)</th>
<th>Additional operation</th>
<th>Outcome*</th>
<th>Post op. follow-up (days)</th>
<th>Postoperative prognosis at the end of follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shiba</td>
<td>4.6</td>
<td>F</td>
<td>6.7</td>
<td>Tachypnea</td>
<td>53.7 10.8</td>
<td>33 8</td>
<td>216 -</td>
<td></td>
<td>Excellent</td>
<td>3,275</td>
<td>Survived with no recurrence</td>
</tr>
<tr>
<td>2</td>
<td>Afghan hound</td>
<td>3.5</td>
<td>M</td>
<td>23.5</td>
<td>Anorexia, lethargy and tachypnea</td>
<td>125 NA</td>
<td>568 22</td>
<td>193 -</td>
<td></td>
<td>Excellent</td>
<td>1,897</td>
<td>Survived with no recurrence</td>
</tr>
<tr>
<td>3</td>
<td>Shiba</td>
<td>4.4</td>
<td>M/N</td>
<td>8.5</td>
<td>Anorexia, lethargy and tachypnea</td>
<td>123 17.6</td>
<td>27 13</td>
<td>233 -</td>
<td></td>
<td>Excellent</td>
<td>2,886</td>
<td>Survived with no recurrence</td>
</tr>
<tr>
<td>4</td>
<td>Shiba</td>
<td>5.8</td>
<td>F</td>
<td>7.7</td>
<td>Anorexia and tachypnea</td>
<td>47.7 8.0</td>
<td>32 22</td>
<td>190 -</td>
<td></td>
<td>Poor</td>
<td>117</td>
<td>Died of respiratory failure caused by continued chylothorax</td>
</tr>
<tr>
<td>5</td>
<td>Shiba</td>
<td>4.3</td>
<td>M/N</td>
<td>10.6</td>
<td>Nausea, anorexia and lethargy</td>
<td>39.5 9.8</td>
<td>34 22</td>
<td>167 -</td>
<td>Lung lobectomy for lung torsion</td>
<td>Excellent</td>
<td>2,610</td>
<td>Survived with no recurrence</td>
</tr>
<tr>
<td>6</td>
<td>Borzoi</td>
<td>8.3</td>
<td>M/N</td>
<td>32.1</td>
<td>Anorexia and tachypnea</td>
<td>28 14.0</td>
<td>27 6</td>
<td>234 L</td>
<td></td>
<td>Good</td>
<td>1,349</td>
<td>Survived with pleural effusion of modified transudate</td>
</tr>
<tr>
<td>7</td>
<td>Mix</td>
<td>12.2</td>
<td>F/S</td>
<td>9.4</td>
<td>Cough, anorexia and weight loss</td>
<td>72.3 14.5</td>
<td>33 33</td>
<td>188 -</td>
<td></td>
<td>Good</td>
<td>1,521</td>
<td>Survived with no recurrence</td>
</tr>
<tr>
<td>8</td>
<td>Shiba</td>
<td>6.1</td>
<td>M</td>
<td>16.8</td>
<td>Anorexia and tachypnea</td>
<td>34.5 10.7</td>
<td>5 5</td>
<td>166 -</td>
<td></td>
<td>Excellent</td>
<td>1,616</td>
<td>Survived with no recurrence</td>
</tr>
<tr>
<td>9</td>
<td>Shiba</td>
<td>3.7</td>
<td>F</td>
<td>6.7</td>
<td>Tachypnea and exercise intolerance</td>
<td>38.8 5.6</td>
<td>172 29</td>
<td>151 -</td>
<td>Lung lobectomy for lung torsion</td>
<td>Excellent</td>
<td>438</td>
<td>Showed no recurrence, but died of unknown causes</td>
</tr>
<tr>
<td>10</td>
<td>Afghan hound</td>
<td>8.4</td>
<td>M</td>
<td>27.9</td>
<td>Cough and tachypnea</td>
<td>159 10.0</td>
<td>22 4</td>
<td>184 L</td>
<td></td>
<td>Good</td>
<td>1,640</td>
<td>Survived with no recurrence</td>
</tr>
<tr>
<td>11</td>
<td>Shiba</td>
<td>3.8</td>
<td>F</td>
<td>6.9</td>
<td>Tachypnea</td>
<td>14.5 11.6</td>
<td>18 1</td>
<td>169 -</td>
<td></td>
<td>Excellent</td>
<td>1,640</td>
<td>Survived with no recurrence</td>
</tr>
</tbody>
</table>


*Outcome was determined as follows: Excellent- chyloous effusion disappeared with no medical management and the patient's quality of life was improved; Good- chyloous effusion disappeared and the patient's quality of life was improved, but the medical management was needed for major complications; Poor- chyloous effusion was continued and the patient's quality of life was not improved.