

박 사 학 위 논 문

An Experiment to Evaluate the Usefulness of Oddi's
Sphincteroplasty for the Treatment of Anomalous
Pancreaticobiliary Duct Union

췌담관합류이상의 치료법으로서의 Oddi씨 괄약근
성형술의 유용성에 대한 연구

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이 논문을 의학박사학위논문으로 제출함

고려대학교 대학원
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한석주의 의학박사 논문심사를 완료함

2004년 12월 일

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위 원 서 성 옥 인

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위 원 김 한 겹 인

감사의 글

본 논문의 연구를 시작하여 완성되기까지 어느덧 4년의 세월이 흐른 것 같습니다.

무엇보다 바쁘다는 핑계로 잘 돌보아 주지 못하여도 묵묵히 옆에서 저를 보필하고 마음 고생한 사랑하는 아내 김 선희와 아빠 얼굴 보기 힘들었던 두 아들(지운, 지혁)에게 이 논문을 바칩니다.

불혹의 나이가 된 아들에 대해 아직도 걱정하시는 부모님이 정정하신 것에 대해 감사드립니다.

의사로서 연구가로서 저의 스승이신 황의호 박사님께도 다시 한번 감사의 말씀을 드립니다.

논문으로 완성되기 까지 연구 지도하여 주신 김 영철교수님과 각 지도위원님에게도 감사의 말씀을 전합니다.

끝으로 실험과정에서 희생 된 어린 강아지의 영혼이 편안하기를 바라며 감사의 글을 마칩니다.

2004년 12월 도곡에서,
저자 씀

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= Abstract =

An Experiment to Evaluate the Usefulness of Oddi's
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Pancreaticobiliary Duct Union

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Background & Aims: The anomalous union between the pancreatic and biliary system was reported to produce various effects in hepatobiliary system. The aim of this experiment is to evaluate the role of the sphincteroplasty for preventing of the adverse effects of anomalous pancreaticobiliary duct union.

Material and Methods: Twelve mongrel puppies were randomly divided into a control group (n=5) and an experimental group (n=7). A well-established model of anomalous pancreaticobiliary duct union was produced in both groups. Transduodenal sphincteroplasty was performed only in the experimental group. The chemical analysis of serum was examined serially, and biliary tree size was measured by magnetic resonance cholangiography

2.5 months after the experimental surgery. At the time of sacrifice 3 months after the experimental surgery, operative cholangiography was performed, and bile juice and tissues were obtained for chemical analysis and histologic examination.

Results: The dilatation of the bile duct and the thickening of the wall of the bile duct were less frequently observed in the experimental group than in the control group. The pancreatic enzyme activity in bile juice did not have any significant difference between two groups. Denudation of the mucosa was predominant mucosal change in experimental group. Epithelial hyperplasia was predominant mucosal change in control group.

Conclusions: The sphincteroplasty may be effective at preventing the adverse effects of the physical pancreaticobiliary reflux in anomalous pancreaticobiliary union.

I. Introduction

Many theories exist regarding the cause of choledochal cyst, but the most widely accepted is that a choledochal cyst is caused by pancreaticobiliary reflux through an anomalous union between the pancreatic and biliary systems (APBDU).¹ Although choledochal cyst is generally believed to be congenital in origin, clinical evidence suggests that a choledochal cyst may be caused by an irreversible bile duct dilatation resulting from long standing pancreaticobiliary reflux through the APBDU.² The other previously reported ill effects of APBDU are hepatobiliary malignancy and recurrent abdominal pain requiring extensive surgery.³⁻⁶ In adult, it was recommended to resect the gallbladder to prevent the gallbladder cancer in APBDU.^{3, 4} In children, previous reports also recommended to resect the common bile duct as a treatment of the recurrent abdominal pain in APBDU without bile duct dilatation.^{5, 6}

The role of APBDU as the only causative factor of these maladies has been doubted because all patients with APBDU do not have choledochal cyst, hepatobiliary malignancy or recurrent abdominal pain. It has been suggested that sphincter of Oddi dysfunction might play an important role in pancreaticobiliary reflux of APBDU.⁷

The hypothesis behind this experiment is that sphincter of Oddi dysfunction may be an important causative factor to produce the adverse effects of pathologies associated with

APBDU, and that these can be prevented by sphincteroplasty. To verify this hypothesis, we used a well-established puppy model of APBDU.⁸⁻¹⁰

II. Material and Methods

A) Materials

Twelve mongrel two months old puppies were randomly divided into a control group (n=5) and an experimental group (n=7). In the control group, APBDU was produced by end-to-side choledochopancreatostomy as previously described.⁸⁻¹⁰ In the experimental group, the transduodenal sphincteroplasty was performed in addition to the formation of an APBDU (Fig. 1).

All puppies were sacrificed three months after surgery. The use and care of laboratory animals in this experiment were based on the Guidelines and Regulations for the Use and Care of Animals at Yonsei University.

B) Methods

a) Surgery to produce APBDU in the Control Group (Fig. 1-B)

Detailed methods of the experimental surgery required for APBDU formation have been previously published.⁸⁻¹⁰ Laparotomy was performed under inhalation anesthesia. The common bile duct was divided at the choledochoduodenal junction, and the duodenal stump of the common bile duct was closed with interrupted absorbable sutures. The dorsal pancreatic duct was identified, and a longitudinal incision was made on its anterior wall for choledochopancreatic anastomosis. The hepatic stump of the common bile duct was pulled down toward the incision site of the dorsal pancreatic

duct, and choledochopancreatic end-to-side ductal anastomosis was performed using interrupted 6-0 Prolene sutures. Thus, the anastomosis site was located definitely outside the duodenum, and APBDU was subsequently produced.

b) Surgery for APBDU formation and Sphincteroplasty in the Experimental Group (Fig. 1-C)

Same procedure as described in the control group was used until the opening of the dorsal pancreatic duct. A longitudinal incision was made in the dorsal pancreatic duct, and a small silver probe was inserted to identify the duodenal opening of the dorsal pancreatic duct. By transduodenal palpation of the probe, the appropriate site for duodenotomy was selected. After duodenotomy, the duodenal papilla of the dorsal pancreatic duct was opened longitudinally over the probe, and sphincteroplasty was performed with interrupted 5-0 Vicryl sutures. Thus, the sphincter function of the duodenal papilla of the dorsal pancreatic duct was lost. The duodenotomy was closed with interrupted sutures. Choledochopancreatic end-to-side ductal anastomosis was performed as described for the control group.

c) Biochemical Assay

The serum amylase and lipase level were examined before experimental surgery, on the postoperative 10th day and on the day of sacrifice. The bile juice was collected from the gallbladder and the common bile duct by direct puncture at

the time of sacrifice. The activity of amylase and lipase in the bile juice were measured to estimate pancreatic juice reflux into the bile duct (enzymatic colorimetric method, Cobas Integra 800[®], Swiss).

d) Roentgenologic Examination

X-ray studies were performed by magnetic resonance cholangiography (MRC) two and half month after the experimental surgery, and operative cholangiography was performed at the time of sacrifice. The diameter of the bile ducts was measured by MRC. Operative cholangiography was not used to determine the diameter of the bile duct because of expected errors due to the magnification of the films and the pressure variation of the injected dye.

e) Histologic Examination

Specimens of liver, gallbladder, bile ducts, pancreas and duodenum were fixed in formalin solution immediately after sacrifice. Specimens were stained with Hematoxylin-Eosin for microscopic examination and reviewed by a pathologist (Hogun Kim, M.D., Department of Pathology, Yonsei University College of Medicine, Seoul, Korea). The thickness of each layer in the wall of the common bile duct and gallbladder was measured at three randomly selected sites of using an image-processing program (Image-Pro plus 4.0, Media Cybernetics, USA).

f) Statistical Analysis.

Results are expressed as mean values \pm the standard deviation, and were analyzed using the Mann-Whitney test. A p value of less than 0.05 was considered to indicate statistical significance.

III. Results

Final data were available on 11 animals (4 in the control group and 7 in the experimental group) because a puppy in the control group died of anastomosis disruption. No statistical differences in sex and body weight were observed at the time of experimental surgery between the two groups (one female and three males in the control group and two females and four males in the experimental group; 9.25 ± 1.35 Kg for the control group and 8.98 ± 0.95 Kg for the experimental group).

A) Biochemical Assay

No statistically significant differences in the biochemical serum assays were noted between the two groups. The pancreatic enzyme activity in the bile juice collected from the biliary tree on the day of sacrifice was similar in the two groups (Table 1).

No statistically significant difference was found between the control group and the experimental groups with respect to pancreatic enzyme activity in the bile juice.

B) Roentgenologic Examination

Although the degree of cylindrical bile duct dilatation was variable, MRC showed that the dilatation of the bile ducts was less definite and less frequently observed in the experimental group than in control group (Fig. 2).

This finding was confirmed by operative cholangiography at the time of sacrifice. Statistical analysis of the bile duct sizes measured by MRC showed that the maximum diameters of the common bile duct in the experimental group were significantly smaller than those of the control group (Table 2).

C) Histologic Examination

The thickness of the mucosal layer of the common bile duct in the experimental group was significantly thinner than those of the control group. The thickness of the muscle layer and of the serosal layers of the common bile duct in the experimental group was also significantly thinner than those of the control group (Fig. 3, Table 3). Diffuse papillary hyperplasia of the tall columnar epithelium, the most significant mucosal change of bile ducts observed in this APBDU model⁸, was less definite and less frequently observed in the experimental group than in the control group (Fig. 3-A, Table 4). The epithelial denudation of the biliary tree was more definitely and more frequently observed in the experimental group than in control group (Fig. 3-B, Table 4). The pathologic findings of acute pancreatitis was not observed in any specimen.

IV. Discussion

It has been suggested that APBDU has various adverse effects on the hepatobiliary-pancreatic system due to refluxes. Pancreaticobiliary reflux is considered the major reflux in APBDU, because the intraluminal pressure of the pancreatic duct is usually higher than that of the common bile duct. Irritation of the bile duct by the refluxed pancreatic juice causes mucosal changes and the weakness of the bile duct. This weakness combined with distal obstruction of the common channel can result in a choledochal cyst. Moreover, long periods of bile duct irritation by the refluxed pancreatic juice can result in malignant transformation. The other reflux in APBDU is the biliary-pancreatic reflux. It is possible that the bile juice flows into the pancreatic duct when the intraluminal pressure of the common bile duct is higher than that of the pancreatic duct such as occurs when the gallbladder contracts without relaxation of the sphincter of Oddi. Biliary-pancreatic reflux may induce pancreatitis.

The real incidence of APBDU in humans is unknown, but the reported incidence of APBDU in the adult population is relatively high, and ranges from 1.5% to 3.2%.^{3, 4, 11, 12} However, all patients with APBDU do not always have an associated choledochal cyst, hepatobiliary malignancy or pancreatitis, which suggests that another factors are involved in these associations. The distal obstruction of the APBDU is thought to be an important factor in the development of the

adverse effects associated with APBDU.¹³ Although, it has been postulated that stone, protein plugs and stenosis cause the distal obstruction of APBDU, the sphincter of Oddi dysfunction was recently reported to have an important role in the production of the symptoms and the other complications of APBDU in humans.^{7, 14-16}

The hypothesis behind our experiment was that the adverse effects of APBDU can be prevented by correcting of the sphincter of Oddi dysfunction. To verify this hypothesis, we used a well-established animal model of APBDU.⁸⁻¹⁰ We had previously confirmed that this model produced APBDU with the similar form as that found in the human and it produced a dilatation of the bile duct that resembled the human choledochal cyst.¹⁰

The results of our experiment demonstrate that sphincteroplasty could prevent dilatation of the common bile duct (Fig. 2 and Table 2) and the pathologic thickening of the common bile duct (Fig. 3, Table 3). The original authors of this APBDU model thought that the stricture of the anastomosis was an important etiologic factor for the dilatation of bile ducts.¹⁷ Their idea concerning anastomotic stricture as a causative factor of bile duct dilatation is not supported by our data, because the sphincteroplasty, which was definitely located distal of the anastomosis (Fig. 1-A), prevented bile duct dilatation (Fig. 2 and Table 2). This reflects that the location of obstruction for producing dilatation of the bile duct may be at the sphincter rather than at the anastomosis site.

We speculate that this puppy model may have a natural sphincter dysfunction of dorsal pancreatic duct. In the normal anatomy of the dog, the ventral pancreatic duct opens to the duodenal lumen conjoined with the ventral pancreatic duct, but the dorsal pancreatic duct opens separately into the duodenum without any connection with the bile duct (Fig. 1-A). Based on this normal anatomy, the dog may have appropriate response of the sphincter muscle of the ventral pancreatic duct to cholecystokin because of the requirement of the coordinated action of the gallbladder and sphincter muscle of the ventral pancreatic duct. However, the sphincter muscle of the dorsal pancreatic duct may not have such well-coordinated response to cholecystokin. Consequently, the sphincter muscle of the artificially made APBDU of dog may be dysfunctional. However, this hypothesis should be proven.

We would like to propose new concept for the explain of our results in which the pancreaticobiliary reflux of APBDU can be divided into two, "the chemical pancreaticobiliary reflux" and "the physical pancreaticobiliary reflux". Chemical pancreaticobiliary reflux is defined as the pancreaticobiliary reflux of chemical substances, such as amylase , lipase and other pancreatic enzymes. Physical pancreaticobiliary reflux is defined as the transmission of the intraluminal pressure of the pancreatic duct into the biliary tree.

It is definitely true that the chemical pancreaticobiliary reflux can occur by simple diffusion without a pressure gradient in the APBDU. Based on this concept, the sphincteroplasty in our

animal model may be ineffective to prevent chemical pancreaticobiliary reflux. It may be the reason why there was no significant difference in the levels of pancreatic enzyme activity in the bile juice between the control group and the experimental groups (Table 1).

It is also a basic physical law that high intraluminal pressure is absolutely required to dilate a tubular structure, even if the wall of tube is weak. If the sphincteroplasty prevent the pressure transmission into bile duct from pancreatic duct, the bile duct would not be dilated despite the presence of a weakness of the bile duct. Based on this concept, the sphincteroplasty in our animal model may be effective to prevent physical pancreaticobiliary reflux. It may be the reason why there was significant difference in the diameter of the bile duct between the control group and the experimental groups (Table 2).

Significant differences in the histologic findings of mucosa existed between the two groups; the denudation of mucosal epithelium is frequently observed in the experimental group and epithelial hyperplasia is the prominent pathologic finding in the control group (Table 4). Miyano et al. reported that diffuse papillary hyperplasia of tall columnar epithelium was the most significant mucosal change of bile ducts in this APBDU model.⁸ It is difficult to interpret the difference in the histologic findings of two groups simply. However, we suggest a hypothesis to explain this difference. The denudation in the experimental group may be solely due to the irritation effects of the chemical pancreaticobiliary reflux without the pressure effect. This chemical

irritation may be more severe in the experimental group than in the control group because the sphincteroplasty in experimental group may promote a reflux of duodenal content into the APBDU, and the refluxed duodenal content may activate the pancreatic enzymes.

The mucosal hyperplasia observed frequently in the control group may be the combined result of the pressure effects and the chemical irritation. Mechanical stretching or strain has been suggested to play an important role in the enhancement of cell proliferation in a number of different tissues.¹⁸ The well known phenomenon of the stretching-enhanced cell proliferation may explain the mucosal hyperplasia in the control group. However, we believe that a long-term experimental study with molecular analysis will be necessary to prove this hypothesis.

The treatment of APBDU without choledochal cyst is controversial. Ando et al. and Miyano et al. reported that chronic recurrent intractable pain of children could be associated with APBDU in which the common bile duct was not dilated or minimally dilated.^{5, 6} They also recommended resection of the extrahepatic bile duct as a surgical treatment.¹⁹ Moreover, a prophylactic cholecystectomy has also been recommended in adult APBDU without choledochal cyst, because of a high incidence of gallbladder carcinoma in these patients.^{3, 20} Take et al. found elevated basal sphincter of Oddi pressure in 9 patients with choledochal cyst and APBDU,²¹ and it has been reported that biliary-pancreatic reflux could occur when the common channel is obstructed temporarily by sphincter of Oddi dysfunction.¹⁴ Guelrud et al. reported that

recurrent pancreatitis in APBDU are associated with sphincter of Oddi dysfunction in children, and stated that endoscopic sphincterotomy is beneficial in these patients.⁷ The results of the our animal study definitely support Guelrud's clinical experience. However, the long term animal experiment should be performed to prove the clinical usefulness the sphincteroplasty in APBDU, because the duration of our experiment was relatively short, and it did not support that the sphincteroplasty would prevent all adverse ill effects of pancreaticobiliary reflux.

V. Conclusions

1. Our experiment shows that sphincteroplasty is effective to prevent the bile duct dilatation and thickening that may be caused by pancreaticobiliary reflux occurring secondary to sphincter dysfunction in the APBDU puppy model.
2. We would like to propose new concept for the explain of our results in which the pancreaticobiliary reflux of APBDU can be divided into two, "the chemical pancreaticobiliary reflux" and "the physical pancreaticobiliary reflux".
3. The sphincteroplasty may be effective at preventing the adverse effects of the physical pancreaticobiliary reflux in the APBDU puppy model.
4. However, it may be ineffective at preventing the ill effect of chemical pancreaticobiliary reflux secondary from simple diffusion in the APBDU puppy model.

VI. References

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VII. Figures

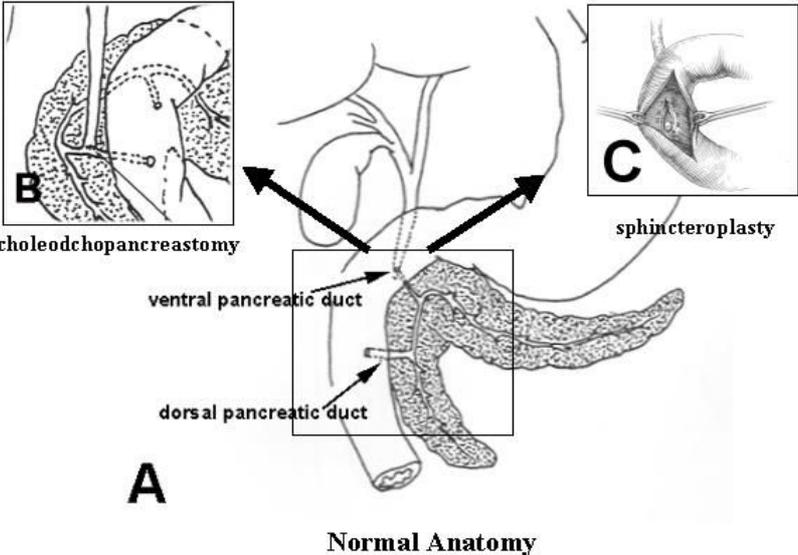


Fig. 1. A schematic drawing of the normal anatomy of the pancreaticobiliary system (A), experimental surgery for anomalous pancreaticobiliary duct union (B) and transduodenal sphincteroplasty (C)

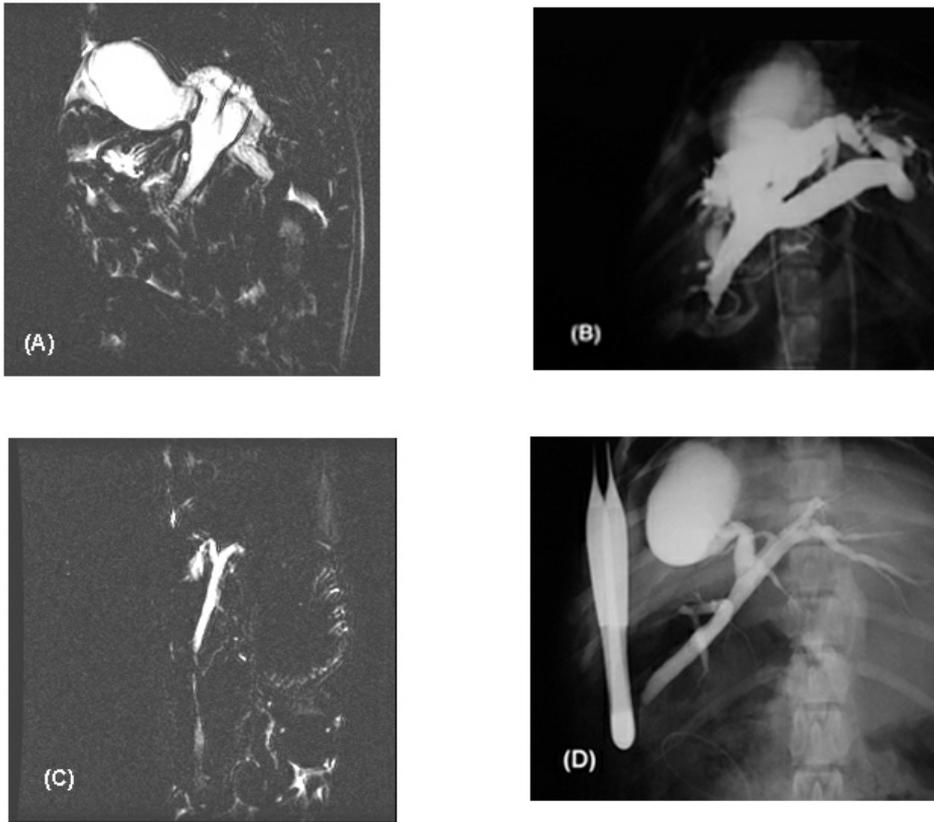


Fig. 2. The magnetic resonance cholangiography (MRC) in the control group showing extensive dilatation of the bile ducts (A). However, the MRC in the experimental group does not show such bile duct dilatation (C). This finding was confirmed by operative cholangiography (B; operative cholangiography of control group, D; operative cholangiography of experimental group).

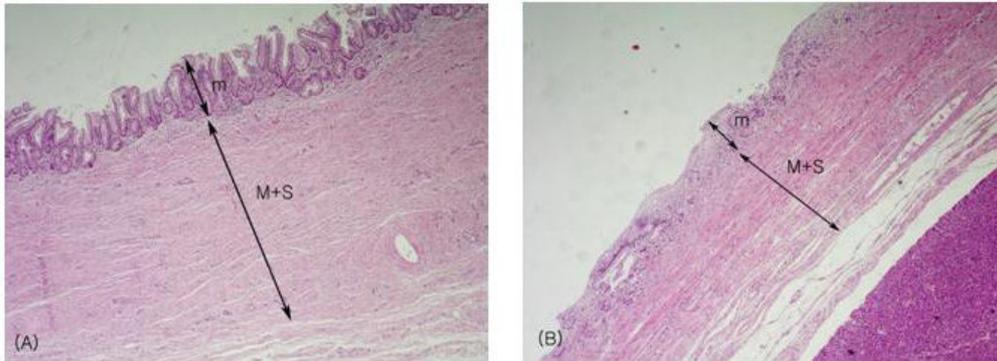


Fig. 3. (A) Microscopic examination of the common bile duct in control group showing diffuse prominent epithelial hyperplasia without definite epithelial denudation (H & E, x 40). (B) Microscopic examination of the common bile duct in the experimental group showing diffuse epithelial denudation without definite epithelial hyperplasia (H & E, x 40). The wall of the common bile duct in experimental group (B) is thinner than that in control group (A) (arrows). Abbreviations: m; thickness of mucosal layer, M+S; thickness of muscle and serosal layer.

VIII. Tables

Table 1. The activity of pancreatic enzymes in bile juice collected from common bile duct at sacrifice.

	Control group (n=4)	Experimental group (n=7)	P values
Amylase (IU/L)	69500.00±37311.57	94335.00±110241.29	<i>0.705</i>
Lipase (IU/L)	8200.00±11391.52	26907.00±42950.22	<i>0.450</i>

Table 2. Comparison of bile duct maximum diameters measured by MRC at 2.5 month after experimental surgery.

Diameter of bile ducts (mm)	Common bile duct	Right intrahepatic bile duct	Left intrahepatic bile duct
Control group (n=4)	10.1±5.91	9.43± 3.61	9.08±4.77
Experimental group (n=7)	5.46±1.25	7.21±3.00	5.46±1.42
<i>P value</i>	<i>0.038</i>	<i>0.345</i>	<i>0.131</i>

Table 3. Comparison of bile duct thickness changes in the control and experimental groups.

Abbreviations: m; the thickness of the mucosal layer, M+S; the thickness of muscle and serosal layer.

Thickness of Bile Ducts (μm)	Common Bile Duct		Gallbladder	
	m	M+S	m	M+S
Control group (n=4)	308.50 \pm 64.53	587.23 \pm 167.21	613.35 \pm 97.52	550.47 \pm 134.56
Experimental group (n=7)	199.49 \pm 99.27	360.92 \pm 95.43	221.45 \pm 48.33	510.45 \pm 151.73
<i>P value</i>	0.003	0.001	0.005	0.477

Table 4. Comparison of mucosal changes in the control and experimental groups.

Mucosal Changes	Denudation	Hyperplasia	Denudation	Hyperplasia
Control group (n=4)	1 (25%)	4 (100%)	0 (0%)	4 (100%)
Experimental group (n=7)	6 (86%)	1 (14%)	6 (86%)	3 (43%)

한글요약

췌담관합류이상의 치료법으로서의 Oddi씨 괄약근 성형술의 유용성에 대한 연구

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한 석주의 박사논문
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서론 및 목적: 췌담관합류이상은 총담관낭, 담도암, 담낭암, 췌장염등을 일으키는 것으로 알려져 있다. 본 연구의 목적은 동물실험을 통하여 이런 췌담관합류이상의 췌담도계에 미치는 나쁜 영향을 Oddi씨 괄약근 성형술로 예방 할 수 있는지 알아보는데 있다.

대상 및 방법: 12마리의 잡종 강아지를 대조군(n=5)과 실험군(n=7)으로 나누었다. 대조군과 실험군 모두에게 이미 정립된 수술방법을 통하여 췌담관합류이상을 만들었다. 실험군에게는 췌담관합류이상 외에 경십이지장 괄약근성형술을 동시에 시행하였다. 수술 후 일련의 혈청 생화학검사를 시행하였으며 수술 후 2.5 개월에 자기공명담도촬영을 통하여 담도의 변화를 관찰하였다. 수술 후 3개월에 실험동물을 희생하면서 수술적 담도촬영을 시행하였으며 생화학적 및 조직학적 검사를 위하여 담즙 및 췌담도계의 조직을 얻었다.

결과: 실험군에서 대조군에 비하여 통계학적으로 유의 있게 담도의 확장과 담도벽의 비후가 적게 관찰 되었다. 담즙 체장효소 활성도는 두 군간에 통계학적으로 차이가 없었다. 조직학적 소견은 실험군에서는 점막 탈락이 주로 관찰되었으며 대조군에서는 상피의 과형성이 주로 관찰되었다.

결론: 괄약근 성형술은 체담관합류이상의 물리적 체담관역류의 영향을 예방하는데 효과가 있는 것을 알 수 있었다.