Effects of Sho-saiko-to and Gorei-san on the modulating mechanism of the sphincter of Oddi. An intraoperative cholangiomanometric study

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Abstract

Female patients suffering from gallbladder stone disease were administered Sho-saiko-to (Xiao-Chai-Hu-Tang (XCHT)) or Gorei-san (Wu-Ling-San (WLS)) preoperatively, and were examined by cholangiomanometry during operation. When compared with a control group, the pressure threshold of the sphincter of Oddi for volume load in the bile duct was considered to be significantly lowered in the XCHT group and also in the WLS group, meaning that the sphincter became more susceptible, and, in the XCHT group, its relaxation occurred significantly more rapidly and completely. The results obtained in the XCHT group would suggest that the modulating mechanism of the sphincter of Oddi is activated, preventing the transpapillary reflux of duodenal fluid and yet preventing the stasis of bile, which would be one of the main reasons why this drug is used for hypochondriac fullness and distress. The results obtained in the WLS group would mean that the transpapillary reflux of excessive intestinal fluid can be prevented in those patients with disturbances of water absorption, more effectively than with XCHT.

Key words cholangiomanometry, gallbladder stone disease, Gorei-san, hypochondriac fullness, Sho-saiko-to, sphincter of Oddi, watery absorption disturbance.

Abbreviations AD converter, analogue-digital converter; BP, basal pressure; CPU, central processing unit; PP, perfusion pressure; RAM, random access memory; ROM, read only memory; T, declining time; WLS, Gorei-san (Wu-Ling-San) 五苓散; XCHT, Sho-saiko-to (Xiao-Chai-Hu-Tang), 小柴胡湯.

Introduction

XCHT (Xiao-Chai-Hu-Tang, Sho-saiko-to) is effective for hypochondriac fullness and distress. The main cause of this syndrome is considered to be a disorder of bile flow.[1] On the other hand, WLS (Wu-Ling-San, Gorei-san) is recommended for patients with disturbances of water absorption. The authors investigated the effects of both formulas on the modulating mechanism of the sphincter of Oddi using intraoperative cholangiomanometry.

Subjects and Methods

Forty female patients suffering from gallbladder stone disease were investigated. Patients who showed manifest symptoms of cholecystitis such as fever, definite abdominal pain, leukocytosis and positive CRP value were excluded. Patients who had common bile duct stones were also excluded. Abdominal pain or fullness due to gallstones had subsided after hospitalization in all cases. Eight patients were given XCHT-granules (Tsumura Pharmacy) preoperatively, in a dose of 7.5 g daily for 6.6±4.2 days,

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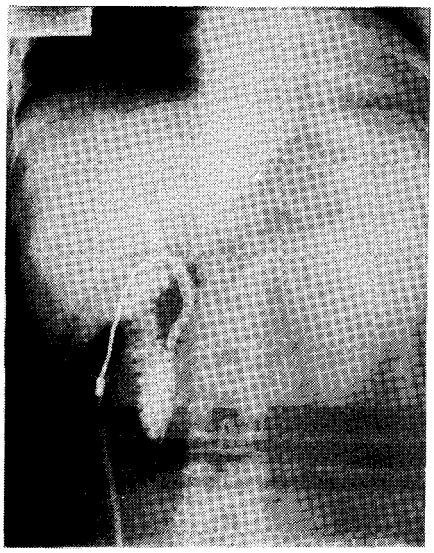
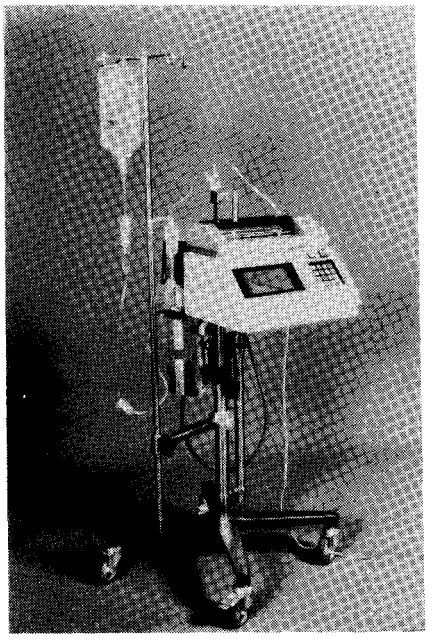


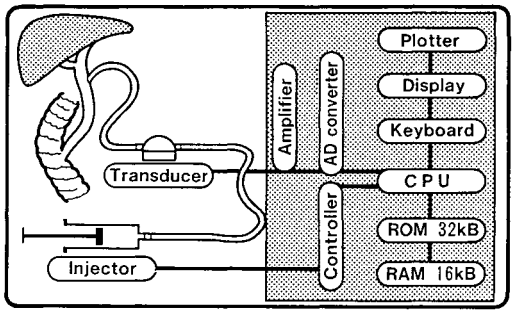
Fig. 1 Special silver cannula introduced into the common bile duct.

and twelve patients were given WLS-granules (Tsumura Pharmacy) preoperatively, in a dose of 7.5 g daily for 7.8±6.0 days, until the day before operation. Twenty patients who were not given either formula were managed as a control group. Cholecystectomy was performed under general anesthesia. Preceding the ligation of the cystic duct, a special silver cannula was introduced into the common bile duct, not deeply enough to stimulate the sphincter of Oddi (Fig. 1), and was connected with a biliary manometer[2] (Nemoto-Kyorindo Co., Model PF 100, Fig. 2).

The manometric zero point was set at the level of the common bile duct or midaxillary line. After the basal pressure (BP) was taken, the perfusion pressure (PP) was measured while saline was injected via a pump (Fig. 3). The pump was then stopped and the declining curve was monitored. The time for the curve to reach the nadir plateau *i. e.* the residual pressure, being the declining time (T). The times taken for the PP to reduce by one half, one fourth, and one fifth towards the BP were measured on the curve as $T_{1/2}$, $T_{1/4}$ and $T_{1/5}$ respectively (Fig. 3). The injection pump was driven first at a rate of 0.1 ml/sec, and then at 0.5 ml/sec.



a. External appearance.



b. The diagram.

Fig. 2 Biliary manometer, Model PF 100 (Nemoto-Kyorindo Co.)

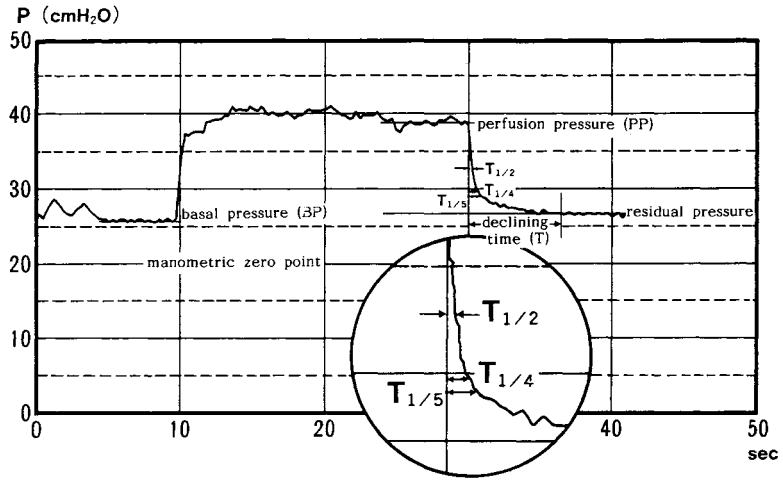


Fig. 3 Cholangiomanometric curve and the related parameters.

During the surgery, drugs stimulating (pentazocine, morphine, neostigmine, phentolamine) or suppressing (atropine, scopolamine-N-buthylbromide, adrenaline, noradrenaline, isoproterenol, phenylephrine, hexamethonium, nitroglycerin, hymecromone, cholecystokinin octapeptide, glucagon, secretin) the sphincter of Oddi were not used.

The data is shown as the mean±standard deviation. For statistical analysis a t-test was applied, and the level of significance was defined as lower than 0.05 of the p value.

Results

There was no significant difference between the three groups as to preoperative clinical symptoms (Table I).

Examination of the drugs used for anesthesia revealed no significant difference between the three groups (Table II). By chance the mean age was significantly higher in the control group(58.3 ±9.1) than in the XCHT group (45.0 ± 11.0) ($p<0.01$)or in the WLS group (48.3±11.7) ($p<0.02$). But as shown in Table III, there was no significant difference according to age in the data of the control group. So the data of the subgroups in the control group were managed as a whole in the following analysis.

BP showed no significant difference between the three groups. The PP of the XCHT group showed no significant difference from the control group at an injection rate of 0.1 ml/sec, but was significantly higher at a rate of 0.5 ml/sec ($p<0.01$). The PP of the WLS group was significantly higher than the control group at an injection rate of 0.1 ml/sec ($p<0.05$)and at 0.5 ml/sec ($p<0.01$). There was no significant difference of PP

Table I Preoperative clinical symptoms.

Group	Preoperative clinical symptoms			
	Hypochondriac pain, Epigastralgia	Heartburn	Lumbago, Backache	Silent stone
Control group	12 cases	0 cases	5 cases	3 cases
XCHT group	6	0	2	0
WLS group	8	2	1	1

Table II Drugs used for anesthesia.

Group	Drugs used for general anesthesia				
	Nitrous oxide with enflurane	Nitrous oxide with halothane	Nitrous oxide with sevoflurane	Nitrous oxide with isoflurane	Nitrous oxide only
Cotrol group	11 cases, 55.0%	4 cases, 20.0%	2 cases, 10.0%	2 cases, 10.0%	1 case, 5.0%
XCHT group	6 cases, 75.0%	2 cases, 25.0%			
WLS group	7 cases,58.3%	3 cases, 25.0%	1 case, 8.3%		1 case 8.3%

Group	Combination rate of extradural block (Th 6/7-10/11)	Special drugs used within twenty minutes before cholangiomanometry
Control group	10 cases, 50.0%	ephedrine 5 mg, intravenous : 1 case nicardipine 0.5 mg, intravenous : 1 case nifedipine 10 mg,nasal : 1 case vancronium bromide 2 mg, intravenous : 2 cases
XCHT group	3 cases, 37.5%	famotidine 20 mg, intravenous : 1 case
WLS group	5 cases, 41.7%	ephedrine 5 mg, intravenous : 1 case succinylcholine chloride, intravenous : 1 case nifedipine 5 mg, nasal : 1 case

Table III Measurement results of bile duct pressure and related parameters.

Group (average age)		cm H_2O BP	Saline injection rate 0.1 ml/sec					Saline injection rate 0.5 ml/sec				
			cm H_2O PP	sec T	sec $T_{1/2}$	sec $T_{1/4}$	sec $T_{1/5}$	cm H_2O PP	sec T	sec $T_{1/2}$	sec $T_{1/4}$	sec $T_{1/5}$
Control group	60 y.o.a.≧ (50.4±8.2)	8.1±3.4 n=9	10.3±3.2 n=9	3.1±1.0 n=5	1.21±0.51 n=5	1.83±0.74 n=5	2.07±0.77 n=5	17.7±5.7 n=9	4.3±2.6 n=8	0.88±0.42 n=8	2.16±0.87 n=7	2.63±0.99 n=7
	61 y.o.a.≦ (64.6±1.7)	6.0±4.2 n=11	10.7±5.6 n=11	4.8±3.0 n=8	1.50±1.44 n=8	3.13±2.05 n=7	4.18±2.93 n=7	17.7±5.0 n=11	5.6±2.9 n=11	1.00±1.14 n=11	2.31±1.80 n=10	3.18±2.55 n=10
	Total (58.3±9.1)	7.0±3.9 n=20	10.5±4.6 n=20	4.1±2.5 n=13	1.39±1.15 n=13	2.59±1.71 n=12	3.30±2.47 n=12	17.7±5.2 n=20	5.1±2.8 n=19	0.95±0.89 n=19	2.25±1.46 n=17	2.95±2.02 n=17
XCHT group (45.0±11.0)		7.6±2.7 n=7	12.1±5.4 n=7	1.8±0.8 n=5	0.29±0.20 n=5	0.52±0.34** n=5	0.65±0.36* n=5	29.1±13.8*** n=7	3.7±1.1 n=7	0.35±0.19 n=7	0.83±0.47* n=6	1.12±0.57* n=6
WLS group (48.3±11.7)		8.3±3.3 n=11	14.8±5.0* n=11	4.4±2.8 n=9	1.17±1.46 n=9	1.69±1.34 n=8	2.01±1.62 n=7	32.9±20.2*** n=11	4.6±2.5 n=10	1.03±1.53 n=8	1.95±2.17 n=9	2.59±2.49 n=9

(m±S.D.)

Significant difference when compared with control group : $*p<0.05$, $**p<0.02$, $***p<0.01$

between the XCHT group and the WLS group. T and $T_{1/2}$ at both injection rates tended to be shorter in the XCHT group than in the control group, but this did not reach a significant difference. The XCHT group showed a significant reduction in both $T_{1/4}$ and $T_{1/5}$ at both injection rates ($p<0.02$-0.05). T, $T_{1/2}$, $T_{1/4}$ and $T_{1/5}$ of the WLS group showed no significant difference from the control group at both injection rates.

Discussion

Because the normal flow rate of bile is about 0.01 ml/sec, the saline injection rates adopted in this study are more than ten times greater than the physiological flow rate. So the significantly high PP recognized at an injection rate of 0.5 ml/sec in the XCHT group and that recognized in the WLS group at both injection rates might

suggest that the susceptibility threshold of the sphincter of Oddi to high volume load was lowered and that spasms[3] or some spastic conditions were induced. But when the load was discontinued, the decline of biliary pressure occurred promptly and T showed no significant difference between the two groups and the control group. The significantly shorter $T_{1/4}$ and $T_{1/5}$ recognized in the XCHT group at both injection rates also suggests an effective and complete relaxation of the sphincter of Oddi. The phenomena noticed in the XCHT group would prevent the transpapillary reflux of duodenal fluid, which is one of the main etiologic factors causing pancreatitis or cholangitis, and yet also prevent stasis of bile. The significantly high PP noticed in the WLS group (0.1 ml/sec and 0.5 ml/sec) and in the XCHT group (0.5 ml/sec) also suggests that the transpapillary reflux of duodenal fluid can be prevented. But there is no literature directly demonstrating this phenomenon and further investigation is required. Many published studies already support Oddi's original description that the sphincter has a major role in the control of the flow of bile and pancreatic juice into the duodenum, and equally importantly helps to prevent the reflux of duodenal fluid into the pancreaticobiliary ductal systems.[4] The present study proves the effects of XCHT and WLS on further activating the modulating mechanism of the sphincter of Oddi.

XCHT is used to treat hypochondriac fullness and distress. This syndrome is caused mainly by a disorder of bile flow and partly by inflammation or autonomic nerve disturbances.[1] When the modulating mechanism of the sphincter of Oddi is activated by XCHT, hypochondriac fullness and distress would surely be improved. WLS is recommended for patients who have thirst and oliguria, in spite of the presence of excessive fluid in the gastrointestinal tract. The etiology of this condition is considered to be due to a disturbance of water absorption, resulting in the loss of an effective watery component in the functional system.[1] In this condition, excessive intestinal fluid can reflux into the pancreaticobiliary tract across the sphincter of Oddi. This will be prevented by the lowered susceptibility threshold of the sphincter to the high volume load by the administration of WLS. For this purpose, WLS is presumably more suitable than XCHT, because the latter did not significantly lower the threshold at an injection rate of 0.1 ml/sec. In addition, the patients will also benefit by the water regulating function inherent in WLS.[5]

There are no constituent herbs or main ingre

Table IV Constituent herbs and main ingredients of XCHT and WLS.

Xiao-Chai-Hu-Tang		Wu-Ling-San	
Herb	Main ingredient	Herb	Main ingredient
Chai-Hu (柴胡) (Bupleuri Radix)	saikosaponin, α-spinasterol, stigmasterol, etc.	Ze-Xie(沢瀉) (Alismatis Rhizoma)	alisol, starch, protein, etc.
Ban-Xia (半夏) (Pinelliae Tuber)	homogentisic acid, aminoacid, 3, 4-dihydroxybenzaldehyde, sterol, etc.	Cang-Shu(蒼朮) (Atractylodis Lanceae Rhizoma)	hinesol, β-eudesmol, elemol, atractylodin, etc.
Huang-Jin (黄芩) (Scutellariae Radix)	baicalin, wogonin, oroxylin A, sterol, etc.	Zhu-Ling(猪苓) (Polyporus)	glucan, ergosterol, etc.
Sheng-Jiang (生姜) (Zingiberis Rhizoma)	gingerol, shogaols, zingiberene, bisabolene, etc.	Fu-Ling(茯苓) (Hoelen)	eburicoic acid, dehydroeburicoic acid, ergosterol, pachyman, etc.
Da-Zao(大棗) (Zizyphi Fructus)	fructose, glucose, sucrose, arabinan, glucuronan, triterpenoid, zizyphus saponin, jujuboside B, zizybeoside, vomifoliol, roseoside, zizyvoside, rutin, etc.	Gui-Pi(桂皮) (Cinnamomi Cortex)	cinnamaldehyde, cinnamic alcohol, cinnzeylanin, cinncassiol, procyanidin, cinnamtannin, etc.
Ren-Shen (人参) (Ginseng Radix)	ginsenoside, β-elemene, panaxynol, panaxydiol, glucose, sucrose, etc.		
Gan-Cao (甘草) (Glycyrrhizae Radix)	glycyrrhizin, liquiritin, isoliquiritin, licoricone, glycyrol, etc.		

dients[6] common to XCHT and WLS (Table IV).

So it is reasonable to presume that the lowered susceptibility threshold of the sphincter of Oddi is due to different pharmacological actions of the formulas on the sphincter.

The contents of this study were presented in part at the 6 th International Congress of Oriental Medicine, Tokyo, 1990, and at the 8 th Congress of Medical and pharmaceutical Society for WAKAN-YAKU, Osaka, 1991.

和文抄録

胆嚢結石症の女性患者に術前に小柴胡湯または五苓散を投与し，術中に胆道内圧測定を行なった。対照群に較べて，胆道内の容量負荷に対するOddi括約筋の圧閾値は，小柴胡湯群と五苓散群で有意に低下していると考えられ，これは括約筋がより敏感となっていることを示しており，また小柴胡湯群では，その弛緩が有意に迅速に，かつ十分に起こった。小柴胡湯群で得られた結果は，Oddi括約筋の調整機転が活性化され，十二指腸液が乳頭を通って逆流することを防止し，かつ胆汁の鬱滞を防止していることを示唆しており，このことはこの薬剤が胸脇苦満に用いられる主な理由の1つであろう。五苓散群で得られた結果は，水分吸収障害のある患者において過剰の腸液が乳頭を通って逆流することが，小柴胡湯による場合よりももっと効率的に防止されうることを物語っているだろう。

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