

Effects of laparoscopic and choledochoscopic gallbladder-preserving cholecystolithotomy on levels of operation indicators, gallbladder function, and cholecystokinin type-A receptor in patients with gallstones

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Abstract

Introduction: Gallstones are a common digestive system disease.

Aim: To assess the effects of laparoscopic and choledochoscopic gallbladder-preserving cholecystolithotomy on the levels of operation indicators, gallbladder function, and cholecystokinin type-A receptor (CCKAR) in patients with gallstones.

Material and methods: The medical records of 100 patients with gallstones receiving operation from July 2019 to August 2022 were collected for retrospective analysis. They were divided into a laparoscopic group ($n = 48$) and a laparoscopic + choledochoscopic group ($n = 52$). The laparoscopic group received totally laparoscopic cholecystolithotomy, while the laparoscopic + choledochoscopic group underwent laparoscopic and choledochoscopic cholecystolithotomy. Their perioperative indicators, gallbladder function, stress indicators (cortisol (Cor), norepinephrine (NE), and C-reactive protein (CRP)), serum biochemical indicators (liver receptor homologue 1 (LRH-1), CCKAR, and vasoactive intestinal peptide (VIP)), and complications were compared.

Results: The fasting gallbladder volume and gallbladder contraction rate increased, and the minimum residual volume and gallbladder wall thickness decreased in the laparoscopic + choledochoscopic group in comparison with those of the laparoscopic group 6 months after operation ($p < 0.05$). The levels of serum Cor, NE, CRP, and CCKAR were elevated, whereas the levels of serum LRH-1 and VIP were lowered in both groups 3 d after operation compared with those before operation ($p < 0.05$). The levels of serum Cor, NE, CRP, LRH-1, and VIP were lower, and the level of serum CCKAR was higher in the laparoscopic + choledochoscopic group than those in the laparoscopic group 3 d after operation ($p < 0.05$).

Conclusions: Both laparoscopic gallbladder-preserving cholecystolithotomy and laparoscopic and choledochoscopic cholecystolithotomy are effective for treating gallstones. However, the latter combination method is superior in enhancing postoperative gallbladder function, decreasing the recurrence risk, regulating the expressions of LRH-1, CCKAR, and VIP, and promoting the postoperative recovery of gastrointestinal function.

Key words: cholecystokinin type-A receptor, cholecystolithotomy, choledochoscopy, gallbladder, gallstone, laparoscopy.

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Introduction

Clinically, gallstone is a common digestive system disease that frequently occurs in “3F” (fat, fertile, and forty) women, with abdominal pain, jaundice, fever, and vomiting as the main clinical manifestations, which can lead to cholecystitis, hydrocholecystis, and even shock in severe cases, posing a serious threat to life [1]. Characterized by acute onset and complex conditions and proneness to recurrence, gallstones generally cannot be completely cured by non-surgical means, so surgical treatment is the most important method for the disease in the clinic [2]. In previous clinical practice, open cholecystectomy was mostly applied in the treatment of gallstones, but it has been replaced by minimally invasive cholecystectomy along with the maturation of laparoscopic technology due to its large trauma and slow postoperative recovery [3]. As a major treatment scheme for gallstones that has been widely recognized clinically, laparoscopic cholecystectomy has a small trauma and rapid postoperative recovery, but it still possesses such disadvantages as long operation time, high difficulty in stone localization, and easy damage to the gallbladder mucosa [4]. In recent years, some scholars have pointed out that laparoscopic and choledochoscopic gallbladder-preserving cholecystolithotomy can overcome the above-mentioned disadvantages, further reduce operative trauma, and maximize the preservation of gallbladder function [5, 6]. As a specific receptor in gallbladder smooth muscle, cholecystokinin type-A receptor (CCKAR) is able to promote gallbladder contraction and exert a certain regulatory effect on small intestinal peristalsis. It has been researched that the CCKAR level is closely associated with the postoperative recovery of gastrointestinal function of patients with gallstones [7]. However, the majority of previous studies focused on laparoscopic cholecystolithotomy, and no uniform conclusion has been made on the influence of laparoscopic and choledochoscopic gallbladder-preserving cholecystolithotomy on serum CCKAR level.

Aim

In view of this, the medical records of 100 patients with gallstones, who underwent surgical treatment, were retrospectively analysed in this study, to explore the effects of laparoscopic and choledochoscopic gallbladder-preserving cholecystolithotomy on the levels of operation indicators, gallbladder function, and CCKAR in such patients.

Material and methods

General data

The medical records of 100 patients with gallstones treated by operation in our hospital from July 2019 to August 2022 were collected for retrospective analysis. The surgical procedure was approved by the Ethics Committee of our hospital, and written informed consent was obtained from all patients. There were 45 males and 55 females aged 20–60 years, with an average age of 39.88 ± 5.37 years. The body mass index was $21\text{--}26 \text{ kg/m}^2$, and $23.06 \pm 1.40 \text{ kg/m}^2$ on average, and the diameter of common bile duct was 6–9 mm, with an average of 8.10 ± 1.22 mm. In addition, 39 and 61 patients had a single stone and multiple stones, respectively. As to the concomitant diseases, 19 cases were complicated with hypertension and 33 cases were complicated with type 2 diabetes mellitus. The patients were allocated into the laparoscopic group ($n = 48$) and the laparoscopic + choledochoscopic group ($n = 52$) based on different operative schemes. The baseline data of the 2 groups were comparable ($p > 0.05$) (Table I).

Inclusion and exclusion criteria

The inclusion criteria were set as follows: 1) patients meeting related diagnostic criteria [8] and confirmed by B-mode ultrasound examination, 2) those with no common bile duct dilatation and good gallbladder contraction, 3) those with no more than 4 gallstones with a diameter of no more than 4 cm, and 4) those with complete clinical medical records. The following exclusion criteria were used: 1) patients complicated with gallbladder atrophy, hydrocholecystis, or other biliary tract diseases, 2) those with a history of upper abdominal operation, 3) those complicated with malignant tumour or failure of liver, kidney, or other important organs, 4) those with infectious diseases, or 5) pregnant or breastfeeding women.

Methods

Corresponding hypotensive and hypoglycaemic drugs were given to the patients with concomitant diseases before the operation. The patients in the laparoscopic group received totally laparoscopic cholecystolithotomy as follows: After general anaesthesia and tracheal intubation of the patient, an arc incision (2 cm) was made at about 1 cm above the

Table I. Baseline data

Group	N	Gender (male/female)	Age [years]	Body mass index [kg/m ²]	Diameter of common bile duct [mm]	Number of calculi		Concomitant disease	
						Single/ multiple		Hypertension/type 2 diabetes mellitus	
Laparoscopic	48	21/27	39.52 ±5.44	23.18 ±1.46	8.08 ±1.19	18/30		10/16	
Laparoscopic + choledochoscopic	52	24/28	40.06 ±5.27	22.96 ±1.39	8.13 ±1.25	21/31		9/17	
<i>t/χ²</i>		0.058	0.504	0.772	0.205	0.087		0.202/0.005	
<i>P</i> -value		0.809	0.615	0.442	0.838	0.768		0.653/0.946	

umbilicus on the left side, and a 10 mm Trocar was inserted into the incision after the establishment of pneumoperitoneum. Next, another incision (2 cm) was made at about 2 cm below the subcostal margin, in which a 10 mm Trocar was placed to probe the gallbladder condition. Subsequently, the bottom of the gallbladder was lifted out using non-invasive forceps, the gallbladder was cut open with an electric hook, and the gallstones were repeatedly and thoroughly removed by lithotomy forceps. Finally, the gallbladder incision was sutured and closed. In the laparoscopic + choledochoscopic group, laparoscopic and choledochoscopic cholecystolithotomy was performed according to the following steps: With the patient under general anaesthesia and tracheal intubation, an arc incision was made at the umbilical shoulder and inserted with a 10 mm Trocar to establish an artificial pneumoperitoneum. Then a 5 mm Trocar was inserted into the incision below the right costal margin and xiphoid to explore the gallbladder, and the bottom of the gallbladder was lifted and fully exposed using graspers. Subsequently, the avascular area at the bottom of the gallbladder was cut open by the electric hook. After the bile in the gallbladder was completely sucked by an aspirator, the choledochoscope was placed into the gallbladder through the Trocar below the xiphoid for observation, and the stones were eliminated using a stone extraction basket. After examination, the choledochoscope was withdrawn, and the incision at the bottom of the gallbladder was sutured and closed layer by layer.

Observation indicators

- (1) Perioperative indicators.
- (2) Gallbladder function: Gallbladder function was evaluated by means of abdominal ultrasound before

operation and at 6 months after operation, including fasting gallbladder volume, minimum residual volume, gallbladder wall thickness, and gallbladder contraction rate. Among them, gallbladder wall thickness was measured after 6 h of fasting. Gallbladder contraction rate = difference in volume before and after meal/volume after meal. Gallbladder volume was calculated based on Dodds formula.

- (3) Stress indicators: Fasting venous blood (3 ml) was collected from each patient in the 2 groups before operation and at 3 d after operation, which was centrifuged at 3000 rpm for 6 min ($r = 15$ cm) to obtain the serum for measurement. Later, cortisol (Cor), norepinephrine (NE), and C-reactive protein (CRP) were determined by enzyme-linked immunosorbent assay.
- (4) Levels of liver receptor homologue 1 (LRH-1), CCKAR, and vasoactive intestinal peptide (VIP) in the serum: Blood was collected before operation and at 3 d after operation to acquire the serum through the aforementioned methods. Then LRH-1 was determined using the double-antibody sandwich method, CCKAR was measured by radioimmunoassay, and VIP was detected via enzyme-linked immunoassay. The assay kits for these serum indicators were purchased from Shanghai Yanqi Biotechnology Co., Ltd.
- (5) Complications and recurrence rate: Complications involved cholestasis, incisional infection, abdominal infection, bile reflux gastritis, and bile leakage, and the recurrence rate was calculated within 6 months after operation.

Statistical analysis

SPSS 24.0 software was employed for statistical analysis. All measurement data were subjected to

normal distribution test. The normally distributed measurement data (perioperative indicators, gallbladder function, stress indicators, and levels of serum LRH-1, CCKAR, and VIP) were represented as ($\bar{x} \pm s$). When the variances were homogeneous, the independent sample *t*-test was used for intergroup comparison, and the paired samples *t*-test was utilized for intragroup comparison. The adjusted *t*-test was used in the case of heterogeneous variance. The measurement data with skewed normal distribution were described by median (M) and interquartile range (QR) and compared using the Mann-Whitney *U* test. The count data (recurrence rate and complication rate) were expressed by percentage and subjected to the χ^2 test. *P* < 0.05 suggested a significant difference.

Results

Perioperative indicators

Compared with the laparoscopic group, the laparoscopic + choledochoscopic group had shortened operation time, bowel sound recovery time, defecation time, and exsufflation time, as well as decreased intraoperative blood loss (*p* < 0.05). The hospitaliza-

tion time was comparable between the 2 groups (*p* > 0.05) (Table II).

Gallbladder function

The fasting gallbladder volume and gallbladder contraction rate were increased, while the minimum residual volume and gallbladder wall thickness were decreased in the laparoscopic + choledochoscopic group in contrast with those in the laparoscopic group at 6 months after operation (*p* < 0.05) (Table III).

Stress indicators

The levels of serum Cor, NE, and CRP were elevated in both the laparoscopic + choledochoscopic group and the laparoscopic group at 3 d after operation compared with those before operation (*p* < 0.05), and they were lower in the laparoscopic + choledochoscopic group than those in the laparoscopic group (*p* < 0.05) (Table IV).

Levels of serum LRH-1, CCKAR, and VIP

The levels of serum LRH-1 and VIP declined, while the level of serum CCKAR rose in both groups at

Table II. Perioperative indicator ($\bar{x} \pm s$)

Group	N	Operation time [min]	Intraoperative blood loss [ml]	Bowel sound recovery time [h]	Defecation time [h]	Exsufflation time [h]	Hospitalization time [days]
Laparoscopic group	48	65.38 ±9.17	14.85 ±3.51	12.23 ±2.41	36.75 ±5.83	16.54 ±3.62	3.83 ±0.59
Laparoscopic + choledochoscopic group	52	54.27 ±8.62	8.94 ±2.04	10.42 ±2.26	34.10 ±5.67	14.91 ±3.31	3.73 ±0.61
<i>t</i>		6.245	10.391	3.876	2.304	2.352	0.832
<i>P</i> -value		0.000	0.000	0.000	0.023	0.021	0.407

Table III. Gallbladder function ($\bar{x} \pm s$)

Group	N	Fasting gallbladder volume [ml]		Minimum residual volume [ml]		Gallbladder wall thickness [mm]		Gallbladder contraction rate (%)	
		Before operation	6 months after operation	Before operation	6 months after operation	Before operation	6 months after operation	Before operation	6 months after operation
Laparoscopic group	48	21.53 ±3.38	25.66 ±4.1 ^{1*}	10.19 ±2.06	5.02 ±1.4 ^{1*}	3.37 ±0.42	2.95 ±0.3 ^{6*}	47.73 ±12.09	57.68 ±13.4 ^{3*}
Laparoscopic + choledochoscopic group	52	21.86 ±3.55	28.71 ±4.6 ^{9*}	10.11 ±1.98	4.16 ±1.2 ^{4*}	3.41 ±0.46	2.59 ±0.3 ^{1*}	48.14 ±11.86	65.13 ±13.9 ^{7*}
<i>t</i>		0.475	3.446	0.198	3.245	0.453	5.370	0.171	2.714
<i>P</i> -value		0.636	0.001	0.843	0.002	0.652	0.000	0.864	0.008

**P* < 0.05 vs. before operation within the group.

Table IV. Stress indicators ($\bar{x} \pm s$)

Group	N	Cor [ng/ml]		NE [ng/ml]		CRP [mg/l]	
		Before operation	3 d after operation	Before operation	3 d after operation	Before operation	3 d after operation
Laparoscope group	48	190.58 ±15.67	258.61 ±30.1 ^{1*}	285.93 ±31.35	357.91 ±38.9 ^{9*}	6.15 ±1.16	35.89 ±6.1 ^{0*}
Laparoscopic + choledochoscopic group	52	191.70 ±16.09	233.89 ±26.8 ^{1*}	287.46 ±32.08	322.35 ±35.6 ^{0*}	6.24 ±1.24	30.14 ±5.5 ^{2*}
<i>t</i>		0.352	4.342	0.241	4.768	0.374	4.948
<i>P</i> -value		0.725	0.000	0.810	0.000	0.709	0.000

**P* < 0.05 vs. before operation within the group.

3 d after operation in comparison with those before operation (*p* < 0.05). However, the levels of serum LRH-1 and VIP were lower, and the level of serum CCKAR was higher in the laparoscopic + choledochoscopic group than those in the laparoscopic group (*p* < 0.05) (Table V).

Complications and recurrence rate

The total incidence rate of complications in the laparoscopic + choledochoscopic group was comparable to that in the laparoscopic group (9.62% vs. 12.50%, *p* > 0.05). The laparoscopic + choled-

ochoscopic group had a lower recurrence rate at 6 months after operation than the laparoscopic group (1.92% vs. 14.58%, *p* < 0.05) (Table VI).

Discussion

The incidence of gallstones is related to a variety of factors, including obesity, liver cirrhosis, genetics, and diet. According to relevant data, the incidence rate of gallstones is rising year by year with the accelerated pace of life and altered dietary habits, and it is higher in females than in males, as well as being higher in economically developed regions than

Table V. Levels of serum LRH-1, CCKAR, and VIP ($\bar{x} \pm s$)

Group	N	LRH-1 [ng/l]		CCKAR [pg/ml]		VIP [pg/ml]	
		Before operation	3 d after operation	Before operation	3 d after operation	Before operation	3 d after operation
Laparoscope group	48	67.79 ±10.48	44.18 ±8.1 ^{2*}	106.82 ±10.98	117.91 ±14.7 ^{3*}	65.18 ±6.90	57.45 ±6.6 ^{6*}
Laparoscopic + choledochoscopic group	52	68.26 ±10.39	39.96 ±7.5 ^{3*}	104.63 ±11.30	125.59 ±15.4 ^{8*}	65.63 ±7.06	52.38 ±6.4 ^{7*}
<i>t</i>		0.225	2.697	0.984	2.537	0.322	3.860
<i>P</i> -value		0.822	0.008	0.329	0.013	0.748	0.000

**P* < 0.05 vs. before operation within the group.

Table VI. Complications and recurrence rate in the 2 groups [*n* (%)]

Group	<i>n</i>	Incision infection	Bile reflux gastritis	Abdominal infection	Cholestasis	Bile leakage	Total incidence rate	Recurrence rate 6 months after operation
Laparoscope group	48	1 (2.08)	2 (4.17)	0 (0)	1 (2.08)	2 (4.17)	6 (12.50)	7 (14.58)
Laparoscopic + choledochoscopic group	52	0 (0)	1 (1.92)	1 (1.92)	2 (3.85)	1 (1.92)	5 (9.62)	1 (1.92)
χ^2		–	–	–	–	–	0.212	3.852
<i>P</i> -value		–	–	–	–	–	0.645	0.049

in economically backward regions [9, 10]. Previously, the gallbladder was resected in most cases in both laparotomy and laparoscopic operation. However, the gallbladder is not a useless organ in the human body. It can not only concentrate and excrete bile, but also has an intimate correlation with the synthesis of IgA antibody, so patients often suffer from complications such as steatorrhoea and diarrhoea after cholecystectomy [11].

Cholecystectomy has been gradually replaced by gallbladder-preserving cholecystolithotomy in recent years. Totally laparoscopic cholecystolithotomy and laparoscopic and choledochoscopic gallbladder-preserving cholecystolithotomy are the 2 fairly common types of gallbladder-preserving cholecystolithotomy in clinics, and the former is prone to damaging the gallbladder mucosa and makes it difficult to locate the calculi [12]. As for laparoscopic and choledochoscopic gallbladder-preserving cholecystolithotomy, choledochoscope is applied based on laparoscopic cholecystolithotomy, which helps improve the operative visual field and complete the stone extraction under direct vision. It not only reduces the difficulty of stone extraction, shortens the operation time, and facilitates postoperative recovery, but also avoids unnecessary injury of the gallbladder due to operation errors, causes less microstructure damage of the gallbladder, and contributes to postoperative recovery of gallbladder function [13–15]. The results of this study showed that the operation time was shortened and the intraoperative blood loss was reduced in the laparoscopic + choledochoscopic group. At 6 months after operation, the laparoscopic + choledochoscopic group showed raised fasting gallbladder volume and gallbladder contraction rate, and decreased minimum residual volume and gallbladder wall thickness compared with the laparoscopic group. Moreover, the levels of serum Cor, NE, and CRP were lower in the laparoscopic + choledochoscopic group than those in the laparoscopic group at 3 d after operation, suggesting that laparoscopic and choledochoscopic gallbladder-preserving cholecystolithotomy outperforms laparoscopic gallbladder-preserving cholecystolithotomy in reducing operative trauma and enhancing postoperative gallbladder function. The main reason for previous cholecystectomy is that calculi cannot be completely removed by cholecystectomy. It has been indicated by related data that the recurrence rate at 1–2 years after gallbladder-preserving cholecystolithotomy can

reach 30% or even higher [16]. This is because the surgical treatment fails to fundamentally change the environment in which gallstones are easily formed, and the internal structure of the gallbladder cannot be directly observed during previous laparoscopic gallbladder-preserving cholecystolithotomy, where the small stone debris is easily omitted [17]. It was discovered through this study that the recurrence rate at 6 months after operation was 1.92% in the laparoscopic + choledochoscopic group, lower than that in the laparoscopic group (14.58%), implying that laparoscopic and choledochoscopic gallbladder-preserving cholecystolithotomy also has some advantages in lowering the risk of postoperative recurrence, which is related to the operative visual field being improved by choledochoscopy as well.

The intestinal motility of patients is strengthened after gallbladder-preserving cholecystolithotomy, but the amount of bile discharged into the intestinal tract and the water in the colon are decreased due to certain impairment of the gallbladder function, thus easily affecting gastrointestinal function [18]. Li *et al.* [19] noted that the recovery of gastrointestinal function in patients after gallbladder-preserving cholecystolithotomy had certain correlations with the level of serum CCKAR. In other words, patients with a high CCKAR level manifest better recovery of gallbladder function and gastrointestinal function than those with a low CCKAR level. Widely distributed in the digestive system, CCKAR plays a role in accelerating bile secretion, promoting fat digestion, and regulating common bile duct pressure. High-level CCKAR can enhance the contraction and emptying ability of the gallbladder, thus avoiding the formation of gallstones due to residue retention. Furthermore, high-level CCKAR can increase the water in the colon and promote adequate absorption of bile salts after operation, thereby preventing bile salts from entering the intestines to induce stress responses [20, 21]. Low-level CCKAR can lead to abnormal gallbladder function, which is unfavourable for the recovery of digestive function and even triggers gastrointestinal complications like biliary tract infection, peritonitis, and haemobilia [22]. LRH-1 can enhance the transformation of total cholesterol and promotes the transfer of total cholesterol from hepatocytes to bile, and the supersaturated precipitation of total cholesterol in bile can accelerate the formation of gallstones. The level of VIP, a neurotransmitter with

intestinal inhibitory properties, can reflect the contractile function of gallbladder to a certain extent. In the present study, it was indicated that the laparoscopic + choledochoscopic group had lower levels of serum LRH-1 and VIP and a higher serum CCKAR level than the laparoscopic group at 3 d after operation, and the bowel sound recovery time, defecation time, and exsufflation time were decreased in the laparoscopic + choledochoscopic group in contrast with those in the laparoscopic group, denoting that laparoscopic and choledochoscopic gallbladder-preserving cholecystolithotomy is beneficial to the postoperative recovery of gastrointestinal function. The specific reason has not been fully clarified, which is probably associated with the small gallbladder injury caused by this operation. In addition, the results of this study showed that there was no significant difference in the total incidence rate of complications between the laparoscopic + choledochoscopic group and the laparoscopic group, which may be attributed to the excessively small sample size of this study. Meanwhile, relevant conclusions still need to be further verified by prospective randomized controlled trials due to such limitations as the retrospective analysis and the short follow-up period of this study.

Conclusions

Both laparoscopic gallbladder-preserving cholecystolithotomy and laparoscopic and choledochoscopic cholecystolithotomy are effective for treating gallstones. However, the latter combination method is superior in enhancing postoperative gallbladder function, decreasing the recurrence risk, regulating the expressions of LRH-1, CCKAR, and VIP, and promoting the postoperative recovery of gastrointestinal function.

Acknowledgments

Chen Zhang and Jian Feng contributed equally to this study.

Conflict of interest

The authors declare no conflict of interest.

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