PAPERS OF THE 133RD ASA ANNUAL MEETING

Acute Cholecystitis

Early Versus Delayed Cholecystectomy, A Multicenter Randomized Trial (ACDC Study, NCT00447304)

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Annals of Surgery • Volume 258, Number 3, September 2013

2014.02.10

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背景

- 膽囊炎是常見疾病，因常反覆發作，建議接受經內視鏡膽囊切除手術
- 手術時間
  - (1) 早期手術
  - (2) 先接受抗生素治療，待數週後發炎趨緩，再手術

研究目的

- 成人急性膽囊炎患者，接受早期手術，相較於先接受抗生素治療再手術，是否有較少的Morbidity rate

方法

- Multi-center, prospective, randomized trial
- *NCT00447304, 2007*
- 急性膽囊炎成人(至少符合下列三項)
  - 右上腹痛
  - Murphy sign
  - Leulocytosis
  - 肛溫大於38◦C
- 排除
  - ASA IV and V, 敗血性休克, 膽囊破裂或膿瘍, 預期生命少於兩日, 懷孕或哺乳, 抗生素禁忌症

方法

- 分組
  - 早期手術 (Group ILC)
  - 抗生素治療後 7 至 45 天再手術 (Group DLC)
- Moxifloxacin, 400mg, QD
- Primary endpoint
  - 第75日的 Morbidity score
- Secondary outcome
  - 改行開腹手術比率，改抗生素比率，75日內死亡率，經濟效益，住院時間

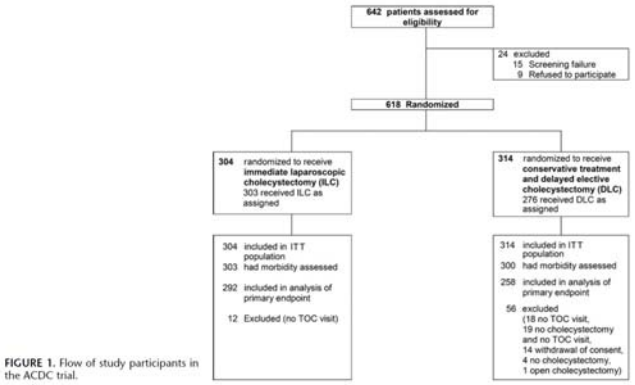


FIGURE 1. Flow of study participants in the ACDC trial.

結果

TABLE 1. Baseline Characteristics by Treatment Group (ITT Population)

Characteristics	Group ILC (n = 304)	Group DLC (n = 314)
Female sex,* n (%)	191 (62.8)	172 (54.8)
Age, mean (SD), yr	55.6 (16.3)	56.8 (17.1)
Body mass index, mean (SD), kg/m^2	28.9 (5.8)	29.5 (6.6)
Body temperature, mean (SD), °C	37.2 (0.8)	37.3 (0.8)
Blood pressure,† mean (SD), mm Hg		
Systolic	134.9 (20.1)	136.9 (21.5)
Diastolic	78.5 (10.9)	79.3 (11.7)
Coexisting conditions, n (%)		
Renal insufficiency	5 (1.6)	8 (2.5)
Cancer*	2 (0.7)	11 (3.5)
Diabetes mellitus	29 (9.5)	46 (14.6)
Hypertension*	106 (34.9)	137 (43.6)
Respiratory insufficiency*‡	8 (2.6)	20 (6.4)
Congestive heart failure*	15 (4.9)	31 (9.9)
Previous intra-abdominal surgery	88 (28.9)	109 (34.7)
Biliary colic in medical history, n (%)	125 (41.1)	126 (40.1)
Cholecystolithiasis, n (%)	269 (88.5)	277 (88.2)

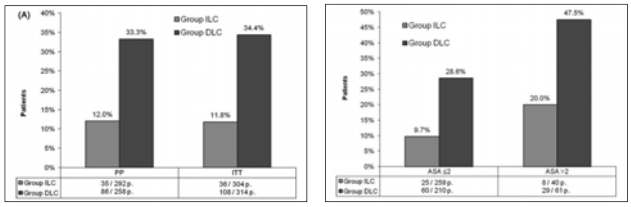
*$P < 0.05$ for the between-group comparison.
†Values are missing for 12 and 10 patients.
‡Mainly dyspnea under physical stress.

結果

- 接受手術時間點
  - ILC: 平均 0.6 天
  - DLC: 平均 25.1 天 (中位數 23 天，25位患者小於4天)
- 接受抗生素時間
  - ILC: 平均 4.96 天
  - DLC: 平均 8.72 天

結果

- Primary outcome



結果

TABLE 3. Seventy-five-Day Morbidity Rates for Morbidity Score Items by Treatment Group (ITT Population)

Complications*	Score Points	Group ILC (n = 303/304),† n (%)	Group DLC (n = 300/314),† n (%)	P
Persistent abdominal pain >72 h	1	7 (2.3)	30 (10.0)	<0.001
Persistent fever >72 h	1	1 (0.33)	10 (3.33)	0.006
Persistently raised signs of infection >72 h	1	17 (5.6)	35 (11.7)	0.009
Wound-healing complication	2	6 (2.0)	8 (2.7)	0.59
Thrombosis	3	0	0	
Bleeding	3	1 (0.33)	1 (0.33)	0.99
Pneumonia	3	2 (0.66)	2 (0.67)	0.99
Cholangitis/cholecystitis	3	4 (1.32)	31 (10.33)	<0.001
Icterus	3	3 (0.99)	1 (0.33)	0.31
Abscess	3	1 (0.33)	2 (0.67)	0.57
Bile leak	3	3 (0.99)	1 (0.33)	0.31
Peritonitis‡	4	0	4 (1.33)	0.045
Pancreatitis	4	1 (0.33)	3 (1.0)	0.32
Embolic lung disease	4	0	0	
Renal failure	4	0	0	
Relaparotomy	5	3 (0.99)	4 (1.33)	0.71
Cerebral ischemia or bleeding	5	0	0	
Myocardial infarction	5	0	1 (0.33)	0.32
Septic shock	5	0	4 (1.33)	0.045
Death	63	1 (0.33)	1 (0.33)	0.98

*Patients could have more than 1 complication.
†Number of patients scored/total number of patients.
‡In 3 patients, peritonitis was due to gallbladder rupture.

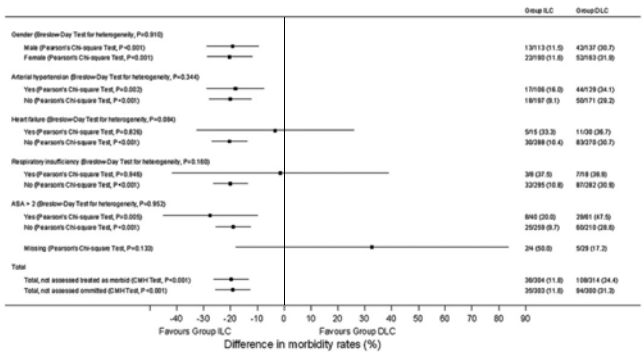
結果

TABLE 2. Secondary Outcomes by Treatment Group (ITT Population)

Secondary Efficacy Outcomes	Group ILC (n = 304)	Group DLC (n = 314)	P
Morbidity score on day 75,* mean [95% CI]	0.53 [0.10–0.96]	1.12 [0.66–1.58]	<0.001
Conversion rate to open surgery, n (%) [95% CI]	30 (9.9) [6.5–13.2]	33 (11.9) [8.1–15.7]	0.44
Adverse events, n (%) patients [95% CI]	43 (14.1) [10.2–18.1]	127 (40.4) [35.0–45.9]	<0.001
Change of antibiotic treatment, n (%)	22 (7.2)	31 (9.9)	0.24
Mortality rate, n (%)	1 (0.3)	1 (0.3)	0.98
Total hospital stay, mean (interquartile range) [95% CI], d	5.4 (4–6) [5.08–5.71]	10.03 (7–12) [9.36–10.69]	<0.001
Duration of hospitalization after cholecystectomy, mean (interquartile range) [95% CI], d	4.68 (3–6) [4.36–5.00]	4.89 (3–6) [4.26–5.51]	0.57
Total hospital costs, mean (interquartile range) [95% CI], €	2919 (2651–2651) [2812–3026]	4262 (3021–4724) [4029–4494]	<0.001
Cost-effectiveness ratio,† mean, € per successful cholecystectomy	3300	6206	—

*Fifteen patients had a missing or implausible morbidity score.
†Ratio based on ITT population without patients with unassessed morbidity status.

結果



結論

- 成人急性膽囊炎接受早期手術有較少的併發症及較佳的經濟效益。
- 兩組死亡率皆約0.3%，無顯著差異。

討論

- Meta-analysis 顯示早期手術較有經濟效益，且生活品質較好
- CONSORT criteria
- 本實驗限制
  - 對照組延遲接受手術的時間差異大，7~45日
  - 以入院時間作為基礎點，而非症狀開始的時間
  - 實驗組和對照組患者略有差異

1. Did the trial address a clearly focused issue? ☑ Yes ☐ Can't tell ☐ No

HINT: An issue can be 'focused' in terms of
- The population studied
- The intervention given
- The comparator given
- The outcomes considered

- 成人急性膽囊炎患者
- 早期手術
- 先接受抗生素治療，再手術
- Primary outcome: 第75日的 Morbidity score

2. Was the assignment of patients to treatments randomised? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider
- How was this carried out?
- Was the allocation sequence concealed from researchers and patients?

- 隨機分派保密信封，Block randomization
- 隨機分配公平並具保密性

3. Were all of the patients who entered the trial properly accounted for at its conclusion? ☑ Yes ☐ Can't tell ☐ No

HINT: Consider
- Was the trial stopped early?
- Were patients analysed in the groups to which they were randomised?

- 少數未依計畫完成實驗，但有作 ITT 和 PP 分析

4. Were patients, health workers and study personnel 'blind' to treatment? ☐ Yes ☐ Can't tell ☑ No

HINT: Think about
- Patients?
- Health workers?
- Study personnel?

- No blinding

5. Were the groups similar at the start of the trial? ☐ Yes ☑ Can't tell ☐ No

HINT: Look at
- Other factors that might affect the outcome such as age, sex, social class

- 實驗組和對照組，在性別和少數Coexisting conditions 有顯著差異。但有附加 Sensitivity test。

6. Aside from the experimental intervention, were the groups treated equally? ☑ Yes ☐ Can't tell ☐ No

- 除手術先後之外，實驗組和對照組所接受治療盡可能無差異

7. How large was the treatment effect?

HINT: Consider

- What outcomes were measured?
- Is the primary outcome clearly specified?
- What results were found for each outcome?

- Primary outcome: 第75日的 Morbidity score
- 早期手術，無論在 ITT/PP 或 ASA 分級，皆有較佳的Primary outcome

8. How precise was the estimate of the treatment effect?

HINT: Consider

- What are the confidence limits?

- 對照組延遲接受手術的時間差異大，7~45日
- 以入院時間作為基礎點，而非症狀開始的時間
- 實驗組和對照組患者略有差異
- 對照組未完成實驗人數過多，56 of 314

9. Can the results be applied in your context? (or to the local population?)

☑ Yes ☐ Can't tell ☐ No

HINT: Consider whether

- Do you think that the patients covered by the trial are similar enough to the patients to whom you will apply this?, if not how to they differ?

10. Were all clinically important outcomes considered?

☑ Yes ☐ Can't tell ☐ No

HINT: Consider

- Is there other information you would like to have seen?
- If not, does this affect the decision?

Thank you :)

Table 2: Morbidity Score

Persistent abdominal pain > 72 h	1	Pain treated by morphine or derivatives > 72 h
Persistent fever > 72 h	1	Rectal temperature > 38.5°C at least twice
Persistently raised signs of infection > 72 h	1	Persistently elevated CRP or leukocytosis
Wound-healing disorder	2	Any problem leading to re-opening of the wound with subsequent open wound treatment
Thrombosis	3	New onset of leg or pelvic thrombosis
Bleeding	3	Need for more than two bags of packed red cells during or after surgery
Cholangitis	3	New increase in AP, GGT (>2× ULN), bilirubin (>1× ULN) plus leukocytosis (> 12 × 10^3/µl) or increase in CRP (> 5× ULN)
Icterus	3	New increase in bilirubin, AP and GGT (>2× ULN)
Bile leakage	3	Persistent leakage shown by CT, MRI or ERCP
Abscess	3	Shown by CT, MRI or ultrasound
Pneumonia	3	Shown by X-ray plus drop in arterial pO_2 plus clinical signs of pneumonia plus leukocytosis plus increased CRP
Embolic lung disease	4	Increased PA pressure (echocardiogram), TNT/TNI, D-dimers
Peritonitis	4	New occurrence of peritonitis
Pancreatitis	4	Increased pancreatic enzymes (> 3× ULN) plus new increase in CRP (> 5× ULN) plus positive clinical signs
Renal failure	4	Drop in urine production below 500 mL/day plus increased creatinine and urea (> 2× ULN)
Relaparotomy	5	Need for follow-up surgery
Cerebral ischemia or bleeding	5	New neurological symptoms with corresponding to changes in cerebral CT
Myocardial infarction	5	Changes in TNT/TNI with or without changes in the ECG meeting the criteria of STEMI of NSTEMI
Septic shock	5	Leukocytosis (> 12 × 10^3/µl) or leukopenia (< 4 × 10^3/µl) plus temperature < 36.5°C or > 38.5°C plus clinical signs
Death	63	(Sum of all complications + 1)

Different complications and side effects that may affect the patients during the study are listed and scored differently in increasing severity. Death as worst outcome is scored the sum of all complications plus 1.

DLC: 只有 68.3% 患者在術中接受預防性抗生素 Moxifloxacin