Fast-track surgery after gynaecological oncological surgery: A Prospective Randomized Trial

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Research

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Abstract

Background: Fast-track surgery (FTS) or enhanced recovery after surgery have been applied to many surgical procedures. The FTS interventions may lead to a major reduction in the undesirable sequelae of surgical injury with improved recovery and reduction in postoperative morbidity and overall costs.

The aim of this study is whether FTS reduces the length of stay in hospital compared to traditional management. The secondary aim is whether FTS is associated with an increase in post-surgical complications compared to traditional management (for both open and laparoscopic surgery).

Methods: A prospective randomized trial included 107 patients undergoing gynaecological oncological surgery. The patients were randomized to the FTS group (n=50) and the traditional group (n=57). LOS (Length of stay in hospital), and complications were assessed.

Results: No significant differences in LOS were observed between the groups. The total costs of hospitalization (RMB), and CRP (C-Reactive protein mg/l) are less in the FTS group (P < 0.05) and the overall complications were lower in the FTS Group, statistically significantly lower ((P < 0.05).

Conclusions: Fast-track surgery after gynaecological oncological surgery is beneficial for patients.

Trial registration number: NCT02687412. Approval Number: SCCHEC20160001. Date of registration: registered on 23 February 2016, https://clinicaltrials.gov/ct2/show/NCT02687412.

Background

Fast-track surgery (FTS) or enhanced recovery after surgery (ERAS) have been applied to many surgical procedures. The FTS interventions may lead to a major reduction in the undesirable sequelae of surgical injury with improved recovery and reduction in postoperative morbidity and overall costs(1). Surgical injuries in the organ are thought to be mediated by trauma-induced endocrine metabolic changes and activation of several biological cascade systems (cytokines, complement, arachidonic acid metabolites, nitric oxide, free oxygen radicals, etc)(2). Although FTS has been adopted in gynaecological, colorectal and upper GI specialties worldwide, and has been used successfully in pancreatic surgery, but initial studies in gynaecology surgery only included hysterectomies for benign indications or precancerous lesions.(3)

A recent surgical study suggested that FTS was as safe as conventional perioperative care and improved recovery of patients undergoing pancreaticoduodenectomy, thus reducing in-hospital costs. The general adoption of FTS protocols during pancreaticoduodenectomy should be recommended.(4) As well as FTS program is safe, feasible, and can be applied successfully in liver resection.(5)

It is well known that surgical stress induces a catabolic state that leads to increased cardiac demand, relative tissue hypoxia, increased insulin resistance, impaired coagulation profiles, and altered pulmonary and gastrointestinal function. FTS were developed with the goal of maintaining normal physiology in the
perioperative period, thus optimizing patient outcomes without increasing postoperative complications or readmissions.(6) FTS have been developed in gynecologic surgery since 2006.(7) And guidelines from ERAS have been published and recently updated.(8)

FTS programs have been developed globally to decrease perioperative stress, improving pain management and gut dysfunction, and minimizing postoperative complications which will then lead to hastened patient recovery and reduced time in hospital.(9)

On average, more than 400 gynaecological oncological surgeries were performed in our hospital every year, and no FTS was carried out before 2016, therefore we registered a protocol in clinical trials, trial registration number: NCT02687412. Approval Number: SCCHEC20160001 on 23 February 2016. We did this randomized controlled clinical trial (RCT) during 2017–2018. We finished the RCT and analysed all the data before 23th April 2018, and we release it on clinical trial on 25th August 2019.

Materials And Methods

This trial was approved by an independent ethics committee at Sichuan Cancer Hospital and Research Institute Board Affiliation: SichuanCHRI. After Ethics approval was granted, the FTS Database was searched to identify patients operated upon between May 2016 and May 2018.

Our FTS protocol was already published(9) [This trial prospectively compares FTS and traditional management protocols, see table 1 (Checklist of fast track and traditional management). The primary endpoint is the length of postoperative hospitalization (days, mean ± standard deviation), defined as the number of days between the date of discharge and the date of surgery. The secondary endpoints are total costs of hospitalization, complications in both groups (FTS versus traditional protocol) occurring during the first 3 months postoperatively including infection (wound infection, lung infection, intraperitoneal infection), postoperative nausea and vomiting, ileus, post-operative hemorrhage, post-operative thrombosis.

Table 1
Inclusion criteria

| 1. Patients scheduled for gynaecological oncology surgery (including radical hysterectomy and lymphadenectomy, hysterectomy and lymphadenectomy, and cytoreductive procedures for both open and laparoscopic surgery); |
|---|
| 2. Age: ≥ 18 years; |
| 3. Signed informed consent provided. |

Inclusion criteria

1. Patients scheduled for gynaecological oncology surgery (including radical hysterectomy and lymphadenectomy, hysterectomy and lymphadenectomy, and cytoreductive procedures for both open
and laparoscopic surgery);
2. Age: ≥ 18 years;
3. Signed informed consent provided.

**Exclusion criteria**

1. Patients with a documented infection at the time of surgery;
2. Age ≥ 71 years; (we discussed in ethics committee)
3. Patients with ileus at the time of surgery;
4. Patients with hypocoagulability;
5. Patients with psychological disorders, alcohol dependence, or drug abuse history;
6. Patients with primary nephrotic or hepatic disease;
7. Patients with severe hypertension defined as systolic blood pressure ≥ 160 mmHg and diastolic blood pressure > 90 mmHg.

**Criteria for discontinuing**

1) the trial appears causing unexpected harm or severe adverse events to participants, or the evidence that the risks outweigh the benefits, with the discontinuance decision of the ethics committees.

2) the enrollment indicates the trial can’t be finished in a period of 3 months.

**Fast track and traditional management**

See table 1 Checklist of fast track and traditional management

**Discharge criteria**

Discharge criteria were stability of vital signs, alert and oriented state of consciousness, absence of complications or symptoms, autonomous walking, possibility of feeding with a solid diet, successful first flatus, spontaneous diuresis, good control of pain numeric rating scale (NRS) < 4 with oral medications, self-sufficiency in basic daily activities and the desire expressed by the patient to go home.

**Randomization**

Women who met the eligibility and completed a baseline visit were randomized into one of the two groups at a ratio of 1:1. Women were allowed to complete the baseline and randomization visit on the same day. The allocation sequences were generated by investigators utilizing computer-generated
random number. To reduce predictability of a random sequence, details of any planned restriction (e.g. blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.

Data will be analyzed using SPSS 18.0 (IBM Corp., Armonk, NY, USA) and expressed as mean ± SD. LOS, postoperative hemorrhage, post-operative thrombosis in the FTS and traditional groups will be compared and analyzed using the Student’s t-test. The chi-square test or Fisher’s exact test will be used to analyze the categorical secondary endpoints (complications). P < 0.05 will be considered statistically significant.

Results

119 Patients assessed for eligibility and 12 patients were excluded. The study group included 107 patients, 50 in FTS group and 57 in control group with a mean age of 48.62 and 55.25 years. The patient data in the two groups are summarized in the FTS group (50) contains cervical cancer 27 (54%), endometrial cancer 14 (28%), ovarian cancer 9 (18%). Traditional group (57) contains cervical cancer 29 (50%), endometrial cancer 9 (16%), ovarian cancer 19 (34%). The mean body surface area of the FTS group (1.55) was similar to the traditional group (1.54), and the mean body mass index of the FTS group (22.68) was similar to the traditional group (23.17) as well. Operative time of the FTS group was 195.30 (min) while the traditional group was 200.37 (min). The estimated blood loss during surgery of the FTS group was 320.00 and the traditional group was 280.18. The patient data in the two groups are summarized in Table 5.

Table 2
Exclusion criteria

| 1. Patients with a documented infection at the time of surgery; |
| 2. Age ≥ 71 years; (we discussed in ethics committee it will); |
| 3. Patients with ileus at the time of surgery; |
| 4. Patients with hypocoagulability; |
| 5. Patients with psychological disorders, alcohol dependence, or drug abuse history; |
| 6. Patients with primary nephrotic or hepatic disease; |
| 7. Patients with severe hypertension defined as systolic blood pressure ≥ 160 mmHg and diastolic blood pressure > 90 mmHg. |

Table 3
Criteria for discontinuing

| 1. the trial appears causing unexpected harm or severe adverse events to participants, or the evidence that the risks outweigh the benefits, with the discontinuance decision of the ethics committees. |
| 2. the enrollment indicates the trial can’t be finished in the period of 3 months. |
|                          | FTS management                                                                 | Traditional management                                                                 |
|--------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| **Allocation**           | Computer-generated random numbers                                                | Computer-generated random numbers                                                     |
| **Pre-operative**        | Pre-operative assessment, counseling and FT management education                 | No FT management education                                                             |
|                          | Information of the fast track treatment and the informed consent                  | Information of the traditional treatment and the informed consent                     |
|                          | Preoperative nutritional drink up to 4 h prior to surgery (Slight liquid diet    | Pre-operative fasting at least 8h                                                     |
|                          | produced by Methuselah (Shanghai) Medical Technology Co., Ltd)                   |                                                                                        |
|                          | Fast solid food before 6 h and liquid food intake of clear fluids 2 h before     |                                                                                        |
|                          | anaesthesia                                                                      |                                                                                        |
|                          | Patients are not received mechanical bowel preparation, only oral intestinal     | Oral bowel preparation or mechanical bowel until liquid stool                          |
|                          | cleaner 12 h pre-operation can be accepted, but no need of liquid stool          |                                                                                        |
|                          | Antimicrobial prophylaxis and skin preparation                                   | Antimicrobial prophylaxis and skin preparation                                         |
|                          | Preoperative treatment with carbohydrates 10% Glucose 400 ml p.o. 2-3 h before  | No oral intake in the operation day                                                    |
|                          | operation ➤                                                                             |                                                                                        |
|                          | (patients without diabetes)                                                        |                                                                                        |
| **Intraoperative**       | Avoiding hypothermia, keeping the intra-operative coretemperature at 36 ±0.5°C    | Keeping the intra-operative coretemperature at 34.7 ±0.6°C                             |
|                          | Antiemetics at end of anaesthesia                                                  | Not every patient get antiemetics at end of anaesthesia                               |
| **Post-operative**       |                                                                                   |                                                                                        |
| Postoperative glycaemic control | Postoperative glycaemic control only with diabetes |
|--------------------------------|-------------------------------------------------|
| Preventive postoperative nausea and vomiting (PONV) control | Postoperative nausea and vomiting (PONV) control when it happens |
| Early postoperative diet (3-6 h after surgery, patients resumed a liquid diet, 12 h after surgery patients began to take solid diet) | 6 h after surgery, patients resumed a liquid diet, patients began to take solid diet after anal exhaust |
| Early mobilisation | Early mobilisation |
| Time to drain removal less than 24h (Eliminate postoperative bleeding and urinary fistula, intestinal fistula) | Time to drain removal less than 48h (Eliminate postoperative bleeding and urinary fistula, intestinal fistula) |

audit

Systematic audit improves compliance and clinical outcomes
Table 5
Patient demographic and operative characteristics

|                          | FTS group (50) | Traditional group (57) |
|--------------------------|----------------|------------------------|
| Age (years)              | 48.62          | 55.25                  |
| Disease                  |                |                        |
| Cervical cancer          | 50             | 57                     |
| Endometrial cancer       | 27 (54%)       | 29 (50%)               |
| Ovarian cancer           | 14 (28%)       | 9 (16%)                 |
|                          | 9 (18%)        | 19 (34%)               |
| Body surface area BSA    | 1.55           | 1.54                   |
| Body Mass Index BMI      | 22.68          | 23.17                  |
| Operative time (min)     | 195.30         | 200.37                 |
| Intraoperative blood loss (ml) | 320.00   | 280.18                 |
| Laparotomy surgery number | 39            | 48                     |
| Laparoscopic surgery number | 11        | 9                      |
| Blood transfusion number | 8             | 6                      |
| Day of drainage          | 1.44           | 1.63                   |
| Day of fasting           | 1.02           | 1.79                   |

For patients of FTS group, mean length of stay (LOS) was 8.92 days (95% CI: −0.278–1.771) and for those traditional group was also 9.67 days (95% CI: −0.278–1.771). Although the LOS of the FTS group was shorter, there was no statistical significance (Table 6).

Table 6
LOS (Length of hospitalization post-operation between two groups)

|                          | FTS group (32) | Traditional group (33) |
|--------------------------|----------------|------------------------|
| Mean                     | 8.92           | 9.67                   |
| Standard deviation       | 2.029          | 3.119                  |
| 95% CI                   | -0.278–1.771   | -0.278–1.771           |
| Sig                      | 0.141          | 0.151                  |
The total cost of hospitalization (RMB) was significantly lower in the FTS group compared with the traditional group (38882.44 versus 42864.12 P: 0.029). The CRP (C-Reactive protein mg/l) was also significantly lower in the FTS group compared with the traditional group (42.125 versus 62.499 P: 0.02). The days of fasting was also significantly shorter in the FTS group compared with the traditional group (1.02 versus 1.58 P: 0.00). Table 7.

Table 7
Characteristics found to be significantly different between two groups

|                        | FTS group  | Traditional group | Significance |
|------------------------|------------|-------------------|--------------|
| The total cost (RMB)   | 38882.44   | 42864.12          | 0.029        |
| CRP (C-Reactive protein mg/l) | 42.125 | 62.499            | 0.002        |
| Days of fasting        | 1.02       | 1.58              | 0.000        |

The cost of surgical therapy (RMB) and Calcitonin original PCT were (9703.22 versus 9538.47 and 0.5595 versus 0.5212 respectively) but these differences had no statistical significance. Table 8.

Table 8
Characteristics found to be different between two groups

|                        | FTS group  | Traditional group | Significance |
|------------------------|------------|-------------------|--------------|
| Cost of surgical therapy (RMB) | 9703.22 | 9538.47          | 0.605        |
| PCT Calcitonin original | 0.5595    | 0.5212            | 0.838        |

There was no severe complication in both groups.

There were 11 patients who had complications including wound infection, lung infection, intraperitoneal infection, ileus, and postoperative hemorrhage. There were 3 patients had complications in the FTS group including 2 intraperitoneal infections, and 1 ileus. There were 8 patients who had complications in the traditional group including 3 wound infection, 1 lung infection, 4 intraperitoneal infections, 1 ileus. There was one patient who had two complications including wound infection and intraperitoneal infection.

Statistical analysis including descriptive statistics, and the chi-squared test for complication.

The overall complications (3 in the FTS group, 13 in the traditional group) were not significantly different statistically (sig 0.014) (Table 9). While the complication of infections in the FTS group was found to be less compared to the traditional group (sig 0.034). Table 9.
Table 9
Postoperative complications

|                          | FTS group | Traditional group | Significance |
|--------------------------|-----------|-------------------|--------------|
| Overall Complications    | 3         | 13                | 0.014        |
| Infection                | 2         | 12                | 0.034        |
| wound infection          | 0         | 4                 | 2.38         |
| lung infection,           | 0         | 1                 | 1.0          |
| intraperitoneal infection,| 2         | 7                 | 0.170        |
| postoperative nausea      | 0         | 0                 | /            |
| and vomiting (PONV)      |           |                   |              |
| Ileus                    | 1         | 1                 | 1.0          |
| Postoperative haemorrhage | 0         | 0                 | /            |
| Postoperative thrombosis  | 0         | 0                 | /            |

Discussion

FTS has been already widely accepted after many types of surgeries. There are some studies demonstrate that FTS implementation in gynaecologic oncological surgery is associated with LOS decrease without increases of morbidity or readmission rates. (10,11). But in this prospective randomized clinical trial, it appears that the LOS is nearly the same between two groups. The reasons seem are as follows. First compared with general surgical oncology surgery, gynecological oncological surgery leads to less damage, almost has done no serious damage to the digestive tract. Second, compared with general surgical oncology surgery, gynecological oncological surgery hardly has a serious complication such as digestive tract fistula or leakage and death. Third, we did not include older patients (age ≥ 71 years) after discussion with the ethics committee, considering the slow recovery of digestive system and more basic diseases. Finally, part of patients continued to receive chemotherapy after surgery, and we do not discharge on the weekend or holidays, this made the criteria for discharge unstable.

We are happy to see the total cost of hospitalization (RMB) was significantly lower in the FTS group compared with the traditional group. One of the important procedures we conducted was using a heating blanket to avoid hypothermia, keeping the intra-operative core-temperature at 36 ±0.5°C. Unintentional hypothermia is defined as an accidental low body temperature.(12)

The National Institute for Health and Care Excellence (NICE) estimates that 70% of patients admitted to the anesthetic recovery room suffer from hypothermia.(13) The accidental perioperative hypothermia is a common event during surgical interventions and increases itself perioperative morbidity impairing
hemostasis, wound healing, and increasing cardiac events.\((14)\) Because intraoperative body temperature maintenance significantly shortened the postoperative anesthesia resuscitation time, the application time of ventilator was reduced and the cost was significantly reduced. Meanwhile, fast-track surgery reduced the overall complications and complications of infections and was found statistically significant, while there was no statistical difference in some other complications. Therefore, the cost of treatment was lower than that of the traditional group.

The early oral feeding and shorter duration of intravenous infusion, reduce the costs for parenteral nutrition and prevention of thrombosis and so on. The CRP (C-Reactive protein mg/l) was also significantly lower in the FTS group compared with the traditional group. Fasting from midnight increases insulin resistance, a complex clear carbohydrate-rich drink designed for use within 2h before anesthesia reduced hunger, thirst, anxiety as well as postoperative insulin resistance.\((15)\) Preventing hypothermia during surgery can alleviate stress status. Numerous meta-analyses and RCTs have shown that preventing hypothermia during major abdominal surgery reduces the occurrence of wound infections.\((16)\)

Early postoperative diet speeded up gastrointestinal motility, so we found days of fasting is much shorter in the FTS group.

In this prospective randomized trial, the cost of surgical therapy (RMB) is nearly the same between the two groups. And there was no significant difference in the cost of surgical therapy (RMB) as the two groups had the same operators.

The incidence of total postoperative complications and lower infection rates were considered to be closely related to preoperative anxiety reduction, intraoperative temperature control, and postoperative glycaemic control. FTS program shortens preoperative and postoperative fasting time and decreases the amount of time patients staying in bed. This can be detrimental to recovery as it can result in a negative nitrogen balance.\((17)\) The FTS program's early oral feeding protocol assists in optimal wound healing. Research shows that unrelieved pain can inhibit the immune system, decrease gastrointestinal motility and lead to respiratory dysfunction by increasing oxygen demand.\((18)\) As early mobility is an essential component of the FTS program, analgesia must allow mobilization and participation in recovery by the patient. Patients of ovarian cancer after appendectomy would fast until anal exhaust in the traditional sense, but early feeding proved safe and effective in the recent consensus guidelines for enhanced recovery after gastrectomy and pancreaticoduodenectomy.\((19,20)\) It is also safe for ovarian cancer patients.

In summary, gynecological oncological surgeries have little damages to the digestive tract, so fast track surgery is appropriate and safe for them. This approach not only decreases the complications of infection also decreases the total cost of hospitalization. The ultimate benefits of FTS are improving outcomes, decreasing total cost and faster recovery.
Abbreviations

| Abbreviations | Definition                           |
|---------------|-------------------------------------|
| FTS           | Fast-track surgery                  |
| LOS           | Length of hospitalization post-operation |
| PONY          | postoperative nausea and vomiting    |

Declarations

Compliance with Ethical Standards

Disclosure of potential conflicts of interest: There is no potential conflicts of interest.

Research involving human participants

Informed consent: All participants signed informed consent.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of an independent ethics committee at Sichuan Cancer Hospital and Research Institute. Board Affiliation: SichuanCHRI. After Ethics approval was granted, the FTS Database was searched to identify patients operated upon between May 2016 and May 2018.

Approval Number:

SCCHEC20160001

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Xunwei Shi and Ling Cui contributed equally to this work.

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Authors’ contributions
L. C. conceived and designed the study, performed the statistical analysis and drafted the manuscript. XW. S. performed the data collection, statistical analysis and drafted the manuscript. Y. S. participated in the design of the study and performed the statistical analysis. GN. Z. participated in study design and coordination and helped to draft the manuscript. DF. W. and ZR. Y. participated in the data collection. All authors read and approved the final manuscript.

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- Studyflowdiagram.docx
- CONSORT2010Checklist.doc
- protocol.pdf