原著

Efficacy of routine intravenous acetaminophen compared with continuous infusion of fentanyl for postoperative pain management after laparoscopic inguinal hernia repair

Masanori GO[1], Natsuki ABE[2], Toshiki NARITANI[1], Fumiaki MINATO[1], Michihisa KATO[1], Ritsuko GO[1]

1) Division of Anesthesiology, Tokushima Red Cross Hospital
2) Department of Anesthesiology, Tokushima University Graduate School

Abstract

Purpose: The transabdominal preperitoneal approach (TAPP) is being used more frequently for laparoscopic inguinal hernia repair. Intravenous acetaminophen administration is also important in the perioperative period. We examined whether intravenous acetaminophen was more useful than fentanyl continuous infusion after TAPP. Methods: Forty patients were enrolled into this study and divided into two groups. Thirty minutes before surgery completion, 1,000 mg or 15 mg/kg acetaminophen was administered intravenously in Group A, and every 6 hours thereafter. In Group F, intravenous fentanyl (0.3 μg/kg/h) was administered continuously. NSAIDs were used at the patient's request. The primary outcome was the number of rescue NSAID doses, and the secondary outcomes were the numerical rating scale (NRS) for pain at three time points after surgery until the next morning (NRS 1, 2, 3), patient satisfaction (11-point scale: 0, poor to 10, excellent) the next morning, and anesthesia side effects. Results: There were no differences between NRS 1 (median, 4 vs. 3 in groups A and F, P=0.54), NRS 2 (5 vs. 2, P=0.26), NRS 3 (2 vs. 1, P=0.22), patient satisfaction (8 vs. 9, P=0.20), number of NSAID doses, and anesthesia side effects. Conclusion: Intravenous acetaminophen injection every 6 hours is not different from continuous fentanyl injection after TAPP.

Key words: acetaminophen, laparoscopic inguinal hernia repair, fentanyl, postoperative pain

Introduction

The transabdominal preperitoneal approach (TAPP) is commonly used to treat inguinal hernias because of its low risk of recurrence, early recovery, and low risk of chronic pain[1]. At our facility, surgeons began using TAPP when this technique was first developed. However, few studies have examined postoperative pain following this operation, and various analgesic techniques are used[2].

Intravenous acetaminophen (APAP) administration was approved by the Food and Drug Administration in Japan in 2010. Before this approval, intravenous administration of the APAP prodrug (paracetamol) or APAP administration via an alternative route (oral or transrectal) were the approved treatments. However, alternative routes of administration are often difficult for patients after surgery and the intravenous route for APAP administration is thought to have a stronger effect than other routes[3]. Additionally, paracetamol has been used in the USA and other Western countries, but it was previously unavailable in Japan. Now that it is available in Japan, intravenous APAP is now more frequently used for postoperative pain. Moreover, the approved APAP dose is now higher in Japan compared with the approved dose before November 2011.

In the present study, we aimed to clarify whe-

ther APAP administration at regular time intervals is more useful than continuous infusion of fentanyl (FN) to relieve pain after TAPP. In the ASA guidelines for acute pain management, reducing the opioid dose is recommended[4]. If APAP is more useful than FN at reducing pain, FN use can be reduced. Before intravenous APAP was approved, low dose of FN, about 0.3 μg/kg/h, was used for postoperative analgesia after TAPP at our facility. However, because intravenous APAP has been approved, we hypothesized that APAP would provide acceptable analgesia compared with FN.

The primary outcome was the number of rescue non-steroidal anti-inflammatory drugs (NSAIDs) (60 mg of oral loxoprofen or 50 mg of intravenous flurbiprofen) doses. The secondary outcomes were the numerical rating scale (NRS) score for pain at three time points after surgery, patient satisfaction, and anesthesia-related side effects (postoperative nausea and vomiting, shivering) in the recovery room and the morning after surgery.

Methods

This prospective study was performed in accordance with the Declaration of Helsinki. This was a randomized, nonblinded, two-group parallel trial. The study was conducted with the approval of the Medical Ethics Committee at Tokushima Red Cross Hospital and was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) (UMIN000014487).

Patients and study design

We decided to enroll 40 patients in this study and divided into two groups. After completed this study, we aimed to start new study in the same protocol, in which study the number of patients will calculated by the results of this study. From July 2014 to November 2014, we enrolled 40 patients, aged 20 to 80 years, who underwent TAPP to treat inguinal hernia. We did not limit the surgeons' years of experience or whether the surgery side was unilateral or bilateral because the affected side changed in some patients after observing the inside of the peritoneum. The exclusion criteria were hepatic toxicity (preoperative aspartate transaminase, alanine transaminase, or both exceeding 100 U/L), obesity (body mass index of ≥ 30kg/m^2), habitual use of analgesic drugs, and patients who could not understand the protocol (e.g. patients with dementia).

Intervention, randomization, and blinding

All patients provided written informed consent. They were divided into two groups using the sealed envelope method : those in Group A received intravenous APAP injections (20 patients), and those in Group F received continuous FN infusion (20 patients). Blinding to these medications was not possible because of the differences in their administration techniques.

Standard protocol for anesthesia and surgery

TAPP was performed in all patients. Patients with bilateral hernias were included. General anesthesia was used in all patients and no local anesthesia was administered. Anesthetic induction was performed using propofol, remifentanil, and rocuronium, and was maintained using remifentanil, desflurane, and rocuronium. The dose was determined by the individual anesthesiologist. At the beginning of surgery, a single dose of 3 μg/kg FN was injected intravenously for patients in groups A and F. Patients in Group A were administered APAP about 30 minutes before the end of surgery and every 6 hours after the first administration. The amount of APAP was 1000 mg for patients weighing more than 50 kg and 15 mg/kg for patients weighing less than 50 kg. In Group F, FN infusion was started at about 0.3 μg/kg/h approximately 30 minutes before the end of surgery.

Remifentanil and desflurane were discontinued after surgery was completed, and sugammadex was administered. The patients were extubated when they recovered normal respiration. The patients then entered the recovery room (postanesthesia care unit; PACU), and after a 30- to 60-min observation period, they were transferred to the ward. Patients who requested analgesics were administered 60 mg of oral loxoprofen or 50 mg of intravenous flurbiprofen.

Data collection

After surgery, the NRS score for pain was obtained at three time points: immediately after entering the PACU (NRS 1), 30 min after entering the PACU (NRS 2), and the morning after the operation (NRS 3). To collect the NRS score for pain, a Likert scale with 11 degrees was used (0, no pain to 10, the worst pain the patient can imagine). NRS 1 and NRS 2 were obtained by the anesthesiologist involved in the operation, and NRS 3 was obtained by one of the researchers. Side effects of anesthesia (nausea/vomiting, shivering) were recorded 30 min after entering the PACU and the next morning. Patient satisfaction during the perioperative period was also determined the morning after surgery. Satisfaction during the perioperative period was evaluated on an 11-point scale (0, poor to 10, excellent). Additionally, the number of doses of rescue NSAIDs and the time points at which the patient requested these NSAIDs were recorded.

Statistical analysis

The Student's *t*-test for continuous variables, and the Chi-square test for categorical variables were used to compare the baseline of the two groups. A Fisher's analysis was performed to eva -luate the number of NSAID doses, shivering, and nausea and vomiting. The Mann-Whitney *U* test was performed to analyze the NRS score for pain and patient satisfaction. For both analyses, a P value of <0.05 was considered statistically significant.

Sample size was calculated as described above, and all statistical analyses were completed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[5], which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). It is a modified version of R commander designed to add statistical function frequently used in biostatistics.

Results

Forty patients were enrolled into the study. Three patients were excluded from Group A because of insufficient data or because asthmatic attacks occurred, and additional treatment was required. Thus, 17 patients in Group A and 20 patients in Group F were included in the analysis (Figure 1). The background characteristics of each group

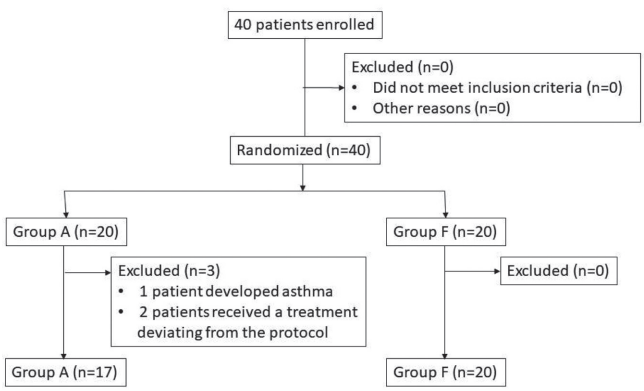

Figure 1. Flow diagram of patients enrolled into the study

Table 1 Characteristics of patients

		Group A (n=17)	Group F (n=20)	P value
Body weight (kg)		63.7±8.3	64.0±11.1	0.912
Height (cm)		163.6±8.3	165.03±8.6	0.616
Body mass index (kg/m2)		23.6±1.9	23.4±2.8	0.882
ASA-PS	1	5(88.2)	9(45.0)	0.498
	2	12(70.6)	11(55.0)	
Sex	Female	2(11.8)	2(10.0)	1
	Male	15(88.2)	18(90.0)	
Age (years)		65.8±12.9	64.5±11.1	0.741
Surgical side	Unilateral	15(88.2)	19(95.0)	0.584
	Bilateral	2(11.8)	1(5.0)	
Anesthesia duration (min)		117.7±29.8	116.2±31.2	0.774
Surgery duration (min)		90.0±30.2	88.7±28.4	0.894
Temperature at end of surgery (℃)		36.2±0.4	36.1±0.4	0.522
Total FN dose during surgery (μg)		200(150−225)	900(625−1150)	<0.001

Data are presented as n (%) or mean±standard deviation.
Patients received intravenous acetaminophen injections during and after surgery (Group A) or continuous FN infusion beginning before the end surgery (Group F).
There were no significant differences between the groups using a Student's *t*-test for continuous variables, and using a Chi−square test for categorical variables (p>0.05), except for the FN dose. ASA-PS, American Society of Anesthesiologists physical status; FN, fentanyl; SD, standard deviation

are shown in Table 1. The baseline characteristics were not significantly different (P>0.05) between the two groups before the first FN dose during the perioperative period.

There was no significant difference in the primary outcome, which was the number of NSAID doses required between the two groups (Table 2).

There were also no significant differences in the secondary outcomes between the two groups. For Groups A and F, respectively, the median NRS 1 was 4 vs. 3 (P=0.536), NRS 2 was 5 vs. 2 (P=0.257), and NRS 3 was 2 vs. 1 (P=0.221; Table 3). Patient satisfaction scores were 8 vs. 9, respectively (P=0.20), also showing no sig-nificant difference (Table 4). There were no sig-nificant differences in the side effects of anesth-esia (nausea/vomiting and shivering; Table 5).

Discussion

TAPP is used during inguinal hernia repair, and this technique is being used with increased frequency. The main pain pattern after TAPP is deep celiac pain, which peaks on the first postoperative day[2]. There is no evidence that acute postoperative pain becomes chronic pain, but the presence of pain reduces patients' quality of life, delays hospital discharge, and causes cardiovascular dysfunction. Therefore, reducing pain is important.

Currently, the main postoperative analgesic technique is multimodal analgesia involving a combination of two or more drugs. This improves the analgesic effect and decreases side effects[4]. In particular, the dose of opioids is often reduced or discontinued because these drugs cause nausea, vomiting, excessive sedation, and suppression of breathing and digestion. According to established guidelines for postoperative nausea and vomiting (P-ONV)[6], postoperative opioid use is an independent risk factor for PONV[7], and the guidelines thus advise reducing the opioid dose.

APAP is an analgesic agent that should be

Table 2 Numerical rating scale scores

	Group A (n=17)	Group F (n=20)	P value
NRS 1	4[0.5−5]	3[0−5]	0.536
NRS 2	5[2.5−5]	2[1−5]	0.257
NRS 3	2[1−3]	1[1−2]	0.221

NRS 1, numerical rating scale score upon entering the recovery room; NRS 2, numerical rating scale score 30 minutes postoperatively; NRS 3, numerical rating scale score the morning after surgery. Patients received intravenous acetaminophen injections during and after surgery (Group A) or continuous FN infusion beginning before the end surgery (Group F).
Data are expressed as the median [interquartile range]. P refers to Mann-Whitney U test

Table 3 Dose frequency of rescue drugs after surgery

Number of rescue drugs	Group A (n=17)	Group F (n=20)	P value
0	6	9	0.943
1	7	8	
2	2	3	
3	1	0	

Patients received intravenous acetaminophen injections during and after surgery (Group A) or continuous FN infusion beginning before the end surgery (Group F).
P refers to Fisher's exact test

Table 4 Patient satisfaction

	Group A (n=17)	Group F (n=20)	P value
Patient satisfaction	8[5−10]	9[7−10]	0.195

Patients received intravenous acetaminophen injections during and after surgery (Group A) or continuous FN infusion beginning before the end surgery (Group F).
Data are expressed as the median [interquartile range]. P refers to Mann-Whitney U test

Table 5 Postoperative nausea/vomiting and shivering until leaving the PACU or until the next morning

		Group A (n=17)	Group F (n=20)	P value
Nausea	PACU	2	1	0.584
	until the next morning	3	4	1
Vomiting	PACU	0	0	1
	until the next morning	0	2	0.489
Shivering	PACU	0	0	1
	until the next morning	0	0	1

Patients received intravenous acetaminophen injections during and after surgery (Group A) or continuous FN infusion beginning before the end surgery (Group F).
PACU, postanesthesia care unit
P refers to Fisher's exact test

used in the perioperative period because its analgesic duration is comparatively long and its administration frequency of three to four times per a day ensures its effect (around-the-clock regimen). In one study, paracetamol, the prodrug of APAP, showed a pain-reducing effect for > 4 hours and allowed for a reduced FN dose[8]. Moreover, APAP can reportedly reduce the frequency or degree of PONV[9] or shivering[10], making it a useful analgesic agent in the perioperative period.

In this study, we compared continuous infusion of FN with intermittent APAP injections after TAPP. We found no significant differences in postoperative pain control or side effects between the two groups. We showed that APAP administration at regular time intervals is not inferior to continuous FN infusion. However, we were unable to clarify the effect of APAP on reducing PONV or shivering. We believe that this was because of a lack of statistical power. Although we met the requirement of at least 15 patients, as determined by a power analysis, we were unable to analyze the NRS score for pain as a continuous variable, resulting in potential inaccuracy. It also may have been because the patients' pain was mild, which prevented us from observing the full ability of the analgesics. Moreover, the FN bolus administered in each group to raise the blood FN concentration might have produced misleading results, leading to the lack of differences in side effects. Another limitation of this study was the inability for study staff to be blinded to the drug that was administered. Additional studies are required to clarify these issues.

Conclusion

Intravenous injection of APAP every 6 hours is not different from a continuous infusion of FN for analgesia after laparoscopic inguinal hernia repair using TAPP. There was also no difference in the postoperative requirement for rescue analgesics, pain, PONV, and adverse events such as shivering.

Conflict of Interest (COI)

No potential COIs to disclose.

Acknowledgements

We thank the Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

References

1) Chung RS, Rowland DY : Meta-analyses of randomized controlled trials of laparoscopic vs conventional inguinal hernia repairs. Surg Endosc 1999 ; 13 : 689－94
2) Tolver MA, Rosenberg J, Bisgaard T : Early pain after laparoscopic inguinal hernia repair. A qualitative systematic review. Acta Anaesthesiol Scand 2012 ; 56 : 549－57
3) Lachiewicz PF : The Role of Intravenous Acetaminophen in Multimodal Pain Protocols for Perioperative Orthopedic Patients. Orthopedics 2013 ; 36 : 15－ 9
4) Apfelbaum JL, Ashburn MA, Connis RT, et al : Practice guidelines for acute pain management in the perioperative setting : an updated report by the American Society of Anesthesiologists Task Force on Acute Pain management. Anesthesiology 2012 ; 116 : 248－73
5) Kanda Y : Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013 ; 48 : 452－ 8
6) Gan TJ, Diemunsch P, Habib AS, et al : Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014 ; 118 : 85－113
7) Takeda T, Shirakami G : Non-opioid Analgesics. J Japan Soc Clin Anesth 2014 ; 34 : 203－ 9
8) McNicol ED, Tzortzopoulou A, Cepeda MS, et al : Single-dose intravenous paracetamol or propacetamol for prevention or treatment of pos-

toperative pain : a systematic review and meta-analysis. Br J Anaesth 2011；106：764－75
9）Apfel CC, Turan A, Souza K, et al : Intravenous acetaminophen reduces postoperative nausea and vomiting : A systematic review and meta-analysis. Pain 2013；154：677－89
10）Khalili G, Sajedi P, Alinaghian A : The effect of intravenous infusion of paracetamol before anesthesia induction on the core and peripheral temperature changes and postoperative shivering in patients undergoing general anesthesia. Adv Biomed Res 2014；3：89

腹腔鏡下鼠径ヘルニア修復術の術後鎮痛において，フェンタニル持続静注と比較したアセトアミノフェン定時投与の有用性

郷　正憲[1)]　阿部　夏季[2)]　成谷　俊輝[1)]
湊　文昭[1)]　加藤　道久[1)]　郷　律子[1)]

1）徳島赤十字病院　麻酔科
2）徳島大学医学部　麻酔科

目的：経腹アプローチの腹腔鏡下鼠径ヘルニア修復術（TAPP）はよく用いられる手技である．一方で，アセトアミノフェン静注製剤は周術期の疼痛管理で重要な地位を示すようになった．我々は，フェンタニル持続静注に比較して，アセトアミノフェン静注製剤の定時投与が有用であるかどうかを調べた．方法：40人の患者が登録され，2群に分けられた．両群ともに麻酔方法は共通とし，執刀時に3μg/kgのフェンタニルが静注された．アセトアミノフェン定時投与群（A群）は，手術終了30分前に，1,000mgもしくは15mg/kgのアセトアミノフェンが投与され，その後6時間毎に投与された．フェンタニル持続静注群（F群）では手術終了30分前からフェンタニル持続静注（0.3μg/kg/h）が開始された．NSAIDsが患者の要望に応じて投与された．主要評価項目はレスキューのNSAIDs使用量とし，副次評価項目は，翌朝まで術後3回の痛みの評価スケールNumerical Rating Score（NRS1，2，3）と，患者満足度（11段階：0の不満から10の満足）と麻酔に伴う副作用とした．結果：NSAIDsの使用量に有意差無く，NRS1（中央値，A群4対F群3，P＝0.54），NRS2（5対.2，P＝0.26），NRS3（2対.1，P＝0.22），患者満足度（8対9，P＝0.20），副作用にも有意差は無かった．結語：6時間毎のアセトアミノフェン投与はTAPPの術後においてフェンタニル持続静注と有意な差を認めなかった．

キーワード：アセトアミノフェン，腹腔鏡下鼠径ヘルニア修復術，術後痛，フェンタニル

Tokushima Red Cross Hospital Medical Journal 23 : 22－28, 2018