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## GYNAECOLOGY

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# Multimodal Pain Management for Laparoscopic Adnexal Surgery: A comparative cohort study

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## ABSTRACT

**Objectives:** To determine the morphine-sparing effect of multimodal pain management for laparoscopic surgery.

**Materials and Methods:** A retrospective cohort study was carried out in 210 patients who underwent laparoscopic adnexal surgery from August 2008 to November 2013 at the Songklanagarind Hospital. The patients were divided into three groups ( $n = 70$  each) according to analgesic management. Group I received parecoxib 40 mg intravenously 2 hours preoperatively with postoperative paracetamol/NSAIDs around the clock, Group II received parecoxib 40 mg intravenously 15-30 minutes preoperatively with postoperative paracetamol/NSAIDs as needed, and Group III received only postoperative paracetamol/NSAIDs as needed. Morphine or fentanyl was used during operation and morphine was used as needed for severe postoperative pain in all cases. Patients in each group were matched by the operation in the same time period. The consumption of analgesic agents during surgery and 24 hours postoperation, pain scores, and adverse events were evaluated.

**Results:** Intraoperative morphine consumption was not different among the 3 groups. However, in the 24 hours postoperation, 40% of patients in Group I received morphine (mean 1.1 mg) compared to 68.6% in Group II (mean 6.1 mg) and 80% in Group III (mean 9.6 mg) ( $p < 0.01$ ). Group I received more postoperative paracetamol/NSAIDs than both Group II and Group III ( $p < 0.01$ ). Group I had 88.5% morphine-sparing effect compared to Group III and 82% compared to Group II. The pain scores were similar between the groups.

**Conclusions:** Preemptive parecoxib and postoperative paracetamol/NSAIDs provide a significant morphine-sparing effect in laparoscopic adnexal surgery.

**Keywords:** Laparoscopic surgery, Preemptive analgesia, Parecoxib sodium, Multimodal analgesia, Postoperative pain management

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## การจัดการความปวดแบบมัลติโมดาลสำหรับการผ่าตัดปีกมดลูกผ่านกล้องส่องช่องท้อง: การศึกษาเปรียบเทียบ

อังศุมาลิน วิรัตน์, แทมมี่ ตินธารา, ศศิกานต์ นิมมานรัชต์

### บทคัดย่อ

**วัตถุประสงค์:** เพื่อประเมินผลการลดความอี้ฟีนของการจัดการความปวดแบบมัลติโมดาลสำหรับการผ่าตัดปีกมดลูกผ่านกล้องส่องช่องท้อง

**วัสดุและวิธีการ:** การศึกษาย้อนหลังแบบแบ่งกลุ่ม (retrospective cohort) ในผู้ป่วยผ่าตัดปีกมดลูกผ่านกล้องส่องช่องท้องจำนวน 210 ราย ระหว่าง สิงหาคม พ.ศ.2551 ถึง พฤษภาคม พ.ศ.2556 ที่โรงพยาบาลสงขลานครินทร์แบ่งผู้ป่วยเป็น 3 กลุ่ม กลุ่มละ 70 ราย ตามการได้รับยาลดปวด โดยกลุ่มที่ 1 ได้รับยาพารีโคกซิบ 40 มก. ฉีดเข้าหลอดเลือดก่อนการผ่าตัด 2 ชม. และได้รับยาพาราเซตามอลหรือ NSAID หลังผ่าตัดตามเวลา กลุ่มที่ 2 ได้รับยาพารีโคกซิบ 40 มก. ก่อนการผ่าตัด 15-30 นาที และได้รับยาพาราเซตามอล หรือ NSAID หลังผ่าตัดเมื่อปวด ผลกระทบที่ 3 ไม่ได้รับยาพารีโคกซิบ แต่ได้รับยาพาราเซตามอลหรือ NSAID หลังผ่าตัดเมื่อปวด ผู้ป่วยทุกรายได้รับยาอมอีฟีนหรือยา芬芬 แบบฉีด雾化 ระหว่างการผ่าตัด และได้รับยาอมอีฟีนแบบฉีดหลังผ่าตัดเป็นครั้งคราว สำหรับรังับปวดที่รุนแรง ผู้ป่วยแต่ละรายในทุกกลุ่มจะได้รับการจับคู่ด้วยการผ่าตัดที่เหมือนกันในเวลาที่ใกล้เคียงกันมากที่สุด ประเมินปริมาณการใช้ยาลดปวดในระหว่างการผ่าตัดและหลังการผ่าตัดใน 24 ชม. รวม คะแคน ความปวด และผลข้างเคียงของยาลดปวด

**ผลการศึกษา:** ปริมาณการใช้ยาอมอีฟีนในระหว่างการผ่าตัดไม่ต่างกันในทั้ง 3 กลุ่ม ใน 24 ชม. หลังการผ่าตัด ร้อยละ 40 ของผู้ป่วยในกลุ่มที่ 1 ได้รับยาอมอีฟีนเฉลี่ย 1.1 มก. เทียบกับกลุ่มที่ 2 ต้องการร้อยละ 68.6 และได้รับยาเฉลี่ย 6.1 มก. และกลุ่มที่ 3 ต้องการร้อยละ 80 และได้รับยาเฉลี่ย 9.6 มก. อย่างมีนัยสำคัญ ( $p < 0.01$ ) ในขณะที่ผู้ป่วยในกลุ่มที่ 1 ได้รับยาพาราเซตามอล หรือยา NSAID มากกว่ากลุ่มที่ 2 และกลุ่มที่ 3 อย่างมีนัยสำคัญ ( $p < 0.01$ ) กลุ่มที่ 1 สามารถปริมาณการใช้ยาอมอีฟีนลงได้ร้อยละ 88.5 เมื่อเทียบกับกลุ่มที่ 3 และร้อยละ 82 เมื่อเทียบกับกลุ่มที่ 2 คะแคนความปวดไม่ต่างกันในทั้ง 3 กลุ่ม

**สรุป:** การบริหารยาลดปวดแบบมัลติโมดาลด้วยยาพารีโคกซิบก่อนการผ่าตัดร่วมกับการให้ยาพาราเซตามอล หรือ NSAID หลังผ่าตัดแบบตามเวลา สามารถลดปริมาณการใช้ยาอมอีฟีนสำหรับการผ่าตัดปีกมดลูกผ่านกล้องส่องช่องท้องได้อย่างมีนัยสำคัญ

**คำสำคัญ:** การผ่าตัดผ่านกล้อง, การให้ยาแก้ปวดก่อนผ่าตัด, พารีโคกซิบโซเดียม, การจัดการความปวดแบบมัลติโมดาล, การให้ยาแก้ปวดหลังผ่าตัด

## Introduction

Parecoxib sodium has been used successfully as preemptive analgesia for laparoscopic surgery. Most of the previous studies recommended administration of parecoxib sodium 40 mg 15-30 minutes before surgery<sup>(1-3)</sup>. According to pharmacodynamic properties and therapeutic trial, clinically meaningful analgesia was demonstrated within 30 minutes and the peak effect occurred within 2 hours following administration of a single dose of 40 mg parecoxib intravenously and the duration of analgesia was around 8 hours<sup>(4,5)</sup>. In Songklanagarind Hospital, there were three groups of pain management for laparoscopic adnexal surgery. In the first group, patients received 40 mg single dose parecoxib intravenously 2 hours at ward before surgery with postoperative paracetamol/NSAIDs around the clock. In the second group, patients received a single dose of 40 mg parecoxib intravenously 15-30 minutes before surgery with paracetamol/NSAIDs as needed for mild to moderate postoperative pain and the third group of patients did not receive parecoxib but received paracetamol/NSAIDs as needed for mild to moderate postoperative pain. In all cases intravenous morphine or fentanyl was used during operation and intravenous morphine 1 or 3 mg as needed every 1 or 3 hours was used for severe postoperative pain. In the first group, the operation began at the peak effect of parecoxib which was administered 2 hours before surgery. It is questionable whether giving parecoxib preoperatively at 2 hours (operation at the peak analgesic effect) or at 15–30 minutes preoperatively (operation at the time of analgesic onset) will provide a morphine-sparing effect. Thus, this study aimed to evaluate the morphine-sparing effect when parecoxib is administered preoperatively at 2 hours in comparison to 15–30 minutes preoperatively and the effectiveness of postoperative paracetamol and/or NSAIDs as multimodal pain management in laparoscopic adnexal surgery.

## Materials and Methods

### Study design

This study is a retrospective comparative cohort study in patients undergoing laparoscopic adnexal

surgery. There were 3 groups of patients. The patients in Group I was given 40 mg intravenous parecoxib at 2 hours preoperatively with postoperative paracetamol/NSAIDs around the clock while the patients in Group II was received 40 mg intravenous parecoxib at 15-30 minutes preoperatively with postoperative paracetamol/NSAIDs as needed. The patients in Group III was not received parecoxib preoperatively but was received postoperative paracetamol/NSAIDs as needed.

### Sample size

A previous study indicated that the effect size (i.e., absolute difference of morphine requirement divided by the standard deviation of the morphine requirement) of preoperative parecoxib injection at 30 minutes before surgery compared with control was around 0.5<sup>(1)</sup>. It is expected that the additional analgesic beneficial effect of preoperative parecoxib injection at 2 hours before surgical incision comparing with 15–30 minutes before operation, would also reflect an effect size of around 0.5. Therefore, the required sample size was calculated based on having a power of 80% to detect an effect size of at least 0.5 between Group I and Group II and between Group II and Group III with a type I error of 0.05. As the amount of morphine in these 3 groups was expected to be in order as Group I < Group II < Group III, the effect size to compare Group I with Group III should be > 0.5. The following equation was used to calculate the required sample size of each of the three groups.

$$n_1 = n_2 = n_3 = \frac{2(Z_{1-\frac{\alpha}{2}} + Z_{\beta})^2 \sigma^2}{\Delta^2}$$

The equation indicated that  $n_1 = n_2 = n_3 = 63$ . However, to allow for the possibility of up to 10% of missing patients or otherwise unusable data, the sample size in practice was increased to  $63/(1-0.1) = 70$  per group.

This study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University. The study group (Group I) consisted of 70 consecutive patients who received 40 mg of parecoxib 2 hours before

surgery with postoperative paracetamol/NSAIDs around the clock from August 2008 to November 2013. The two comparative groups were 70 patients receiving 40 mg of parecoxib 15–30 minutes before surgery with postoperative paracetamol/NSAIDs as needed for mild to moderate postoperative pain (Group II) and 70 patients who did not receive parecoxib but received postoperative paracetamol/NSAIDs as needed for mild to moderate postoperative pain (Group III). Each case in all groups was matched by the same operation during the same time period. All patients had laparoscopic adnexal surgery under general anesthesia with endotracheal intubation. The standard laparoscopic surgical techniques were similar in all cases using 3 instrument ports (5–10 mm) at the umbilicus and lower abdomen. The insufflation pressure was less than 15 mmHg and only bipolar forceps and scissors were used in all cases. The standard anesthetic technique was used in all cases with the same anesthetic agents and opioids (fentanyl or morphine) for analgesia and the opioid consumption was expressed as morphine equivalent (mg). During the first 24 hours postoperation, the pain scores were routinely evaluated by the attending nurse during the first 2 hours and then every 4 hours using a verbal numeric rating score (VNRS) ranging from 0 to 10 where 0 = no pain and 10 = worst pain imaginable and were not assessed if the patients were sleeping. All patients were allowed to drink water and take oral analgesic drugs when they had full postoperative awakening. Postoperative pain control in the recovery room consisted of morphine or fentanyl. Pain control at the ward for Group I consisted of paracetamol 1 g per oral every 4 hours except when sleep and/or celecoxib 400 mg once daily that started at 12 hours after parecoxib with intravenous morphine injection 1 mg as needed every 1 hours if the patients had a pain score of 4 or more. For Group II and III, postoperative pain control at ward consisted of oral paracetamol 1 g or ibuprofen 400 mg as needed every 4 hours if the pain score was less than 4. If the pain score was 4 or more, intravenous morphine injection 3 mg as needed every 3 hours was provided. The consumption of analgesic agents during surgery and

24 hours postoperation, pain scores, and adverse events were evaluated. All data were collected from medical and anesthetic records.

### **Statistical analysis**

All data were analyzed using commercially available software (SPSS version 15.0; SPSS, Inc., Chicago, IL). Continuous variables were presented as mean $\pm$ SD, median (interquartile range), and categorical variables as number (%). One-way analysis of variance (ANOVA) and Kruskal-wallis test were used for continuous variables. When significant differences were determined in Kruskal-wallis test, median test was performed using for intergroup comparison. The Chi-square test and Fisher's exact test was used to analyze categorical data. Differences between categorical data of each group were evaluated using the Chi-square test if there was evidence of overall differences among the 3 groups. All outcomes were considered significant only if the p-value was  $< 0.05$ .

## **Results**

There were 54 ovarian cystectomies, 15 salpingo-oophorectomies and 1 salpingectomy in each group. The patient characteristics in all groups including age, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, definite diagnosis, operative times, and estimated blood loss were not significantly different with operative times of around 2 hours (Table 1). Morphine administration during the operation and analgesic requirements during the 24 hours postoperation are shown in Table 2. The intraoperative morphine requirements were not significantly different in all groups. The proportion of patients who needed morphine and the morphine requirements in 24 hours postoperation was significantly less in Group I (mean = 1.1 mg) than Group II (mean = 6.1 mg) and Group III (mean = 9.6 mg) ( $p < 0.01$ ). However, paracetamol and NSAIDs were utilized more in Group I than Group II and III ( $p < 0.01$ ) because paracetamol and/or NSAIDs were prescribed on a regular basis in Group I patients. There were no severe adverse effects in

the 3 groups. The pain scores during the first 24 hours postoperation were not significantly different between groups (Fig. 1). When the morphine-sparing effect was considered, Group I provided 88.5% morphine-sparing compared to Group III and 82% compared to Group II, while Group II provided 36.5% morphine-sparing compared to Group III.

Adverse effects were infrequent in all 3 groups.

The numbers (%) of patients who experienced adverse effects in Group I, Group II, and Group III were 10 (14.3), 23 (33.3), and 16 (22.9), respectively ( $p=0.513$ ). Nausea and vomiting were the most common adverse effects found in 5 cases in Group I, 13 cases in Group II, and 16 cases in Group III. Gastritis was found in 5 cases in Group I and in 8 cases in Group II. Urinary retention was found only in 2 cases in Group II.

**Table 1.** Patient characteristics and surgical data.

Variables	Group I (n = 70)	Group II (n = 70)	Group III (n = 70)	P
Age (years)	33.7±7.6	35.1±6.4	36.5±12.1	0.672*
BMI (kg/m <sup>2</sup> )	21.4±2.7	22.1±3.2	21.9±3.2	0.322*
ASA class				0.099**
I	20 (28.6)	33 (45.7)	24 (34.3)	
II	50 (71.4)	37 (52.9)	46 (65.7)	
Diagnosis				0.984**
Ovarian cyst	65 (92.9)	64 (91.4)	66 (94.3)	
Paratubal cyst	4 (5.7)	5 (7.1)	3 (4.3)	
Hydrosalpinx	1 (1.4)	1 (1.4)	1 (1.4)	
Operative time (min)	114.1±27.6	126.0±30.6	122.4±34.9	0.071*
EBL (mL)	41.1±45.0	47.3±66.9	39.4±48.1	0.681*

Data presented as mean±SD or number (%)

BMI = body mass index, ASA = American Society of Anesthesiologists, EBL = estimated blood loss

\*ANOVA, \*\*Chi-square test, \*\*\*Fisher's exact test

**Table 2.** Analgesic requirements and morphine consumption.

Analgesic agents	Group I (n = 70)	Group II (n = 70)	Group III (n = 70)	P
Intraoperative				
Morphine equivalent (mg)	70 (100) 10 (8, 14)	70 (100) 10 (10, 14)	70 (100) 11.5 (8, 13)	0.321*
Postoperative 24 hours				
Morphine (mg)	28 (40) 0 (0, 1)	48 (68.6) 3 (0, 9)	56 (80) 9 (3, 5)	< 0.01** < 0.01*
Paracetamol (g)	68 (97.1) 3 (2, 4)	40 (57.1) 1 (0, 2)	35 (50) 0.5 (0, 1.2)	< 0.01** < 0.01*
Celecoxib (mg)	64 (91.4) 400 (400, 800)	7 (10) 0 (0, 0)	9 (12.9) 0 (0, 0)	< 0.01** < 0.01*

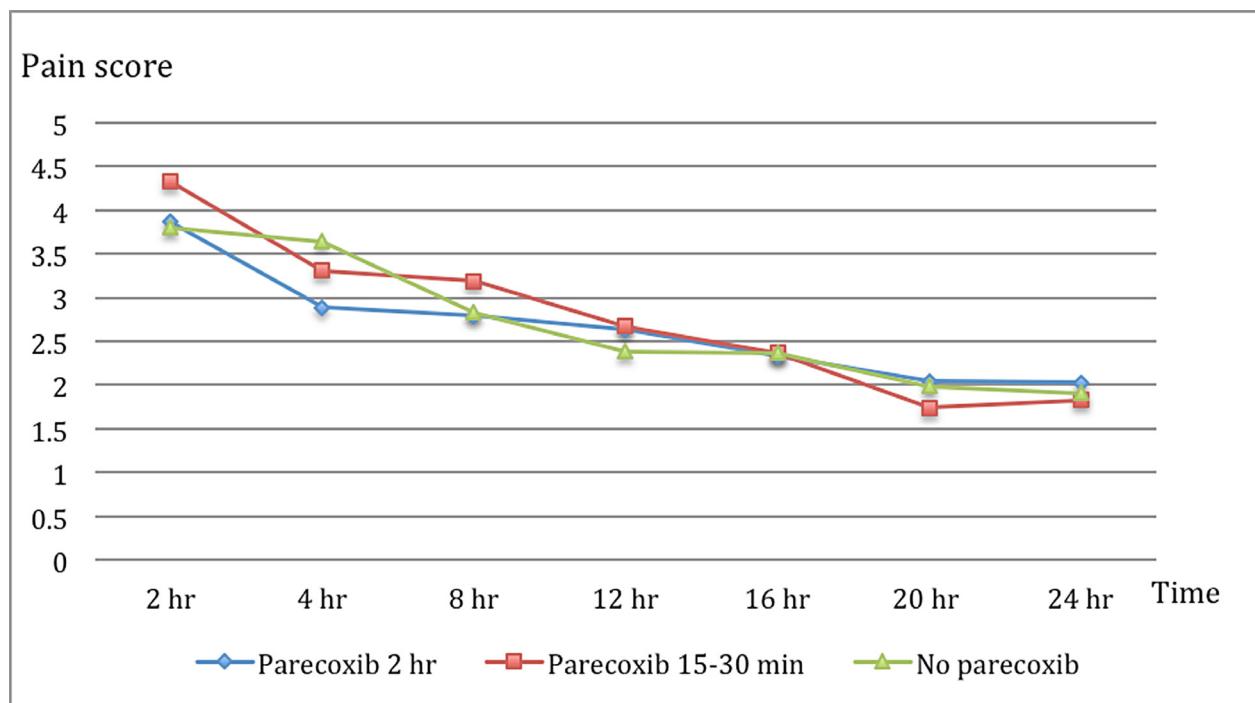
**Table 2.** Analgesic requirements and morphine consumption. (Cont.)

Analgesic agents	Group I (n = 70)	Group II (n = 70)	Group III (n = 70)	P
Ibuprofen (mg)	1 (1.4)	22 (31.4)	25 (35.7)	< 0.01**
	0 (0, 0)	0 (0, 400)	0 (0, 400)	< 0.01*

Data presented as number (%) or median (interquartile range)

\* ANOVA and Kruskal-wallis test

\*\* Chi-square test

**Fig. 1.** Postoperative pain scores for 24 hours using a verbal numeric rating score.

## Discussion

This study demonstrates that the administration of 40 mg parecoxib at either 2 hours or 15–30 minutes prior to surgery does not reduce the doses of morphine utilized during an operation. However, the patients in Group I who received parecoxib preoperatively and regular paracetamol and/or NSAIDs in the postoperative period had significantly fewer morphine requirements in comparison to the patients of Group II and III who received paracetamol and/or NSAIDs as needed in the postoperative period. Although adverse effects of

analgesia were not significantly different among these groups, 16 cases in Group III experienced the side effects of nausea and vomiting.

The present study found that the patients in all groups received nearly equal amounts of morphine during the operations whether they received parecoxib or not. This could be because morphine administration during an operation does not depend only on pain. There are many other factors such as 1) initial induction dose of anesthesia which depends on the body weight of the patient, 2) additional doses of morphine for

continual pain control (top up doses) at an interval of 45–90 minutes, and 3) vital signs during the operation if the patient has tachycardia and/or hypertension and when other causes are ruled out, morphine is likely to be given to reduce sympathetic response to noxious stimuli<sup>(6)</sup>.

Pandazi et al demonstrated that giving 40 mg parecoxib intravenously 30 minutes before skin incision can reduce postoperative morphine consumption by 38.6% compared to 30 minutes after incision<sup>(7)</sup>. This finding suggested that giving 40 mg parecoxib intravenously 30 minutes before operation is enough time to allow clinically meaningful analgesia before nociceptive stimulus<sup>(4,5)</sup>. Giving parecoxib after nociceptive stimulus, even 2 hours before completion of an operation, also can not reduce postoperative morphine consumption<sup>(7)</sup>. The best time to administer 40 mg parecoxib as preemptive analgesia should be around 30 minutes before surgery. If preoperative parecoxib is administered too early, it can not provide an additional morphine-sparing effect and it can decrease the duration of postoperative analgesia.

Ratchanon et al reported that parecoxib 40 mg given intravenously 30 minutes before an operation without regular postoperative analgesia in gynecologic laparoscopic surgery cases can provide a 32.7% morphine-sparing effect<sup>(1)</sup>. However, Bunyavejchevin et al found that giving multimodal analgesia in patients undergoing diagnostic laparoscopy with 40 mg parecoxib 15 minutes before surgery plus postoperative local anesthesia at the surgical wound and regular paracetamol can provide a 62.6% morphine-sparing effect<sup>(2)</sup>. Compared to the present study, patients in Group I and Group II received preemptive parecoxib with enough time for clinically meaningful pain relief, but the patients in Group I who received regular postoperative oral analgesia required significantly less postoperative morphine consumption. This finding suggests that regular oral analgesic as multimodal analgesia can add a morphine-sparing effect to preemptive parecoxib administration and should be encouraged<sup>(8)</sup>.

Although the adverse effects are infrequent,

nausea and vomiting were still the most common opioid side effects<sup>(9)</sup> as found in the present study. These adverse effects can be minimized by using analgesic agents with a high morphine-sparing effect with a multimodal technique<sup>(8)</sup>.

Preemptive analgesia should be used as a part of multimodal pain management<sup>(10)</sup>. The present study showed that preemptive analgesia alone cannot maximize postoperative analgesia. Multimodal pain management in postoperative period should be used together with preemptive pain management, which is so called preventive analgesia<sup>(8)</sup>.

Pain after operative laparoscopy consisted of local pain associated with incision for the operative ports, lower abdominal pain that depended on the extent of intraperitoneal manipulation, upper abdominal pain including shoulder tip and postural high back pain that likely were caused by residual intraperitoneal carbon dioxide gas<sup>(11)</sup>. Hohlrieder et al found that 70% of patients experienced the worst postoperative pain after gynecologic laparoscopic surgery in the first 24 hours<sup>(12)</sup>. Therefore, this present study focused only on postoperative pain in 24 hours.

The present study was a retrospective study that did not randomize the patients and the study conditions in all cases could not be controlled, but it showed the potential benefit of multimodal pain management in laparoscopic adnexal surgery. A randomized control study should be conducted to evaluate the real benefit of this strategy especially in laparoscopic gynecologic surgery.

## Conclusions

Parecoxib administered at 2 hours preoperatively can not reduce intraoperative morphine consumption. However, parecoxib administration in conjunction with postoperative regular non-opioid multimodal analgesic administration leads to less morphine consumption in the first 24 hours postoperation in patients undergoing laparoscopic adnexal surgery.

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## Potential conflicts of interest

The authors declare no conflict of interest.

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