

การศึกษาเปรียบเทียบผลของยาผสม ترامาดอล/อะเซตามิโนเฟน
และยาไอบูโพรเฟนในการลดความเจ็บปวดเฉียบพลัน
หลังจากการผ่าตัดฟันกรามล่างซี่ที่สามคุด
Comparative study of efficacy of tramadol/acetaminophen
combination tablet and ibuprofen in acute pain control
after impacted mandibular third molar surgery

รพีพร มั่งไผศพรณ์¹ กาญจนา สิงขรโทย¹ ภณทิรา สุวรรณวลัยกร² ธนชชา สุกาญจนพงษ์²
ธนนันท์ จันทโรหิต² ภูษนิศา วิบูลย์วุฒิวงศ์² พิมพ์ไท อุมะวรรณ² พรเทพ พานทอง²
Rapeeporn Malungpaishrope¹ Kanjana Singkharotai¹ Pantira Suwanwalaikorn² Thanatcha Sukanjanapong²
Tananan Chandharohit² Phusanisa Viboonwuthiwong² Pimtai Umawan² Phornthep Phanthong²

¹อาจารย์ ²นักศึกษาทันตแพทย์ คณะทันตแพทยศาสตร์ มหาวิทยาลัยรังสิต
52/347 ต.หลักหก อ.เมือง จ.ปทุมธานี 12000

¹Lecturer, ²Dental student, Faculty of Dental Medicine, Rangsit University
52/347 Lakhok, Mueang Pathum Thani District, Pathum Thani 12000 Thailand

บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบฤทธิ์ระงับปวดของยาผสม ترامาดอล 37.5 มก./อะเซตามิโนเฟน 325 มก. (Tr/Ac) และไอบูโพรเฟน 400 มก. (Ibu) ในการควบคุมความเจ็บปวดเฉียบพลันหลังผ่าตัดฟันกรามล่างซี่ที่สามคุด ทำการศึกษาแบบปิดบังสองทาง สุ่มตัวอย่างแบบบล็อกในอาสาสมัครอายุระหว่าง 18-40 ปี ซึ่งได้รับการผ่าตัดฟันกรามล่างซี่ที่สามคุดที่จำเป็นต้องกรอกระดูกและแบ่งฟัน อาสาสมัครที่มีความเจ็บปวดหลังผ่าตัดในระดับปานกลางหรือมาก จะถูกแบ่งเป็น 2 กลุ่มจำนวนเท่ากัน โดยได้รับยา Tr/Ac หรือ Ibu จากนั้นอาสาสมัครจะต้องประเมินความเจ็บปวดโดยใช้การบอกความรู้สึกเป็นตัวเลขด้วยเลข 0-10 และประเมินระดับการบรรเทาอาการปวดโดยใช้ตัวเลข 5 ระดับ โดยประเมินทุกชั่วโมงจนครบ 6 ชั่วโมง จากนั้นทำการคำนวณผลรวมระดับการบรรเทาความเจ็บปวดเมื่อครบ 6 ชั่วโมง

Corresponding author: รพีพร มั่งไผศพรณ์

คณะทันตแพทยศาสตร์ มหาวิทยาลัยรังสิต 52/347 ต.หลักหก อ.เมือง จ.ปทุมธานี 12000

โทร. 08-9890-3812

E-mail address: kwang055@yahoo.com

(TOTPAR6) และผลรวมระดับความเจ็บปวดที่เปลี่ยนแปลงเมื่อครบ 6 ชั่วโมง (SPID6) เมื่อสิ้นสุดการศึกษา อาสาสมัครจะประเมินความพึงพอใจโดยใช้ตัวเลข 5 ระดับ ผลการศึกษาพบว่า จากอาสาสมัครกลุ่มละ 33 คน ค่า TOTPAR6 ของกลุ่ม Tr/Ac (11.61 ± 4.61) และกลุ่ม Ibu (13.18 ± 4.60) ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (Wilcoxon rank sum test, $p > 0.05$) ค่า SPID6 ของกลุ่ม Tr/Ac (19.76 ± 11.43) และกลุ่ม Ibu (20.27 ± 10.37) ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (Wilcoxon rank sum test, $p > 0.05$) อาสาสมัครในกลุ่ม Ibu ไม่ได้มีความพึงพอใจมากกว่ากลุ่ม Tr/Ac อย่างมีนัยสำคัญทางสถิติ (chi-square, $p > 0.05$) อาจสรุปได้ว่ายาผสม ترامาดอล 37.5 มก./อะเซตามิโนเฟน 325 มก. มีฤทธิ์ระงับปวดเฉียบพลันหลังการผ่าตัดฟันคุดได้เทียบเท่ากับยาไอบูโพรเฟน 400 มก.

คำสำคัญ: การลดความเจ็บปวดเฉียบพลัน ยาไอบูโพรเฟน ยาผสม ترامาดอล/อะเซตามิโนเฟน การผ่าฟันกรามคุดล่างซี่ที่สาม

Abstract

The objective of the study is to compare the analgesic efficacy between tramadol 37.5 mg/acetaminophen 325 mg combination tablet (Tr/Ac) and ibuprofen 400 mg (Ibu) in acute pain control after surgical removal of mandibular third molar. A double-blinded, block randomized controlled study was performed in subjects aged between 18-40 years who had surgical removal of impacted mandibular third molar with overlying bone removal and tooth sectioning. Sixty-six subjects who sustained moderate to severe pain after surgery were randomized equally into two groups to receive either Tr/Ac or Ibu. The pain intensity using numeric pain rating scale of 0-10 and the pain relief using 5-point scale were recorded hourly after drug intake for the period of 6 hours. The total pain relief of 6 hours (TOTPAR6) and the sum of pain intensity difference of 6 hours (SPID6) were calculated. At the end of the study, overall satisfaction was recorded as a global assessment score on 5-point scale. For the results, the collected data from 33 subjects of each group were analyzed. TOTPAR6 of Tr/Ac (11.61 ± 4.61) and Ibu (13.18 ± 4.60) were not statistically significantly different (Wilcoxon rank sum test, $p > 0.05$). Likewise, SPID6 of Tr/Ac (19.76 ± 11.43) and Ibu (20.27 ± 10.37) were not statistically significantly different (Wilcoxon rank sum test, $p > 0.05$). Satisfaction was not significantly greater in Ibu group than Tr/Ac group (chi-square, $p > 0.05$). For conclusion, the analgesic efficacy of tramadol 37.5 mg/acetaminophen 325 mg in acute pain control after mandibular third molar surgery was comparable to those of ibuprofen 400 mg.

Keywords: acute pain control, ibuprofen, tramadol/acetaminophen combination tablet, mandibular third molar surgery

modol 37.5 mg/acetaminophen 325 mg combination tablet (Tr/Ac, Ultracet; Janssen Pharmaceuticals, South Korea) or ibuprofen 400 mg (Ibu, Coprofen: Community Pharm PCL, Thailand) was unpacked and prescribed after the surgery. If the response of study drug was inadequate, supplementary medication in the form of acetaminophen 500 mg was available.

Assessment

The primary efficacy variables were the total pain relief of 6 hours (TOTPAR6), the sum of pain intensity differences of 6 hours (SPID6) and the global assessment. TOTPAR, SPID in the period of 2 hours and the need of supplement medication were also analyzed as a secondary efficacy variable. The incidence of adverse effect was reported for a safety profile analysis.

When pain was initiated, pain intensity was recorded on a numeric pain rating scale of 0-10 (0 = none, 1-3 = mild, 4-6 = moderate, 7-10 = severe) and prescribed dose was taken. This score was defined as a baseline pain. Subjects with "moderate" to "severe" pain were included in the study while subjects with none or mild pain were excluded. Then, the pain intensity was recorded hourly for the period of 6 hours after drug administration.

One hour after drug administration, pain relief was recorded on 5-point scale rated from 0-4 (0 = none, 1 = a little relief, 2 = some relief, 3 = a lot of relief, 4 = complete relief). The pain relief score was then recorded hourly for the period of 6 hours as well.

At the end of the study, subjects were asked to assess their overall satisfaction. The positive and the negative drug effect were compared and recorded as a global assessment score on 5-point scale (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent). If the subjects were experiencing the adverse drug reactions, the effects were reported in listed checkboxes.

When subject took a supplementary medication, the time was recorded. The pain relief was set to no relief and the pain intensity was set to pain intensity immediately prior to supplementary medication.

Statistical analysis

The study was designed to include 66 subjects who were qualified according to the criteria. After data collection, statistical analysis was done using IBM SPSS Software Version 24.

The TOTPAR6 and SPID6 were calculated as indices of drug efficacy.

TOTPAR is the sum of pain relief score, time weighted for time since last measurement.⁽¹¹⁾ It was calculated as follows:

$$\begin{aligned} \text{PAR}_t &= \text{pain relief score at time } t \\ \text{TOTPAR} &= \sum \text{PAR}_t \times \text{time (hour) elapsed since} \\ &\quad \text{previous observation} \end{aligned}$$

SPID is the sum of pain intensity differences (PID) during a defined study period, time weighted by multiplying with the time since last measurement.⁽¹¹⁾ It was calculated as follows:

$$\begin{aligned} \text{Pain intensity difference (PID)}_t &= \text{PI at baseline} - \text{PI at time } t \\ \text{SPID} &= \sum \text{PAR}_t \times \text{time (hour) elapsed since} \\ &\quad \text{previous observation} \end{aligned}$$

To compare the differences between two groups, TOTPAR6 and SPID6 of Tr/AC and Ibu were tested for statistical significance using Wilcoxon rank sum test. Global assessment was analyzed using the chi-square test. Furthermore, mean TOTPAR and SPID scores were calculated in the intervals from 0-2 hours, 2-4 hours, and 4-6 hours. The level of confidence was accepted at 95% ($p < 0.05$). For the safety profile, the incidences of adverse effects were also analyzed using the chi-

square test.

Results

A total of 66 subjects were enrolled and completed the study, 33 subjects were randomly prescribed with Tr/Ac while Ibu was given to the other 33 subjects. Most of the subjects in both groups were female (72.7% in Tr/Ac and 66.7% in Ibu group).

The ages in both groups ranged from 18-40 years old, and average ages in Tr/Ac group and Ibu group were 23.36 ± 4.49 and 23.97 ± 4.31 years old respectively. Both groups were similar in demographic characteristics. All of the enrolled subjects reported moderate or severe pain with the mean baseline pain scores were 6.85 ± 1.46 in the Tr/Ac group and 6.55 ± 1.73 in the Ibu group (Table 1).

Efficacy evaluation

After the 6-hour observation period, the means of TOTPAR6 were 11.61 ± 4.61 and 13.18 ± 4.60 in the Tr/Ac group and the Ibu group respectively. The mean of TOTPAR6 showed higher value in Ibu group but the differences between two study groups were not statistically significant ($p > 0.05$). Also, the means of TOTPAR at the 2-hour interval of 0-2 hours, 2-4 hours, and 4-6 hours in Ibu group were greater than Tr/Ac group but the differences were not statistically significant ($p > 0.05$) (Table 2).

The means of the SPID6 were 19.76 ± 11.43 in Tr/Ac group and 20.27 ± 10.37 in Ibu group. The difference between two groups was not statistically significant ($p > 0.05$). In addition, the means of SPID at the 2-hour interval of 0-2 hours, 2-4 hours, and 4-6 hours were similar in both groups. No statistically significant difference was shown in these variables (Table 3).

At the end of the study, none of subjects used the supplementary drug within of 6-hour observation

ตารางที่ 1 ข้อมูลทั่วไปของอาสาสมัคร และระดับความเจ็บปวดเริ่มต้น

Table 1 Demographic characteristics and baseline pain intensity

Characteristics		Tr/Ac (n = 33)	Ibu (n = 33)
Sex, number	Female (%)	24 (72.7)	22 (66.7)
	Male (%)	9 (27.3)	11 (33.3)
Age, years	Mean	23.36 ± 4.49	23.97 ± 4.31
	Range	18-40	18-40
Duration of surgical procedure, minutes	Mean	33.55 ± 16.15	35.73 ± 23.62
	Range	13-90	12-120
Difficulty index	Mean	5.06 ± 0.78	5.00 ± 1.73
	Range	4-7	3-8
Baseline pain intensity	4	1	4
	5	6	6
	6	7	9
	7	7	3
	8	8	5
	9	3	5
	10	1	1
	Mean	6.85 ± 1.46	6.55 ± 1.73

Ibu = ibuprofen 400 mg, Tr/Ac = tramadol 37.5 mg/acetaminophen 325 mg.

ตารางที่ 2 ผลรวมระดับการบรรเทาความเจ็บปวดทุก 2 ชั่วโมงและผลรวมระดับการบรรเทาความเจ็บปวดเมื่อครบ 6 ชั่วโมงหลังการรับประทานยา

Table 2 The total pain relief (TOTPAR) at 2-hour interval and the total pain relief of 6 hours (TOTPAR6) after drug administration.

TOTPAR	Tr/Ac (n = 33)	Ibu (n = 33)	p value
0-2 hours	3.45 ± 1.87	4.03 ± 1.89	0.198
2-4 hours	3.85 ± 1.82	4.61 ± 1.87	0.097
4-6 hours	4.30 ± 1.89	4.55 ± 2.03	0.529
6 hours	11.61 ± 4.61	13.18 ± 4.60	0.111

Ibu = ibuprofen 400 mg, Tr/Ac = tramadol 37.5 mg/acetaminophen 325 mg.

period. In each group, 29 (87.9%) of subjects rated their overall global assessment for their assigned medication as good or better. While 4 (12.1%) of sub-

ตารางที่ 3 ผลรวมระดับความเจ็บปวดที่เปลี่ยนแปลงทุก 2 ชั่วโมง และผลรวมระดับความเจ็บปวดที่เปลี่ยนแปลงเมื่อครบ 6 ชั่วโมง หลังการรับประทานยา

Table 3 Sum of pain intensity difference (SPID) at 2-hour interval and the sum of pain intensity difference of 6 hours (SPID6) after drug administration.

SPID	Tr/Ac (n = 33)	Ibu (n = 33)	p value
0-2 hours	5.55 ± 4.35	5.64 ± 3.54	0.832
2-4 hours	6.64 ± 3.67	7.12 ± 4.02	0.767
4-6 hours	7.58 ± 4.32	7.52 ± 4.46	0.908
6 hours	19.76 ± 11.43	20.27 ± 10.37	0.773

Ibu = ibuprofen 400 mg, Tr/Ac = tramadol 37.5 mg/acetaminophen 325 mg.

jects in each group rated fair. None of the subjects rated poor in an overall global assessment. There was a greater number of subjects who rated very good or excellence in Ibu group, but the difference was not statistically significant ($p > 0.05$) (Table 4).

Safety evaluation

All enrolled subjects were included in the safety analysis. There were 12 (36.4%) of the subjects in Tr/Ac group and 7 (21.2%) of the subjects in Ibu group who encountered at least one adverse effect. This difference was not statistically significant ($p > 0.05$). Some subjects reported more than one event of adverse effect. Affected subjects in Tr/Ac group reported 22 events, while affected subjects in Ibu group reported 9 events of adverse effect. The overall reported events of adverse effect in Tr/Ac group was significantly higher than Ibu group ($p < 0.05$). Drowsiness was the most frequently occurred adverse effect experienced in both groups. There were 8 (24.2%) of 33 subjects in Tr/Ac group and 5 (15.2%) of 33 subjects in Ibu group who suffered from drowsiness. Dizziness was experienced in 5 of the subjects in Tr/Ac group but not experienced

ตารางที่ 4 การประเมินความพึงพอใจของอาสาสมัครภายหลังจากที่ได้รับยา Tr/Ac หรือ Ibu

Table 4 The overall satisfaction of the subjects after administration studied medication of either Tr/Ac or Ibu

Overall satisfaction	Tr/Ac (33 subjects)		Ibu (33 subjects)	
	Subjects	%	Subjects	%
Poor	0	0	0	0
Fair	4	12.1	4	12.1
Good	16	48.5	12	36.4
Very good	12	36.4	15	45.5
Excellent	1	3.0	2	6.1

Ibu = ibuprofen 400 mg, Tr/Ac = tramadol 37.5 mg/acetaminophen 325 mg.

in Ibu group. Thus, there was a statistically significant difference in the incidence of dizziness between the two groups ($p < 0.05$). In this study, no serious adverse event was reported in both of the study groups (Table 5).

Discussion

Some studies have shown analgesic efficacy of tramadol 75 mg/acetaminophen 650 mg in oral surgery.⁽¹²⁻¹⁴⁾ In many clinical situations, a lower dosage was preferred to decrease the adverse effects. Thus, analgesic efficacy study of tramadol/acetaminophen in lower dose was conducted. In this randomized, double-blind, parallel group study was designed to evaluate the analgesic efficacy of a single dose of tramadol 37.5 mg/acetaminophen 325 mg compared with 400 mg ibuprofen after mandibular third molar surgery.

Although pain after oral surgery can persist for several days, the peak pain intensity is within a day after surgery⁽¹⁵⁾. Assessment period in this study is 6 hours after drug administration due to the recommended interval dosing of both drugs^(16,17) and we think that a longer period of study is likely to get poor com-

ตารางที่ 5 อาการไม่พึงประสงค์ที่เกิดขึ้น ซึ่งน่าจะเกิดจากการใช้ยา

Table 5 Adverse effects considered probably related to study drug

Adverse effects	Tr/Ac (33 subjects)		Ibu (33 Subjects)		p value
	Events	%	Events	%	
Dizziness	5/33	15.2	0/33	0	0.020*
Nausea/vomiting	4/33	12.1	1/33	3.0	0.163
Drowsiness	8/33	24.2	5/33	15.2	0.353
Headache	3/33	9.1	1/33	3.0	0.302
Tremor	1/33	3.0	0/33	0	0.314
Stomachache	1/33	3.0	0/33	0	0.314
Constipation	0/33	0	2/33	6.1	0.151
Total number of events	22	-	9	-	0.001*
Total number of subjects	12/33	36.4	7/33	21.2	0.174

Ibu = ibuprofen 400 mg, Tr/Ac = tramadol 37.5 mg/acetaminophen 325 mg.

* $p < 0.05$, chi-square test.

pliance in the data collection.

There are several tools used for pain assessment in postoperative analgesic clinical study, such as pain intensity and pain relief. To reduce the number of variables analyzed in analgesic trial, summarization of pain intensity or pain relief for relevant period of time were calculated.⁽¹¹⁾ For the purpose of reducing the confounding factors such as many surgeons, baseline pain intensity or level of difficulty index of procedure in this study, therefore, SPID and TOTPAR were analyzed. Even though, in this study showed that Ibu group achieved higher value in most variables, no statistically significant difference was shown in our primary outcome variables. The results of TOTPAR were consistent with SPID. Accompany with the absence of statistical difference allow us to conclude that the analgesic efficacies between both groups were similar.

The absence of need for supplementary medication is a reliable outcome measure in the evaluation of acute pain relief.⁽¹⁸⁾ In this study, supplementary medication was readily available but none of subjects needed for supplementary medication. That implied

the sufficient analgesic efficacy of the medications in mandibular third molar surgery.

In dental pain study of Fricke⁽¹⁴⁾ the frequent adverse effects of tramadol were dizziness, nausea and vomiting (32.7%, 22.2% and 18.3%, respectively). In our study, drowsiness was the most frequently adverse effect reported in both groups. This finding are consistent with the study of Lin⁽¹⁹⁾ in pain control after implantation of an intravenous access device which showed the most frequent adverse effect of tramadol/acetaminophen was drowsiness (13.8%). While the incidence of dizziness in our study was the second most frequently reported in only in Tr/Ac group and significantly greater than those in Ibu group. Many studies showed that tramadol was relatively free of serious adverse effects associated with conventional opioid. It is considered as a safe medication.^(9,10) It is an acceptable alternative even in elderly patients with chronic pain.⁽⁹⁾ In this study, there was no reported serious adverse effect associated with conventional opioids or conventional NSAIDs. We can conclude that the recommended dose of tramadol/acetaminophen

appears to be safe in short-term use.

Even though adverse effects of Tr/Ac in this study were encountered greater than previous studies.^(12,13,19) All the subjects were well tolerated with their medications. None of the subjects in both groups rated poor in global assessment score and mostly rated their condition as good or better. It implied that they were satisfied with their assigned medications.

The limitation of this study is the short-term observation period, conducted only in the population of young healthy patients. Therefore, we suggest to conduct a clinical trial of analgesic efficacy of multiple dosages of tramadol 37.5 mg/acetaminophen 325 mg in a longer period of treatment in the various age-

group of the patients in further study.

Conclusion

In this study, single dose of tramadol 37.5 mg/acetaminophen 325 mg provided sufficient analgesia in postoperative pain in oral surgery compared to ibuprofen 400 mg. In some conditions that NSAIDs are contraindicated, it may be used as an alternative medication for pain control after oral surgery. Although it was associated with many adverse effects, these adverse effects were not serious in short term use. However, it should be used with caution and patients should be informed about these adverse effects.

Reference

- Pozzi A, Gallelli L. Pain management for dentists: the role of ibuprofen. *Ann Stomatol (Roma)* 2011;2:3-24.
- Hass DA. An update on analgesics for management of acute postoperative dental pain. *J Can Dent Assoc* 2002; 68:476-82.
- Koren G, Florescu A, Costei AM, Boskovic R, Moretti ME. Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *Ann Pharmacother* 2006;40: 824-9.
- Borges MS. Clinical management of nonsteroidal anti-inflammatory drug hypersensitivity. *World Allergy Organ J* 2008;1:29-33.
- Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet* 2004;43:879-923.
- World Health Organization, ECDD. Tramadol: update review report. Geneva, World Health Organization 2014. Available from: http://www.who.int/medicines/areas/quality_safety/6_1_Update.pdf
- Jozwiak-Bebenista M, Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. *Acta Pol Pharm* 2014;71:11-23.
- Food and Drug Administration. Announcement of food and drug administration about criteria, methods and conditions of drug selling. Royal Thai Government Gazette Vol. 132 Special Issue 179D page 12 Aug. 4, 2015.
- Rauck RL, Ruoff GE, McMillen JI. Comparison of tramadol and acetaminophen with codein for long-term pain management in elderly patients. *Curr Therap Res* 1994;55: 1417-31.
- Scott LJ, Perry CM. Tramadol: a review of its use in peri-operative pain. *Drugs* 2000;60:139-76.
- Stubhaug A, Breivik H. 9 post-operative analgesic trials: some important issues. *Baillière's Clin Anesth* 1995;9: 555-84.
- Medve RA, Wang J, Karim R. Tramadol and acetaminophen tablets for dental pain. *Anesth Prog* 2001;48:79-81.
- Jung YS, Kim DK, Kim MK, Kim HJ, Cha IH, Lee EW. Onset of analgesia and analgesic efficacy of tramadol/acetaminophen and codeine/acetaminophen/ibuprofen in acute postoperative pain: a single-center, single-dose, randomized, active-controlled, parallel-group study in a dental surgery pain model. *Clin Ther* 2004;26:1037-45.
- Fricke JR, Hewitt DJ, Jordan DM, Fisher A, Rosenthal NR. A double-blind placebo-controlled comparison of tramadol/acetaminophen and tramadol in patients with postoperative dental pain. *Pain* 2004;109:250-7.
- Seymour RA, Meechan JG, Blair GS. An investigation into

- postoperative pain after third molar surgery under local anaesthesia. *Br J Oral Maxillofac Surg* 1985;23:410-5.
16. MIMS Online [database on the internet]. MIMS Thailand; 2017- [cited 2017 Dec 20]. Ultracet; Analgesics (Opioid). Available from: <https://www.mims.com/thailand/drug/info/tramadol%20%2b%20paracetamol/>
 17. MIMS Online [database on the internet]. MIMS Thailand; 2017-[cited 2017 Dec 20]. Ibuprofen; nonsteroidal anti-inflammatory drugs. Available from: <http://www.mims.com/thailand/drug/info/ibuprofen/?type=brief&mtype=generic>
 18. Li-Wan-Po A, Chen S, Peterson B, Wang Y. No need for rescue medication (NNR) as an easily interpretable efficacy outcome measure in analgesic trials: validation in an individual-patient meta-analysis of dental pain placebo-controlled trials of naproxen. *J Clin Pharm Ther* 2013;38:36-40.
 19. Lin FS, Lin WY, Lai CH, et al. Analgesics efficacy of tramadol/acetaminophen and propoxyphene/acetaminophen for pain relief of postoperative wound pain. *Acta Anaesthesiol Taiwan* 2012;50:49-53.