Comparison of Efficacy and Effectiveness between ULTRACET™ and Tramadol/Acetaminophen in Acute Postoperative Pain after Upper Extremity Surgery

Passakorn Sawaddiruk MD*,
Sahattaya Paiboonworachat MD*, Kittichai Janthawichai MD*

** Department of Anesthesiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*

Objective: *To compare the efficacy and effectiveness between ULTRACET™, a new analgesic combination of tramadol/acetaminophen, and tramadol/acetaminophen for acute postoperative pain after upper extremity surgery.*
Study design: *A double blind randomized controlled trial.*
Material and Method: *One hundred and eighty patients who underwent upper extremity surgery under brachial plexus block were randomized to receive either ULTRACET™ (n = 87) or tramadol and acetaminophen (n = 93) immediately after surgery in the postanesthetic care unit (PACU). Total morphine requirement, pain score (VRS) and drug adverse effects were compared between those two groups using independent single t-test, Mann-Whitney U-test, Chi-square test and Fisher-exact test respectively.*
Results: *Total morphine requirement was significantly lower in subjects who used ULTRACET™ when compared with the tramadol and acetaminophen group (0.51 and 0.69 mg in the first 6 hours after the operation, 0.0 and 0.13 mg in hours 6-12 after the operation). Moreover, there were fewer side effects in this ULTRACET™ group too.*
Conclusion: *ULTRACET™ has more efficacy and fewer side effects when compared with tramadol and acetaminophen in acute postoperative pain surgery.*

Keywords: *ULTRACET™, Tramadol, Acetaminophen, Paracetamol, Postoperative pain, Upper extremity surgery*

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Pain is a major problem after surgery. Effective postoperative pain management has been demonstrated to improve clinical outcome[1,2]. Opioids are widely used to relieve postoperative pain due to their efficacy and effectiveness[3]. However, the authors are concerned about their adverse effects such as nausea, vomiting, itching, and respiratory depression.

In patients who underwent upper extremity surgery under brachial plexus block, when local anesthetic was completely absorbed, those patients felt pain and required an analgesic in different doses. Multimodal analgesia, which is a combination of analgesic drugs, provides more effective pain relief than relying on one drug alone and plays an important role in decreasing adverse effects[1-3,13].

Correspondence to: Sawaddiruk P, Department of Anesthesiology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. Phone: 053-945-522, Fax: 053-945-526. E-mail: psawaddi@med.cmu.ac.th

Tramadol is a phenylpiperione analogue of codeine. It is believed to work through modulation of the noradrenergic and serotonergic systems in addition to its mild agonism of the μ-opioid receptor[4]. Tramadol is marketed as a racemic mixture with a weak affinity for the μ-opioid receptor (approximately $1/10^{th}$ that of morphine)[4]. The (+)-enantiomer is approximately four times more potent than the (-)-enantiomer in terms of μ-opioid receptor affinity and 5-HT reuptake, whereas the (-)-enantiomer is responsible for noradrenaline reuptake effects. These actions appear to produce a synergistic analgesic effect, with (+)-tramadol exhibiting 10-fold higher analgesic activity than (-)-tramadol.

Tramadol is available in both injectable and oral preparations. It is not recommended for use with children under 10 years old. It has $T_{1/2}$ elimination half-life at 4-6 hours. Tramadol undergoes hepatic metabolism via the cytochrome P450 isozyme CYP2D6, being O- and N-demethylated to five different

metabolites. Of these, M1 (O-Desmethyltramadol) is the most significant since it has 200 times the μ-affinity of (+)-tramadol and furthermore has an elimination half-life of nine hours, compared with six hours for tramadol itself. Phase II hepatic metabolism renders the metabolites water-soluble and they are excreted by the kidneys. Thus, reduced doses may be used in renal and hepatic impairment[4].

The most common adverse drug reactions are nausea, vomiting, headache, dizziness, itching and hot flushes. Drowsiness is reported, although it is less of an issue than with opioids. Respiratory depression, a common side effect of most opioids, is not clinically significant in normal doses. By itself, it can decrease the seizure threshold. When combined with SSRIs, tricyclic antidepressants, or in patients with epilepsy, the seizure threshold is further decreased[4].

Acetaminophen is widely used as an analgesic and antipyretic. In combination with non-steroidal anti-inflammatory drugs (NSAIDs) or opioids, acetaminophen is also used in the management of more severe pain (such as cancer pain).

Acetaminophen acts via at least two pathways[5-8]. The main mechanism of action of acetaminophen is reducing the oxidized form of the COX enzyme, preventing it from forming pro-inflammatory chemicals, which are important mediators of inflammation, pain, and fever[7,8]. Acetaminophen is metabolized to AM404, a compound with several actions; most important, it inhibits the uptake of the endogenous cannabinoid/vanilloid anandamide by neurons. Furthermore, AM404 inhibits sodium channels, as do the anesthetics lidocaine and procaine[9]. One theory holds that acetaminophen works by inhibiting the COX-3 isoform of the COX family of enzymes[10]. Acetaminophen is metabolized primarily in the liver, into non-toxic products.

ULTRACET™ (tramadol hydrochloride/ acetaminophen) combines two analgesics, tramadol 37.5 mg and acetaminophen 325 mg. Since ULTRACET™ contains only 37.5 mg of tramadol and 325 mg of acetaminophen, the use of 25% less tramadol in the combination product should reduce the incidence of tramadol-related adverse events while the addition of acetaminophen should reduce the onset time of analgesia and possibly improve the degree of analgesia[11]. It also has a synergistic effect whereas using it alone does not[25]. The authors intend to prove the efficacy and effectiveness of ULTRACET™ and tramadol and acetaminophen in management of mild to moderate pain after upper extremity surgery.

Material and Method

The present study was approved by the Faculty of Medicine, Chiang Mai University Ethics Committee for Human Research. One hundred and eighty ASA class I-II patients who underwent elective upper extremity surgery under brachial plexus block (supraclavicular approach) at Maharaj Nakorn Chiang Mai hospital were enrolled in the present study. Informed consent was obtained from all patients. Pregnant women or patients who had a history of allergy to tramadol or acetaminophen, drug addiction, liver disease or alcoholism were excluded.

The computer was used to randomize selection of study medications. Study medications consisted of tramadol/acetaminophen 75/650 mg, or tramadol 100 mg and acetaminophen 1,000 mg. To maintain the double-blind technique, each medication bottle was labeled with a medication code number and packaged with the study medication according to the randomization sequence. The investigator assigned medication code numbers to eligible patients in ascending sequential order. Treatment allocation information was contained in a sealed envelope. Brachial plexus block (supraclavicular approach) was done with 2% lidocaine 15 cc and 2% lidocaine with adrenaline 10 cc.

After the operation was finished, in the postanesthetic care unit (PACU), all patients were randomized to receive a single dose of study medication. Intravenous morphine may be administered to patients whose pain score (VRS) was more than 3.

The pain score and adverse effects were measured at 30 min and at 1, 2, 8, 14, 20, 26, 32, 38 and 44 hours after the study medication. Verbal rating scale was measured between 0 and 10, 0 meant no pain and 10 was the worst imaginable pain. Total morphine consumption and adverse effects were recorded throughout the present study.

Adverse events were recorded throughout the present study. Even after the use of rescue analgesia, an adverse event was considered as serious if it was life threatening, required hospitalization or resulted in a persistent or significant disability.

Patients completed the present study if they had no treatment-limiting adverse event within 48 hours after surgery. All data was analyzed by using SPSS version 16.0. Total morphine requirement, pain score (VRS) and drug adverse effects were compared between those two groups using independent single t-test, Mann-Whitney U test, Chi-square test and

Fisher-exact test accordingly. A p-value less than 0.05 was considered significant.

Results

Screening was done before the patients met the eligibility criteria and received study medication. One hundred and eighty patients were enrolled in the present study. Eighty-seven patients received ULTRACET™ while 93 received tramadol and acetaminophen. Demographic data in both groups was not significantly different ($p > 0.05$) (Table 1).

Total morphine consumption in the ULTRACET™ (U) group was significantly less than the tramadol and acetaminophen (TA) group in the first twelve hours after the operation. During the first 6 hours after the operation, total morphine consumption required by TA group was 0.69 mg while 0.51 mg was needed by patients in U group. Between hours 6-12 after the operation, patients in the TA group needed average 0.13 mg of morphine while U group did not need any. Then, after 12 hours, morphine was not required by the patients in these two groups (Table 2).

The pain score within 6 hours and 36 hours later after surgery was not significantly different between those two groups. However, in the ULTRACET™ group (U), the pain score between 6 to 32 hours after surgery was significantly less than tramadol and acetaminophen (TA) group (Table 3).

Patients who received ULTRACET™ had significantly fewer adverse effects than those who received tramadol and acetaminophen. Only three patients of ULTRACET™group had nausea and vomiting while 17 using tramadol and acetaminophen had the same adverse effect (Table 4). Nausea and vomiting in each group was mild to moderate in severity. There were no serious adverse events or significant changes in vital signs in any group.

Discussion

In the present comparison study of the efficacy and effectiveness between ULTRACET™ and tramadol and acetaminophen for acute postoperative pain after upper extremity surgery, ULTRACET™: tramadol/acetaminophen 75/650 mg provides better analgesia than tramadol 100 mg and acetaminophen 1,000 mg in the management of mild to moderate acute postoperative pain.

By combining drugs with different mechanisms of action and pharmacokinetic profiles, it has been proven that some drugs will have a

Table 1. Demographic data

Group	Tramadol + Acetaminophen (TA)	ULTRACET™ (U)	p-value
Number	93	87	
Sex			
Male	54	48	
Female	39	39	0.764
Age (yr)	38.81 (14.72)	38.69 (14.38)	0.957
Weight (kg)	61.97 (8.94)	59.17 (11.37)	0.068
Height (cm)	165.23 (6.96)	165.66 (7.51)	0.691

Data were presented as number and mean (SD)

Table 2. Average total morphine consumption (mg) after surgery

Postoperative time interval (hours)	TA (SD)	U (SD)	p-value
0-6	0.69 (0.52)	0.51 (0.48)	0.01
6-12	0.13 (0.49)	0	0.01
12-18	0	0	-
18-24	0	0	-
24-32	0	0	-
32-48	0	0	-

Data were presented as number and mean (SD)

Table 3. Average pain score (VRS)

Postoperative time interval (hours)	TA group (SD)	U group (SD)	p-value
0-6	2.35 (1.16)	2.20 (1.01)	0.43
6-12	2.41 (0.83)	1.83 (0.88)	<0.05
12-18	1.71 (0.77)	1.21 (0.89)	<0.05
18-24	1.10 (0.64)	0.76 (0.78)	<0.05
24-30	0.50 (0.57)	0.22 (0.36)	<0.05
30-48	0	0	1.00

Data were presented as number and mean (SD)

Table 4. Number of patients who had adverse events

Adverse effect	TA	U
Any event	0	0
Nausea and vomiting	17	3
Headache	0	0
Dizziness	0	0
Itching	0	0
Hot flush	0	0

synergistic effect, whereas using them alone cannot establish synergy. ULTRACET™ proved that it has a synergistic effect[25]. Therefore, one can enhance efficacy even though, lower doses of the individual drugs are used[26]. Combination therapy based on acetaminophen and an opioid may improve pain relief and provide faster onset and longer duration of action than either component separately[12,13,15,16,18,20-23,29]. In meta-analysis of single dose oral tramadol plus acetaminophen in dental or gynecologic/orthopedic patients with moderate to severe pain, the tramadol/acetaminophen combination was more effective than either of two components administered alone[14,24]. However, in the same study, the adverse effects associated with tramadol/acetaminophen were similar to those associated with the separate components[14]. In the present study, total morphine consumption in the tramadol and acetaminophen group was higher than in the ULTRACET™ group. It may be due to the faster onset of ULTRACET™. In another study about dental pain, the estimated onset of pain relief was 17 minutes for ULTRACET™ while 51 minutes for tramadol and 18 minutes for acetaminophen[17]. In patients who underwent abdominal or orthopedic procedures and had postsurgical pain, the combination of tramadol and acetaminophen tablets were effective and well tolerated. In three single-dose trials of oral surgery patients, treatment with the combination of tramadol/acetaminophen showed superior performance to tramadol alone for overall pain relief, onset time, and duration of action, and showed superior performance to acetaminophen for overall pain relief and duration of action[17]. When compared with codeine 60 mg plus 600 mg acetaminophen given during the immediate post-operative period, tramadol/acetaminophen provided comparable pain relief. However, another study found that tramadol plus acetaminophen was effective and well tolerated for postsurgical pain, had fewer side effects, and showed better tolerability than codeine plus acetaminophen[22]. In combination with other opioids, hydrocodone, tramadol/acetaminophen tablets provided effective and rapid analgesia for the treatment of postoperative dental pain[19].

In addition to the potential for increased efficacy due to combined medications, adverse drug events were expected to decrease. The present study showed that patients who received ULTRACET™ had significantly fewer adverse effects than tramadol and acetaminophen. Nausea and vomiting were the only adverse effects found in the present study, while other studies found that nausea was the most common adverse event. In another study, 40% of patients experienced adverse events while 51% were found in patients taking codeine plus acetaminophen[22]. Dizziness, headache, somnolence and constipation were found less often[23,28]. In a comparative trial of treatment for chronic pain, tramadol plus acetaminophen was better tolerated than codeine plus acetaminophen[27]. There were no serious adverse events or significant changes in vital signs in any group. In another study[22], the examination of tolerability of hydrocodone plus acetaminophen in adults treated for pain after orthopedic surgery found that 89% of patients experienced adverse events.

Therefore, ULTRACET™ may offer good efficacy with a good safety profile when compared with tramadol and acetaminophen.

Conclusion

In the present study, the efficacy and effectiveness of tramadol plus acetaminophen (ULTRACET™) for acute postoperative pain after upper extremity surgery were significantly improved including pain relief, reduced pain intensity, and fewer side effects when compared with tramadol and acetaminophen due to its synergistic property.

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การศึกษาเปรียบเทียบประสิทธิภาพและประสิทธิผลของยา ULTRACET™ เทียบกับการใช้ยา tramadol ร่วมกับยา acetaminophen ในการระงับปวดหลังการผ่าตัดรยางค์ส่วนบน

ภาสกร สวัสดิรักษ์, สหัทยา ไพบูลย์วรชาติ, กิตติชัย จันทวิชัย

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของยาระงับปวด ULTRACET™ เทียบกับการใช้ยา tramadol ร่วมกับยา acetaminophen ในแง่ของผลการระงับปวดและผลข้างเคียงหลังการผ่าตัดรยางค์ส่วนบน*

ชนิดของการศึกษา: *การศึกษาทดลองแบบสุ่มและปกปิดโดยมีกลุ่มควบคุม*

วัสดุและวิธีการ: *ผู้ป่วยที่มารับการผ่าตัดรยางค์ส่วนบนโดยวิธีระงับความรู้สึกแบบเฉพาะที่ (brachial plexus block) จำนวน 180 คน ได้รับการแบ่งกลุ่มแบบสุ่มเป็น 2 กลุ่มคือ กลุ่มที่ได้รับยา ULTRACET™ จำนวน 87 คน และกลุ่มที่ได้รับยา tramadol ร่วมกับยา acetaminophen จำนวน 93 คน โดยผู้เข้ารับการศึกษาจะได้รับยาดังกล่าวทันทีหลังจากผ่าตัดที่ห้องพักฟื้น ศึกษาดูปริมาณยามอร์ฟีนที่ผู้ป่วยได้รับทั้งหมด, คะแนนระดับความเจ็บปวดและผลข้างเคียงจากยาในผู้ป่วยทั้งสองกลุ่ม*

ผลการศึกษา: *ผู้ป่วยกลุ่มที่ได้รับยา ULTRACET™ มีความต้องการยามอร์ฟีนหลังการผ่าตัดเพื่อระงับอาการปวดน้อยกว่ากลุ่มที่ได้รับยา tramadol ร่วมกับยา acetaminophen อย่างมีนัยสำคัญทางสถิติ (0.51 และ 0.69 mg ใน 6 ชั่วโมงแรกหลังการผ่าตัด, 0.0 และ 0.13 mg ใน 6-12 ชั่วโมงหลังการผ่าตัด) และกลุ่มที่ได้รับยา ULTRACET™ มีผลข้างเคียงจากยาน้อยกว่ากลุ่มที่ได้รับยา tramadol ร่วมกับยา acetaminophen อย่างมีนัยสำคัญทางสถิติ*

สรุป: *ยา ULTRACET™ มีประสิทธิภาพในการระงับปวดหลังการผ่าตัดมากกว่า และผลข้างเคียงจากยาน้อยกว่าเมื่อเปรียบเทียบกับกลุ่มที่ได้รับยา tramadol ร่วมกับยา acetaminophen*