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โครงการวิจัย

การศึกษาเปรียบเทียบผลของ ยาผสมทรามาดอล/อะเซตามิโนเฟน และ ยาไอบูโพรเฟน ในการลดความเจ็บปวดเฉียบพลัน หลังจากการผ่าฟันคุดกรามล่างซี่ที่สาม

Comparative Study of Efficacy of Tramadol/Acetaminophen Combination Tablet and Ibuprofen in Acute Pain Control after Mandibular Third Molar Surgery

โดย

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ชื่อเรื่อง : **การศึกษาเปรียบเทียบผลของยาผสมทรามาดอล/อะเซตามิโนเฟน และยาไอบูโพรเฟน ในการลดความเจ็บปวดเฉียบพลัน หลังจากการผ่าฟันคุดกรามล่างซี่ที่สาม**

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บทคัดย่อ

ที่มาและวัตถุประสงค์

ยาต้านการอักเสบชนิดที่ไม่ใช่สเตียรอยด์เป็นยาที่ใช้กันอย่างแพร่หลายในงานศัลยกรรมช่องปาก แต่อย่างไรก็ตามมีบางกรณีที่มีข้อห้ามใช้ยาต้านการอักเสบชนิดที่ไม่ใช่สเตียรอยด์เช่น การแพ้ยาต้านการอักเสบชนิดที่ไม่ใช่สเตียรอยด์ ซึ่งยาผสมทรามาดอลและอะเซตามิโนเฟนเป็นอีกหนึ่งทางเลือกของผู้ป่วยเหล่านี้ โดยในการศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบประสิทธิผลของยาและความพึงพอใจของอาสาสมัคร ระหว่างยาผสมทรามาดอล 37.5 มิลลิกรัม/อะเซตามิโนเฟน 325 มิลลิกรัม (Tr/Ac) กับยาไอบูโพรเฟน 400 มิลลิกรัม (Ibu) ในการควบคุมความเจ็บปวดเฉียบพลันหลังจากการผ่าฟันกรามคุดล่างซี่ที่สาม

วัสดุอุปกรณ์และขั้นตอนการทดลอง

การศึกษาแบบปิดบังสองทาง สุ่มตัวอย่างแบบบล๊อคในอาสาสมัครอายุระหว่าง 18-40 ปี ที่ได้รับการผ่าฟันคุดกรามล่างซี่ที่สามที่จำเป็นต้องกรอกระดูกและแบ่งฟัน อาสาสมัครที่มีความเจ็บปวดหลังผ่าตัดในระดับปานกลางหรือมาก จะถูกแบ่งเป็น 2 กลุ่มจำนวนเท่ากัน โดยได้รับยา Tr/Ac หรือ Ibu จากนั้นอาสาสมัครจะต้องให้ประเมินความเจ็บปวดโดยใช้การบอกความรู้สึกเป็นตัวเลขด้วยเลข 0-10 และประเมินระดับการบรรเทาอาการปวดโดยใช้ตัวเลข 5 ระดับ โดยประเมินทุกชั่วโมงจนครบ 6 ชั่วโมง

เมื่อสิ้นสุดการศึกษาอาสาสมัครจะประเมินความพึงพอใจโดยใช้ตัวเลข 5 ระดับ จากนั้นทำการคำนวณผลรวมระดับการบรรเทาความเจ็บปวดเมื่อครบ 6 ชั่วโมง (TOTPAR6) และผลรวมระดับความเจ็บปวดที่เปลี่ยนแปลงเมื่อครบ 6 ชั่วโมง (SPID6) ภาวะไม่พึงประสงค์จากการใช้ยาได้ถูกบันทึกด้วยเช่นกัน

ผลการทดลอง

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) ไม่มีความแตกต่างกันอย่างไม่มีนัยสำคัญทางสถิติ (Wilcoxon rank sum test, $p>0.05$) อาสาสมัครในกลุ่ม Ibu มีความพึงพอใจมากกว่าอย่างไม่มีนัยสำคัญทางสถิติ (Chi square, $p>0.05$) ภาวะไม่พึงประสงค์ในกลุ่ม Tr/Ac มากกว่ากลุ่ม Ibu อย่างมีนัยสำคัญทางสถิติ(Chi square, $p<0.05$) ภาวะง่วงซึมเป็นภาวะไม่พึงประสงค์ที่พบบ่อยที่สุดในทั้งสองกลุ่ม

สรุปผลการทดลอง

ยาผสมทรามาดอล 37.5 มก./อะเซตามิโนเฟน 325 มก.มีฤทธิ์ระงับปวดเฉียบพลันหลังการผ่าตัดฟันคุดได้เทียบเท่ายาไอบูโพรเฟน 400 มก. โดยทั่วไปอาสาสมัครมีความทนต่อการใช้ยาทั้งสองชนิดได้ดี ไอบูโพรเฟนจะได้คะแนนความพึงพอใจมากกว่ายาผสมทรามาดอลและอะเซตามิโนเฟน โดยที่ยาผสมทรามาดอลและอะเซตามิโนเฟน มีอุบัติการณ์การเกิดภาวะไม่พึงประสงค์สูงกว่า

Title: Comparative Study of Efficacy of Tramadol/Acetaminophen Combination Tablet and Ibuprofen in Acute Pain Control after Mandibular Third Molar Surgery

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Abstract

Background and Objective:

Nonsteroidal anti-inflammatory drug(NSAIDs) is the most common analgesic drug in oral surgery. However, there are certain conditions that NSAIDs is contraindicated such as allergy to NSAIDs. Tramadol/acetaminophen is an alternative. The aim of this study was to compare the analgesic efficacy and subject's overall satisfaction between tramadol 37.5 mg/acetaminophen 325 mg combination tablet(Tr/Ac) and ibuprofen 400 mg(Ibu) in acute pain control after surgical removal mandibular third molar.

Materials and Methods:

This double-blinded, block randomized controlled study in subjects aged between 18-40 years who were underwent surgical removal of 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. At the end of the study, overall satisfaction was recorded as a global assessment score on 5-point scale. The total pain relief of 6 hours(TOTPAR6) and the sum of pain intensity difference of 6 hours(SPID6) were calculated. These adverse drug reactions were also recorded.

Results:

The collected data from 33 subjects for each group was 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, $p>0.05$). The overall reported events of adverse effect in Tr/Ac group was significantly higher than Ibu group(Chi square, $p<0.05$). Drowsiness was the most common adverse effect in both groups.

Conclusion:

The analgesic efficacy of tramadol 37.5 mg /acetaminophen 325 mg in acute pain control after mandibular third molar surgery was comparable to Ibuprofen 400 mg. Both agents were generally well tolerated. Ibuprofen has a better satisfaction score than tramadol/acetaminophen, whereas tramadol/acetaminophen is associated with a higher incidence of adverse effects.

Acknowledgement

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Rapeeporn Malungpaishrope

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Chapter 1

Introduction

Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for management acute pain in oral surgery (Pozzi & Gallielli, 2011; Hass, 2002). However, there are certain conditions that NSAIDs is contraindicated such as third trimester of pregnancy or allergy with cross reactivity to NSAIDs (Koren, Florescu, Costei, Boskovic, and Moretti, 2006 ; Borges, 2008). Thus, there is a need for other groups of analgesics with safety profiles.

Tramadol is a weak opioid. It centrally acts as μ-opioid agonist and inhibits reuptake of serotonin and adrenaline causing inhibitory effects on pain transmission in the spinal cord(Grond & Sablotzki, 2004). Tramadol is used to treat both acute and chronic pain of moderate to severe intensity. Tramadol is generally considered to be a relatively safe analgesic with low potential for dependence relative to morphine. The main adverse reactions are nausea, dizziness, and vomiting, particularly at the start of the therapy (WHO, 2014). Analgesic efficacy of tramadol can be improved by combination with acetaminophen. Tramadol directly acts on the central nervous system, while acetaminophen affects both the peripheral (COX inhibition) and central antinociception processes (Jozwiak-Bebenista & Nowak, 2014). Combination of these two analgesic drugs with different mechanism of action provides better coverage of the target sites and may result in synergistic pain relief.

Athough, it is listed as toxic substance, which can be purchased over the counter in Thailand but has to be documented according to revised Drugs Act B.E. 2530. It's considered a safe medication(Rauck, Ruoff, & McMillen 1994; Scott & Perry, 2000). In some conditions that NSAIDs are contraindicated, tramadol/acetaminophen is an alternative available analgesics. Hence, the purpose of this study is to compare pain relief effect and overall satisfaction of the single dose of tramadol 37.5 mg/acetaminophen 325 mg combination tablet to ibuprofen 400 mg tablet in controlling acute postoperative pain after surgical removal of mandibular third molar. Consequently, we can provide this combination tablet as an alternative drug for those who have certain condition against conventional NSAIDs.

Objectives

1. To compare pain relief effect of tramadol 37.5 mg/acetaminophen 325 mg combination tablet and ibuprofen 400 mg tablet for controlling acute postoperative pain after surgical removal mandibular third molar

2. To compare overall satisfaction of tramadol 37.5 mg/acetaminophen 325 mg combination tablet and ibuprofen 400 mg tablet for controlling acute postoperative pain after surgical removal mandibular third molar

Hypothesis

H_0 : There is no difference of analgesic efficacy between tramadol/acetaminophen combination tablet and ibuprofen

H_1 : Tramadol/acetaminophen combination tablet has different analgesic efficacy from ibuprofen

Scope

This clinical trial study was designed to assess the analgesic efficacy of single dose of tramadol 37.5 mg/acetaminophen 325 mg combination tablet in mandibular third molar surgery. 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. At the end of the study, overall satisfaction was recorded as a global assessment score on 5-point scale. The total pain relief of 6 hours(TOTPAR6) and the sum of pain intensity difference of 6 hours(SPID6) were calculated.

Expected Benefits

To provide tramadol 37.5 mg/acetaminophen 325 mg combination tablet as an alternative for who that are contraindicated to use NSAIDs.

Definition

Efficacy: the ability to produce a desired or intended result

Global assessment: a numeric rating scale used to subjectively measure overall satisfaction of the medication

Pain intensity: the severity of pain experienced

Pain relief: the amount of pain alleviated

SPID (Sum of Pain Intensity Difference): the sum of the time-weighted pain intensity difference between current pain and pain at baseline, multiplied by the interval between ratings

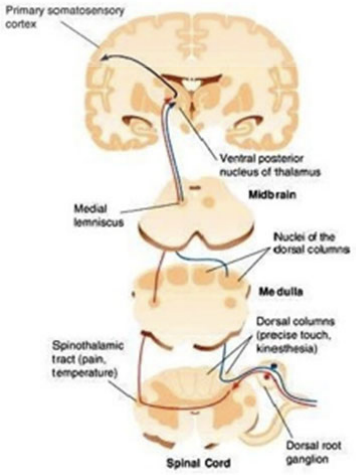
TOTPAR (Total Pain Relief): a time-weighted measure that integrates serial assessments of a subject's pain over the duration of the study

Chapter 2

Review Literature

Pain is an unpleasant feeling that is conveyed to the brain by sensory neurons. The discomfort signals actual or potential injury to the body. However, pain is more than a sensation or the physical awareness, it also includes perception and the subjective interpretation of discomfort. Perception gives information about the pain's location, intensity, and characteristics. Various consciousness and unconsciousness respond to both sensation and perception, including emotional response, adding further definition to the overall concept of pain.

Surgery is an intervention that can endanger tissue and nerve directly, in which the tissue would release chemical mediators such as prostaglandin E2 or histamine as a reaction to harmful stimulus. The chemical mediators would stimulate the nerve endings to be more prone to stimulation in response to painful stimulus, causing tissues to be easily stimulated as well. When pain signal is conducted through nerve endings, it travels along the terminal nerve fibers, delta-A fiber and C-fiber, to dorsal horn of the spinal cord. The signal is then adjusted at substantia gelatinosa. Without pain stimulus in a normal condition, the large nerve fiber in substantia gelatinosa would inhibit the function of T cell in small nerve fibers in signal transduction to the brain. However, in the presence of pain stimulus, the T cell of small nerve fibers would inhibit the inhibition by substantia gelatinosa, allowing itself to conduct signal to the opposite side of the spinal cord and to thalamus in the brain through lateral spinothalamic tract. Thalamus then sends signal to cerebral cortex to process the severity, characteristic, and location of the pain (The national pharceutical Council, 2001).



It is common to experience pain after tooth extraction. Depending on the severity of trauma and the procedure, patient may experience pain, ranging from tolerable to severe, which may last for a few days or longer. Management of pain after tooth extraction by a dentist or oral surgeon usually consists of prescribing medications. Pain after tooth extraction is usually greatest in the first twelve hours after the procedure. The study of oral hygiene and postoperative pain after mandibular third molar surgery by Peñarrocha in 2001 showed that maximum postoperative pain was recorded 6 hours after extraction, with peak inflammation after 24 hours (Penarrocha, Sanchis, Saez, Gay, and Bagan, 2001).

Post-operative pain is related to injury temporarily and resolves during the appropriate healing period. It often responds to treatment with analgesic medications and treatment of the participating cause. Different types of pain management act on different pain pathway.

Analgesic medication can be classified into 2 main groups

1. Opioid drugs function by binding to opioid receptors in the brain, spinal cord, and other areas of the body. They reduce transmission of pain messages to the brain and thus reducing feelings of pain. Opioids are used to treat moderate to severe pain that may not respond well to other analgesics. Few examples including codeine, fentanyl, hydrocodone, meperidine, morphine, tramadol is classified as opioid drug

2. Non-opioid pain relievers that are commonly used as part of a pain management are paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs).

Paracetamol can be effective for mild chronic pain or to supplement other medications. It is important not to take more than the recommended dosage (Becker & Phero,2005).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)

In many cases of chronic pain, inflammation is not the cause, so anti-inflammatory medications may not be helpful. NSAIDS may be able to provide short-term relief during flare-up of pain, but generally they should not be used for long-term pain relief due to their risks. In cases where long-term NSAIDs may be the best option, subjects should be treated under the ongoing supervision of physician.

Ibuprofen

Introduction

NSAIDs are now widely used around the world due to its efficacy in reducing pain and inflammation. It has become a drug of choice for pain management in many clinical disorders because of integrated role in blocking cyclo-oxygenases (COX) which are enzymes used to produce prostaglandins (Ong, Lirk, Tan, and Seymour, 2007). NSAIDs that have been approved by the US Food and Drug

Administration (FDA) as OTC analgesics can be divided into seven categories: salicylic acids, indol and indence acetic acids, hetero acetic acids, arilpropionic acids, fenamates, oxicams and COX II inhibitors (Chou, Helfand, Peterson, Dana, and Roberts, 2006). Ibuprofen is among many drugs in this group that is commonly used nowadays.

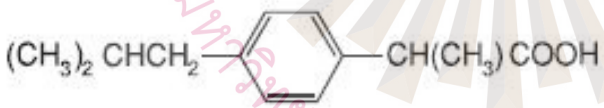
History

Ibuprofen was first discovered half a century ago by Professor Stewart Adams since 1969 at the Boots Company in Nottingham, United Kingdom (Rainsford, 2011). Since then, it has evolved to be amongst the most commonly used drugs available in nearly all countries in the world and provides a variety of properties including analgesic, antipyretic, and anti-inflammation (Rainsford, 2012). Its approved indication is mainly for the treatment of mild to moderate pain, and it is able to treat a wide variety of painful and inflammatory conditions. Ibuprofen was initially used as a prescription-only medicine for the treatment of musculoskeletal pain and inflammation and other painful conditions (Rainsford, 2015). At that time, it had a reputation for good efficacy and lower gastrointestinal adverse effects as it was used in low dosage ranging from 400 up to 1,200 mg per day. Due to this confidence in its safety, Boots Company Ltd. was granted a license in 1983 to market ibuprofen as a non-prescription drug or over-the-counter drug and was used widely up until today (Rainsford, 2012).

Chemical Name: Ibuprofen

IUPAC Name: 2-[4-(2-methylpropyl)phenyl]propanoic acid

Chemical Structure



Molecular Formula : $C_{13}H_{18}O_2$

Pharmacodynamics

Ibuprofen is a non-selective inhibitor of an enzyme Cyclooxygenase (COX) that is required for the synthesis of prostaglandins via the arachidonic acid pathway. The enzyme COX is needed in order to convert arachidonic acid into prostaglandin H_2 and then further converted into prostaglandins that is the key mediators for fever and inflammation. There are two forms of COX in the body – COX-1 that is responsible for the physiological functions through thromboxane A_2 and COX-2 that plays important role in pain and inflammation. Like many other conventional NSAIDs, ibuprofen inhibits both COX-1 and COX-2. This inhibitory effects have been considered to relate to the likelihood of developing upper GI and

possibly renal and other reactions by NSAIDs (Rainsford, 2012). Therefore, the newer class of selective COX-2 inhibitors were developed in attempt to inhibit only the inflammation response and reduce the risks of the conventional NSAIDs.

Pharmacokinetics

Absorption

Ibuprofen is well absorbed after oral administration. The peak plasma concentration are 1-2 hours after oral administration. It is rapidly bio-transformed with serum half life of 1.8-2 hours (Busha, & Aslam, 2010).

Distribution

Ibuprofen is highly protein bound (>98%) at therapeutics concentrations. Consistent with the high degree of plasma protein binding, ibuprofen exhibits a low apparent volume of distribution that approximates plasma volume (~0.1–0.2 l/kg), but it is able to penetrate into the central nervous system (CNS) and accumulate at peripheral sites where its analgesic and anti-inflammatory effects are required (Mazaleuskaya et al, 2015).

Metabolism

Ibuprofen is almost completely metabolized in human body mainly by cytochrome P450 enzymes to inactive metabolites. Two major metabolites are into hydroxylate and carboxylate compound (Mazaleuskaya et al, 2015).

Elimination

The kidney is the major route of excretion. Ibuprofen has a relatively short plasma elimination half-life ($t_{1/2}$) that averages between 1-3 hours which is possibly one of its key safety feature. Due to the very short half- life of ibuprofen rarely affect the liver and kidney as they are absorbed completely and have first-pass-hepatic metabolism (Pozzi, 2011).

Dosage

There are many doses of ibuprofen available nowadays but the commonly used dosage is 400 mg given 1 tablet for 3 times a day as it has the optimal analgesic dose for adults.(Ong et al., 2007) The randomized controlled trials have demonstrated that the analgesic effect does not increase following the increased dosage due to ceiling effect (Chou et al., 2006). All NSAIDs have ceiling effect or plateau,

above which an increase in dosage will not increase its analgesic effect but will only prolong the duration of action and increase the unwanted side effects (Rainsford, 2011).

Adverse Reaction

The common side effects of ibuprofen include gastrointestinal complications such as hemorrhage, perforation and obstruction. Like any other NSAIDs, ibuprofen can cause bleeding as they block the COX-1, enzyme that protects the lining of the stomach from acid. As a result of inhibiting cyclooxygenases, they also decrease the production of thromboxane A2, which is a potent platelet-aggregating agent, thus increasing the risk of postoperative bleeding (Rainsford, 2011). In addition, it can affect the blood pressure and cause hypertension in some subjects as well as an alteration in renal function, hepatic injury and platelet inhibition. COX-2 inhibitor can also cause potential cardiovascular toxicity as they inhibit only the COX-2, but not the COX-1 enzyme. This leads to the metabolism imbalances, resulting in an overproduction of harmful byproducts of leukotriene B4 and thromboxane A2 (TXA2) which are vasoconstriction and pro-aggregatory. On the other hand, there is a reduction of prostaglandin I2 (PGI2) production which is vasodilatory and anti-aggregatory. These harmful byproducts may damage the arterial wall and induce arterial blood clotting, hence increasing a risk for cardiovascular adverse events such as myocardial infarction and sudden cardiac death. Other common minor adverse effects include dyspepsia, nausea vomiting, and diarrhea (Ong et al., 2007; Mazaleuskaya et al, 2015). Many data reviewed by Rainsford,2009 shows that in comparison with other NSAIDs it appears that ibuprofen has relatively low risks for gastrointestinal and cardiovascular adverse reactions.

NSAIDs may induce hypersensitivity reactions that may involve both immunological and non-immunological mechanisms. Reactions may be clinically indistinguishable, they involve different mechanisms. They may present in a variety of clinical manifestations (respirarory, cutaneous, anaphylactic, or other organ-specific) which may developes within minutes to delayed-type response appears days and weeks. Immunological (allergic) reaction is mediated either by IgE(acute reactions) or by T cells(delayed reactions). In contrast, non-immunologically mediated (cross-reactive) hypersensitivity reactions are most likely related to inhibition of COX-1 by NSAIDs, which is a property of ibuprofen. Prostaglandin E2 formation is blocked by the inhibition of COX-1, leading to a relative increase in leukotriene formation and histamine release from mast cells (Kowaslski & Makowska,2015).

Pregnancy and Lactation

US Food and drug administration has categorized ibuprofen as pregnancy category B in the first and second trimester but the usage of ibuprofen during third trimester suddenly changes to pregnancy category D (Black, 2003). This is because ibuprofen can induce various complications in pregnancy, including prolongation of labor, postpartum hemorrhage, and gastric irritation. As for the effects on the fetus, they can include oligohydramnios, intrauterine closure of ductus arteriosus, persistent pulmonary hypertension, or even fetal death. Especially, premature constriction of ductus arteriosus is related to usage of NSAID during third trimester on both human and animal studies (Ong & Seymour, 2003). Therefore, it's important that the risk and benefit should be weighed before use especially in the third trimester of pregnancy.

Drug Interaction

Aspirin

Many literature has reviewed that ibuprofen may interfere with the anti-platelet effects of aspirin by blocking the active site of platelet cyclooxygenase conducted an experiment to test an effect of ibuprofen on aspirin and found that there was a complete inhibition of the effect of aspirin when given either before or after ibuprofen. This is due to the inhibition of serum thromboxane and platelet aggregation (Catella-Lawson et al., 2001).

Antihypertensive drugs

Likewise other NSAIDs, ibuprofen may interferes with efficacy of many antihypertensive agents such as ß-adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics. The mechanism of action of NSAIDs, including ibuprofen involves inhibition of the synthesis of inflammatory prostaglandins and vasodilatory prostaglandins. Prostaglandins plays an important role in regulation of blood pressure. Thereby, antihypertensive drugs appear to be affected by ibuprofen (Mazaleuskaya et al, 2015).

Contraindications (Abbott, 2012)

- Known hypersensitivity to ibuprofen.
- Hypersensitivity (e.g. asthma, rhinitis or urticarial) to aspirin or other non-steroidal anti-inflammatory drugs. As with other non-steroidal anti-inflammatory agents, ibuprofen should not be given to patients vulnerable to gastrointestinal ulceration and bleeding and haemorrhagic diathesis.
- History of gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- During the third trimester of pregnancy.
- Severe heart failure.

- Severe liver failure.
- Severe renal failure (glomerular filtration below 30 mL/min).
- Conditions involving an increased tendency or active bleeding.
- Third trimester of pregnancy

Clinical implication in Dentistry

Ibuprofen that have been approved by the US Food and Drug Administration (FDA) for over the counter(OTC) analgesic. Due to its safety and available as OTC analgesic, ibuprofen is widely used for managing pain in dentistry. The clinical indications reviewed by Pozzi & Gallelli (2011) that ibuprofen could be used include endodontic pain management, wisdom tooth extraction or surgical removal, pediatric dentistry, implant dentistry, orthodontic pain management, periodontal pain management and many more. As for the use in oral surgery, management of pain after third molar removal is important especially as most subjects are treated as day-cases. There is an increased need for effective and safe analgesics that facilitate a rapid recovery. Analgesics with an anti-inflammatory action are effective in controlling postoperative dental pain (Seymour & Walton, 1984) and ibuprofen is one of the many medications that can provide good analgesia after the removal of impacted third molars (Cooper, Schachtel, Goldman, Gelb, & Cohn, 1989). Numerous studies conducted in subjects with postoperative dental pain after third molar surgery confirmed the analgesic effects of ibuprofen. The study of Seymour suggested that a single dose of ibuprofen 400 mg provided significant pain relief in the early postoperative period after third molar surgery (Seymour et al., 1998). In addition, Dionne even suggested that pretreatment with a nonsteroidal anti-inflammatory drug, such as ibuprofen results in a suppression of postoperative pain when compared to standard therapy without an increase in side effects (Dionne, Campbell, Cooper, Hall, & Buckingham, 1983).

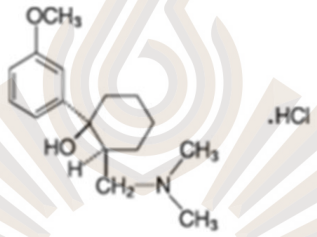
Tramadol with Acetaminophen Combination Tablet

Tramadol/acetaminophen tablet combines two analgesics, tramadol 37.5 mg and acetaminophen 325 mg. Tramadol and acetaminophen are both analgesics, but they possess different mechanism. Tramadol directly acts on the central nervous system which bind to mu-opioid receptors, inhibiting serotonin and adrenaline reuptake(Janssen Pharmaceuticals, 2014). Acetaminophen affects of both the peripheral (COX inhibition) and central antinociception processes(Jozwiak- Bebenista & Nowak, 2014). Combination of these two analgesic drugs with different mechanism of action provides better coverage of the target site and may result in synergistic pain relief. This combination medication is used to manage moderate to moderately severe pain (Frilcke, 2004).

Tramadol

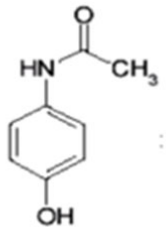
Tramadol, a synthetic, centrally acting analgesic agent used to treat acute and chronic moderate pain, may be useful for the treatment of allodynia. Tramadol has two synergistic mechanisms of action. It acts as a weak opioid agonist and an inhibitor of norepinephrine and serotonin reuptake in the CNS. The chemical structure of tramadol is related to those of morphine and codeine. The action on the μ-receptor can be reversed with the opioid antagonist naloxone, which partially reverses the analgesic effect. The inhibition of norepinephrine and serotonin reuptake is similar to the major action of many antidepressant drugs and the minor action of alpha 2-agonists.

The chemical name for tramadol hydrochloride is (±)cis-2-[(dimethylamino)methyl]-1-(3 methoxyphenyl) cyclohexanol hydrochloride(WHO, 2014). Its structural formula is:



Acetaminophen

Acetaminophen has antipyretic and analgesic reaction but no significant anti-inflammatory effect. It has antipyretic and analgesic properties because it is more effective against enzyme for prostaglandins biosynthesis in the central nervous system than those in the periphery. Acetaminophen is primarily metabolized in the liver and the minor extent the intestine, it is metabolized predominantly by glucuronide conjugation (approximately 60%) and sulphate conjugation (approximately 35%) and both excreted mainly in urine. Paracetamol (Acetaminophen, N-acetyl-p-aminophenol) is a derivative of para-aminophenol. The molecular weight of acetaminophen is 151.2. It is a moderately and lipid soluble weak organic acid with Pka 9.5. The chemical structure for Acetaminophen is as follow (Jozwiak-Bebenista & Nowak, 2014).



Pharmacodynamic

Tramadol with acetaminophen combination tablet contains tramadol and acetaminophen. Tramadol is centrally acting synthetic opioid analgesic. Two complementary mechanisms appear applicable: activating the μ-opioid receptor and acting as a serotonin–norepinephrine reuptake inhibitor.

Acetaminophen is a non-opiate, non-salicylate analgesic (Janssen Pharmaceuticals, 2014).

Pharmacokinetic

Absorption:

Tramadol is administered as a racemate and both the(+) and (-) forms of both tramadol and M1 are detected in the circulation. Although tramadol is rapidly absorbed, it has a slower absorption and longer half-life when compared to acetaminophen. The absolute bioavailability of tramadol from tramadol with acetaminophen combination tablet has not been determined. After oral administration of 100 mg tramadol hydrochloride, the mean absolute bioavailability is approximately 75%. The peak plasma concentration of racemic tramadol and M1 occurs at approximately two and three hours, respectively.

Acetaminophen is rapidly absorbed and almost complete in the small intestine. Peak plasma concentration of acetaminophen occur within 1 hour and are not affected by co-administered with tramadol (Janssen Pharmaceuticals, 2014).

Distribution:

The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 μg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range(Janssen Pharmaceuticals inc, 2014).

Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of acetaminophen is bound to plasma protein(Jozwiak-Bebenista & Nowak, 2014).

Metabolism:

Tramadol is extensively metabolized after oral administration. The major metabolic pathways appear to be N - and O -demethylation and glucuronidation or sulfation in the liver. The metabolism of tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4. 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. In conclusion, tramadol is primarily metabolized in liver and mainly excreted by the kidney, in which half-life of tramadol is approximately about 5-7 hours while acetaminophen has less half-life than tramadol by two to three hours (Janssen Pharmaceuticals Inc, 2014)

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:

a) conjugation with glucuronide

b) conjugation with sulfate

c) oxidation via the cytochrome, P450-dependent

(Jozwiak-Bebenista & Nowak, 2014).

Excretion:

Tramadol and its metabolites are excreted mainly by the kidneys, with a cumulative renal excretion (tramadol and metabolites) of approximately 95%. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5-6 and 7 hours, respectively, after administration of tramadol with acetaminophen combination tablet.

The metabolites of paracetamol are mainly excreted in the urine. 90% of the dose administered is excreted within 24 hours, mainly as glucuronide (60-80%) and sulfate (20- 30%) conjugates. Less than 9% is eliminated unchanged in urine. Plasma half-life is 2-3 hours in adult(Janssen Pharmaceuticals Inc, 2014).

Dosage

For the short-term (five days or less) management of acute pain, the recommended dose of tramadol with acetaminophen combination tablet is 2 tablets every 4 to 6 hours as needed for pain relief, up to a maximum of 8 tablets per day (Janssen Pharmaceuticals Inc, 2014). It is recommended to use the lowest effectiveness dosage for the shortest duration consistent with individual patient treatment goals.

Drug Interaction

Tramadol is metabolized by CYP2D6 to an active metabolite which bind to μ-receptor. Some drugs such as amitriptyline, metoclopramide are inhibitors of CYP2D6. Tramadol also inhibits reuptake of serotonin. Caution should be taken when co-administering tricyclic antidepressants and serotonin reuptake inhibitors, because such a combination inhibits the metabolism of tramadol. It also increases the risk of seizure and serotonin syndrome.

The use of metoclopramide as an antiemetic during tramadol therapy is also unfavourable. Metoclopramide is a strong inhibitor of tramadol metabolism.

Tramadol increases the depressive action of hypnotics, benzodiazepine derivatives and neuroleptics on the CNS. When co-administered with neuroleptics, it may cause seizures. Using tramadol with hypotensive drugs increases the risk of hypotension. (Woron, 2008)

Pregnancy and Lactation

Teratogenic effects: Pregnancy category C

Tramadol has been shown to cross placenta. In animal study at very high dose of tramadol have shown harmful effects in animal without causing malformation. There are no adequate and well-controlled studies in pregnant women. It should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks.

Tramadol with acetaminophen combination tablet is not recommended for nursing mothers because its safety in infants and newborns has not been studied. (Janssen Pharmaceuticals Inc, 2014)

Adverse Effect

The mechanism of tramadol directly affects at μ-opioid receptor and it may induce narcotic effect both physical and psychological which may lead to the drug abuse and illegal usage. The report showed that tramadol has lower narcotic effect than morphine and lower incidence rate of drug abuse than codeine and pentazocine. Tramadol should be used with caution for the patient with history of drug addiction and alcoholic who have higher risk of drug abuse and the patient who prolonged medication. Drug withdrawal may occur upon the abrupt discontinuation or decrease intake of medications or recreational use of drugs. The tapering of drug may be needed.

The most common adverse effects such as nausea/vomiting, headache, constipation, seizure, drowsiness are similar to others opioid group. Over dosage can lead to respiratory depression, drowsiness, constricted pupil, tachycardia, hypertension, and nausea/vomiting. Tramadol can cause more seizure than other opioid group but less common of respiratory depression. The most severe complication is hypotension. Patient who undergoes renal impairment and extensive CYP2D6 metabolizer has increased risk of tramadol effect. Tramadol should not be used during pregnancy unless the benefit outweighs the risk to the fetus. It is categorized as pregnancy category C (Moore,1999).

Clinical implication in Dentistry

Tramadol is the first line drug of centrally acting analgesic that may be a useful alternative to the opioid analgesic. It is usually used for moderate chronic pain in oral surgery patient which has similar therapeutic effect to codeine 60 mg, but less therapeutic effect than opioid combination such as aspirin/codeine or acetaminophen/codeine. Tramadol is useful alternatively for the patient that has acute pain with gastrointestinal side effect which is contraindicated for NSAIDs and in case of opioid combination that is not well tolerated or contraindicated (Moore, 1999).

According to the study of Robert Wood Johnson, in 2001, the purpose of study was to compare the analgesic efficacy of tramadol with acetaminophen combination tablet (75 mg/650 mg) to those of tramadol 75 mg, acetaminophen 650 mg and ibuprofen 400 mg alone. The study shows that tramadol with acetaminophen combination tablet was superior to tramadol or acetaminophen alone with respect to pain relief and pain intensity. It also shows that adverse reaction was generally transient, mild to moderate in severity. Tramadol with acetaminophen combination tablet is more effective and well tolerated for treating acute pain, rapidly acting, and long duration (Medve, Wang, & Karim, 2001).

According to the study of Young-Soo Jung, Hyung-Jun Kim in 2004, the purpose of study was to compare the analgesic onset and efficacy between tramadol 75 mg/acetaminophen 650 mg combination

tablet and combine treatment of codeine 20 mg/acetaminophen 500 mg /ibuprofen 400 mg in third molar surgery. The study demonstrates no significant difference between two groups in early observation period (0-4 hours), but during the last interval (4-6 hours), the combination treatment of codeine/acetaminophen/ibuprofen has significantly greater efficacy in pain relief. For the onset of action, the difference between two groups were not statistically significant. They also suggested that tramadol/acetaminophen combination tablet provides rapid onset and effective analgesia in acute postoperative pain control (Jung et al., 2004).

Chapter 3

Materials and Methods

3.1 Sample Size Calculation

From our pilot study

Where…

n_i = the sample size required in each group (double this for total sample)

$$n_i = \frac{2(z_\alpha + z_\beta)^2 \sigma^2}{(\mu_1 - \mu_2 - \delta)^2}$$

μ_1 = mean of the TOTPAR6 of the tramadol/acetaminophen combination tablet

= 10.6

μ_2 = mean of the TOTPAR6 of the ibuprofen

= 13.4

Z_α = Z0.05 = 1.645 for one-sided study

Z_β = Z0.20 = 0.84

σ = standard deviation = 4.55

δ = the mean difference clinically significant = 0

n_i = 33 for each group

n = 66

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Healthy subject aged between 18 to 40 years old with moderate or severe pain resulting from oral surgery involving surgical removal of impacted third molar which requires overlying bone removal and tooth sectioning.
2. All subject had to be able to understand and communicate with the observer and be able to carry out the study procedure.

Exclusion Criteria

1. Subjects, who are allergic to tramadol, acetaminophen, ibuprofen or articaine.
2. Subjects, who are on medications; tramadol, acetaminophen or ibuprofen within 2 weeks.
3. Subjects, who have severe systemic disease such as alcoholism, asthma, anemia, cirrhosis, gastrointestinal tract toxicity, hepatotoxicity, liver disease, respiratory depression, renal dysfunction, seizure, thrombosis or ASA III, IV, V, VI
4. Subjects, who are pregnant or breastfeeding.

3.2 Materials

Trade name : Ultracet®

Formulations : Tramadol HCl 37.5mg, acetaminophen 325mg

Manufacturer : Janssen Pharmaceuticals, Inc.

Country : Korea

Trade name : Coprofen®

Formulations : Ibuprofen 400 mg

Manufacturer : Community Pharm PCL

Country : Thailand

3.3 Method

3.3.1 Study Design

This study were conducted in Department of Oral Surgery, Faculty of Dental Medicine, Rangsit University. The study protocol and consent form were approved by the Human Ethics Committee of Rangsit University. This double-blinded, controlled study which both subjects and surgeons were blinded. Difficulty index for removal of impacted mandibular third molar described by Pederson were assessed before surgery(Table 1). The subjects underwent a lower third molar surgical removal which required overlying bone removal and tooth sectioning under 4% articaine with epinephrine 1:200,000. With a randomized block design, either tramadol 37.5mg/acetaminophen 375 mg combination tablet(Tr/Ac) or ibuprofen 400 mg(Ibu) was prescribed after the surgery.

Table 1. Difficulty index for removal of impacted mandibular third molars described by Pederson

Classification		Value
Angulation	Mesioangular	1
	Horizontal/transverse	2
	Vertical	3
	Distoangular	4
Depth	Level A	1
	Level B	2
	Level C	3
Ramal relationship	Class 1	1
	Class 2	2
	Class 3	3
Difficulty index	Very difficult	7-10
	Moderately difficult	5-6
	Slightly difficult	3-4

3.3.2 Data collection

When the 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 (fig 1). This score was defined as a baseline pain. Subjects with "moderate" to "severe" pain were included in the study while subjects with no or mild pain were excluded. Then, the pain intensity was recorded hourly for the period of 6 hours after drug administration.

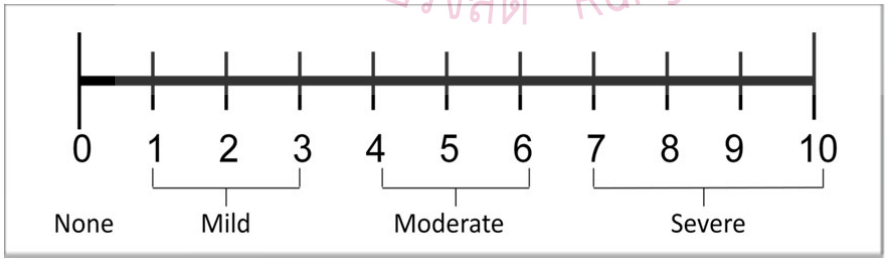


Fig.1 A numeric pain rating scale of 0-10 (0= None, 1-3= Mild, 4-6= Moderate, 7-10= Severe)

One hour after drug administration, subjects were asked to measure how much pain was alleviated in the pain relief scale. The 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) (Fig 2). The pain relief score was then recorded hourly for the period of 6 hours as well.

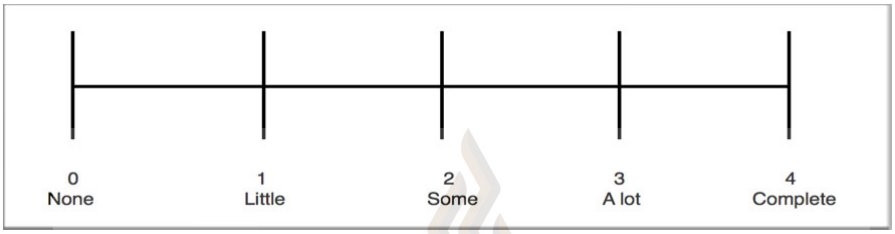


Fig. 2 The pain relief scale of 0-5 (0= None, 1= A little relief, 2= Some relief, 3= A lot of relief, 4= Complete relief)

At the end of the study, subjects were asked to assess their overall satisfaction by comparing between the positive effect (analgesia) and the negative drug effects (side effects) of the study drug. The overall satisfaction was recorded as a global assessment score on 5-point scale (1= Poor, 2= Fair, 3= Good, 4= Very good, 5= Excellent) (Fig 3).

Fig. 3 The overall satisfaction was recorded on 5-point scale (1= Poor, 2= Fair, 3= Good, 4= Very good, 5= Excellent)

Following a single dose of medication, if the subjects was experiencing the adverse drug reactions, the effects were reported in checkboxes which gathered from commonly experienced side effects of the

medications in which the subjects can choose more than one of the following; nausea, vomiting, headache, stomachache, constipation, diarrhea, palpitation, dizziness, drowsiness, difficulty breathing, hallucination, muscle spasm, rash or urticaria, and gastrointestinal irritation. These adverse drug reactions were recorded throughout the 6-hour period after the intake of study drug.

However, during the observation period of 6 hours, if the subject did not experience pain relief or cannot tolerate the pain intensity after taking the study drug, subjects can take supplemental analgesics and need to record additional data. The pain relief was set as "0" and the pain intensity score was set to pain intensity immediately prior to supplement medication. Also, the remedication time were recorded. Global assessment was recorded immediately prior to taking supplemental analgesics as well. As for the name and dosage of supplemental analgesics, only acetaminophen 500 mg tablet was indicated. After observation period of 6 hours, a standard regimen can be taken without having to record the additional data.

3.3.3 Data Analysis

The total pain relief (TOTPAR) and sum of pain intensity difference (SPID) were calculated and used as the primary efficacy endpoints.

Total Pain Relief of 6 Hours (TOTPAR6)

TOTPAR is a time-weighted measure of area under the curve (AUC) or total area under the pain relief curve and is a summary measure that integrates serial assessments of a subject's pain over the duration of the study. The formulation is as follows:

PAR_t = pain relief score at $time_t$

$time_t$ = time in hours

$$TOTPAR = \sum [PAR_t \times (time_t - time_{t-1})]$$

Sum of Pain Intensity Differences of 6 Hours (SPID6)

SPID is a strategy for combining relief magnitude and duration in a single score. It is calculated by the sum of the time-weighted pain intensity difference (difference between current pain and pain at baseline) multiplied by the interval between ratings. For SPID6, pain intensity is assessed by the subject at t=0 (baseline, beginning of the pain episode), 1, 2, 3, 4, 5 and 6 hours after each dose of study medication during each breakthrough pain episode.

The pain intensity difference (PID) is defined as the difference in pain intensity at the various time points versus time 0 (baseline). SPID scores are calculated as follows :

Pain intensity difference (PID_t) = $PI_{\text{at baseline}}$ - $PI_{\text{at time t}}$

$SPID = \sum [PID_t \times (time_t - time_{t-1})(h)]$

The study was designed to include 66 subjects who were qualified according to the criteria. Statistical analysis was done using IBM SPSS Software Version 24. 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 for the intervals from 0 to 2 hours, 2 to 4 hours, and 4 to 6 hours. The level of confidence is accepted at 95% ($p<0.05$).

Chapter 4
Results

4.1 Demographic and Baseline Characteristics

Sixty-six subjects were included and block randomized equally to receive two different medications. Of 66 subjects, 33 subjects were prescribed with tramadol 37.5 mg/acetaminophen 325 mg combination tablet (Tr/Ac) while ibuprofen 400 mg tablet (Ibu) was given to other 33 subjects. All in Tr/Ac group and Ibu group were similar in sex, average age, average weight, duration of surgical procedure, difficulty index for the surgical removal (Table 2). Most of the subjects in Tr/Ac and Ibu group were female with ages range from 18-40 years old, and average age is 23.36 years old for Tr/Ac group and 23.97 years old for Ibu group.The duration of the surgical procedure was 33.55 minutes for Tr/Ac group and 35.73 minutes for Ibu group. The difficulty index for the surgical removal for both groups fell into difficulty index 5, which is moderately difficult described by Pederson. Mean baseline pain scores were 6.85 in the Tr/Ac group and 6.55 in the Ibu group.

Table 2. Demographic characteristics and baseline pain intensity.

Characteristics		Tr/Ac (n = 33)	Ibu (n = 33)
Sex, number	Female(%)	24(72.73)	22(66.67)
	Male(%)	9(27.27)	11(33.33)
Age, years	Mean	23.36 ± 4.49	23.97 ± 4.31
	Range	18-40	18-40
Duration of surgical procedure, mins	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

Tr/Ac = Tramadol 37.5 mg/Acetaminophen 325 mg; Ibu = Ibuprofen 400 mg.

4.2 Efficacy Evaluation

Total Pain Relief Scores of 6 Hours (TOTPAR6)

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 3).

Table 3. The total pain relief (TOTPAR) at 2-hour interval and the total pain relief of 6 hours(TOTPAR6) after drug administration.

	Tr/Ac (n = 33)	Ibu (n = 33)	p value
TOTPAR 0-2 Hours	3.44 ± 1.87	4.03 ± 1.89	0.198
TOTPAR 2-4 Hours	3.85 ± 1.82	4.61 ± 1.87	0.097
TOTPAR 4-6 Hours	4.30 ± 1.89	4.55 ± 2.03	0.529
TOTPAR6	11.61 ± 4.61	13.18 ± 4.60	0.111

Tr/Ac = Tramadol37.5 mg/Acetaminophen 325 mg; Ibu = Ibuprofen 400 mg.

p > 0.05, Wilcoxon rank sum test

Sum of Pain Intensity Differences of 6 Hours (SPID6)

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 4).

Table 4. The sum of pain intensity difference (SPID) at 2-hour interval and the sum of pain intensity difference of 6 hours(SPID6) after drug administration.

	Tr/Ac (n = 33)	Ibu (n = 33)	*p* value
SPID 0-2 Hours	5.55 ± 4.35	5.64 ± 3.54	0.832
SPID 2-4 Hours	6.64 ± 3.67	7.12 ± 4.02	0.767
SPID 4-6 Hours	7.58 ± 4.32	7.52 ± 4.46	0.908
SPID6	19.76 ± 11.43	20.27 ± 10.37	0.773

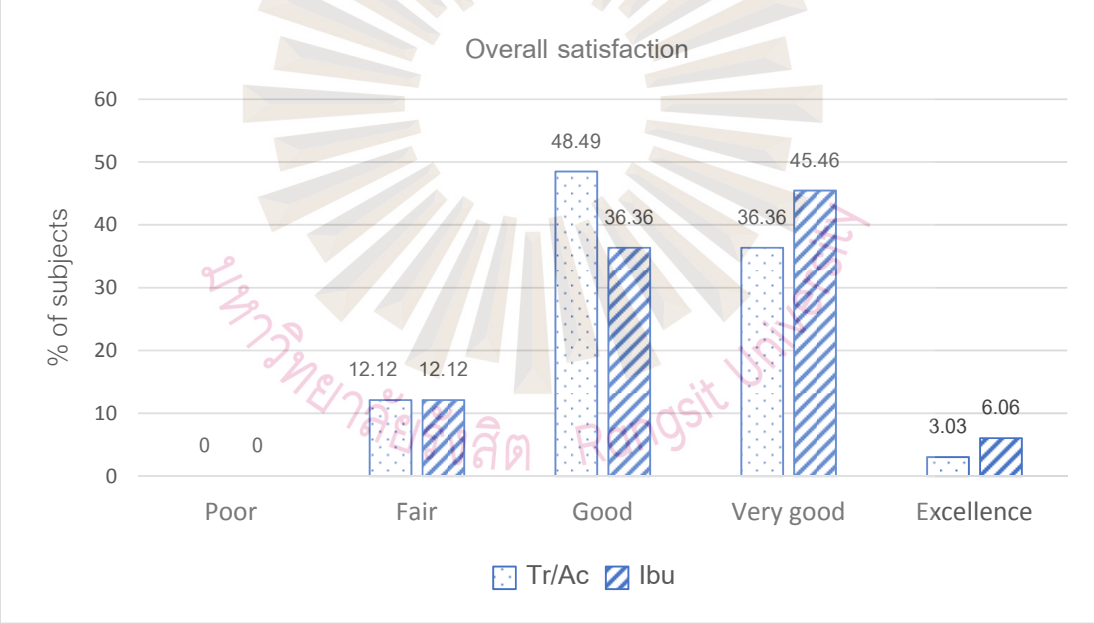
Tr/Ac = Tramado l37.5 mg/Acetaminophen 325 mg; Ibu = Ibuprofen 400 mg.

p > 0.05, Wilcoxon rank sum test

Global Assessment

At the end of the study, none of subjects used the supplement drug within of 6-hour observation period. In each group, 29 (87.88%) of subjects rated their overall global assessment for their assigned medication as good or better. While 4 (12.12%) of subjects 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 different was not statistically significant($p>0.05$) (Figure 4).

Fig. 4 The overall satisfaction of the subjects after studied medication of either Tr/Ac or Ibu was taken. The chart shows that the proportion of subjects rating the medication as very good and excellent in Ibu group was statistically significant greater than Tr/Ac group ($p>0.05$, Chi square test)



4.3 Safety Evaluation

All enrolled subjects were included in the safety analysis. There were 12 (36.37%) of the subjects in Tr/Ac group and 7 (21.21%) 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 (24.24%) of 33 subjects in Tr/Ac group and 5 (15.15%) 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 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).

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	15.15	0/33	0	0.020*
Nausea/Vomiting	4/33	12.12	1/33	3.03	0.163
Drowsiness	8/33	24.24	5/33	15.15	0.353
Headache	3/33	9.09	1/33	3.03	0.302
Tremor	1/33	3.03	0/33	0	0.314
Stomachache	1/33	3.03	0/33	0	0.314
Constipation	0/33	0	2/33	6.06	0.151
Total number of events	22	-	9	-	0.001*
Total number of subjects	12/33	36.36	7/33	21.21	0.174

* $p<0.05$, Chi Square test.

Chapter 5
Discussion and Conclusion

5.1 Discussion

Some studies have shown analgesic efficacy of tramadol 75 mg/acetaminophen 650 mg in oral surgery (Medve, et al., 2001; Yung, et al., 2004; Fricke, et al, 2004). In many clinical situations, a lower dosage was preferred due to decreased 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 and the peak pain intensity is within a day after surgery (Seymour et al., 1985). Assessment period in this study is 6 hours after drug administration due to the recommended interval dosing of both drugs (MIM, 2017) and we think that a longer period of study is likely to get poor compliance in the data collection.

There are several tools used for pain assessment in post-operative 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 (Stubhaug & Breivik, 1995). 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 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 efficacy between both groups were similar.

In a study by Li-Wan-Po et al.(2013) stated that the absence of need for supplement medication is a reliable outcome measure in the evaluation of acute pain relief. In this study, supplement medication was readily available but none of subjects needed for supplement medication. That implied the sufficient of analgesic efficacy of the medications in mandibular third molar surgery.

In dental pain study by Frick et al. (2004) showed that the most frequent adverse effect of tramadol were dizziness, nausea and vomiting commonly reported (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 Feng-Sheng Lin et al in pain control after implantation of an

intravenous access device which showed the most frequent adverse effect of tramadol/acetaminophen was drowsiness(13.79%). 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 were relatively free of serious adverse effects associated with conventional opioid. It is considered a safe medication (Rauck et al.,1994; Scott & Perry, 2000). It is an acceptable alternative even in elderly patients with chronic pain (Rauck et al., 1994). In this study, there was no reported of serious adverse effects 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 (Medve et al, 2001; Jung et al, 2004; Lin et al, 2012). All the subjected were well tolerated with their medication. 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 medication.

Tramadol/acetaminophen is associated with adverse effect seen in opioid. Respiratory depression with tramadol/acetaminophen is less common, but serious. Tramadol/acetaminophen has less risk of respiratory depression than other opioid analgesics. However, it should be used cautiously in patients with respiratory impairment, e.g. asthma, chronic obstructive pulmonary disease and sleep apnea.

Tramadol/acetaminophen is generally considered to have a very low risk of dependence and abuse. There have been case reports of dependence and withdrawal after long-term use. Most cases of individuals who abused tramadol had been in patients with a previous history of substance abuse. In order to reduce incidence of drug dependence, patient's medication history must be carefully reviewed.

Many adverse effects commonly occur and may interfere with daily activities. Due to its sedative effect, which may affect a person's ability to drive or operate machinery. Patient should be advised to avoid driving or operating machinery while taking this medication.

The Food and Drug Administration (FDA) is restricting the use of tramadol and all tramadol-containing products in children. This medication may cause serious risk, including for slowed or difficult breathing and death. Thus, tramadol/acetaminophen is contraindicated in children under 12 years. Also, children younger than 18 years of age who recently had surgery to remove tonsils or adenoids is contraindicated. Because of these serious adverse effects, the use of this medication in breast feeding women is not recommended.

In pregnancy, acetaminophen has demonstrated efficacy and apparent safety in all stages of pregnancy in standard therapeutic doses. It has been used without increasing risks of congenital anomalies or adverse pregnancy outcomes. While, studies describing the use of tramadol in human pregnancies are limited. However, this drug has been used in therapeutic doses by pregnant women for many years and have not been associated with an increase incidence of birth defects. The main concern

about tramadol is that persistent use may lead to dependence and tolerance in the mother with resultant withdrawal. It should be used during pregnancy only if the potential benefit justifies the potential risk to fetus. If necessary, tramadol/acetaminophen may be used as an alternative pain management in certain conditions such as the pain is unresponsive to other analgesics or third trimester of pregnancy which NSAIDs are contraindicated. A smaller dosage of tramadol/acetaminophen may be administered at infrequent intervals. Patients should avoid prolonged use because of the risk of fetal addiction and withdrawal syndrome in the neonatal period.

5.2 Conclusion

Tramadol/acetaminophen is potent analgesics used for moderate to severe pain control. It is associated with a low risk of serious adverse effect. The potential for abuse and dependence is low. Therefore, it is generally considered to have a much better safety profile than other opioid analgesics. Other opioid-like effects occur commonly at normal dose, including drowsiness, dizziness, nausea and vomiting. Thus, it should be used with caution and patients should be informed about adverse effects. It is recommended to only use this medication in adult and should not be used in children. It should not be used during pregnancy unless potential benefit outweighs the potential risk to fetus. It should be prescribed only if other analgesics are inadequate or contraindicated. The lowest beneficial dose is recommended. Treatment should be short and intermittent.

In this study, it should be noted that the dose of tramadol 37.5 mg/acetaminophen 375 mg combination tablet provides good analgesic efficacy in oral surgery and did not induce serious adverse effects. Thus, it could be alternatively prescribed under certain indications in which conventional NSAIDs are contraindicated.

5.3 Suggestion

The limitation of this study is the short-term of treatment. Some adverse reactions may not appear in the short period of treatment. Therefore, we suggest to conduct a clinical trial of analgesic efficacy of tramadol 37.5 mg/acetaminophen 325 mg in a longer period of treatment in further study to assess the efficacy and safety profile. In our study design involves treating established acute pain. Another suggestion in further study is treating pain before it occurs.

Tramadol/acetaminophen has proved to be an effective and well tolerated analgesics. However, it should be used when acetaminophen or NSAIDs is inadequate or contraindicated. It should be used cautiously in patients with impaired respiratory function, pregnancy, and history of drug abuse. Patient factors should be carefully considered and medication history must be carefully reviewed before prescribing.

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ราชกิจจานุเบกษา เล่มที่ 132 ตอนพิเศษที่ 179ง หน้า 12 ลงวันที่ 4 สิงหาคม 2558.

Appendix

ชื่อ _____ นามสกุล _____ ยา _____

<u>คำแนะนำการตอบแบบสอบถาม</u>

1. เมื่อรู้สึกเจ็บปวดให้วงกลมล้อมรอบตัวเลขที่แสดงระดับความเจ็บปวดในขณะนั้น กำหนดให้คะแนนที่ 0-10 โดยที่ 0 = ไม่รู้สึกปวดเลย และ 10 = ปวดมากที่สุด และจากนั้นให้รับประทานแก้ปวดที่จ่ายให้ 1 เม็ด พร้อมทั้งบันทึกเวลาที่รับประทานยา
2. ทุก 1 ชั่วโมงหลังจากรับประทานยา ให้ประเมิน จนกระทั่งครบ 6 ชั่วโมง
    1. ระดับความเจ็บปวด กำหนดคะแนนที่ 0-10
    2. ระดับการบรรเทาความเจ็บปวด เมื่อเทียบกับความรู้สึกปวดก่อนรับประทานยา กำหนดคะแนนที่ 0-4 โดย 0 = ไม่หายปวด และ 4 = หายปวดสนิท
3. หลังจากครบ 6 ชั่วโมงให้ประเมินความพึงพอใจโดยรวมของการใช้ยา โดยเทียบความรู้สึกของการบรรเทาความเจ็บปวดเทียบกับผลข้างเคียงของยา กำหนดคะแนนที่ 0-5 โดยที่ 0 = แย่ และ 5 = ยอดเยี่ยม
4. หากเกิดผลข้างเคียงของยาให้เขียนเครื่องหมาย X หน้าข้อที่ตรงกับอาการที่เกิดขึ้น (สามารถเลือกได้หลายข้อ)
5. ภายใน 6 ชม.ที่อยู่ในช่วงเวลาของการทำวิจัย ถ้าปวดมากและต้องการทานยาเพิ่ม ให้รับประทานยาพาราเซตามอล 500 mg 1 เม็ด พร้อมทั้งบันทึกเวลาที่ทานยาแก้ปวดเสริม

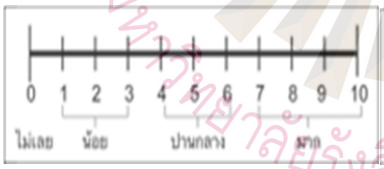
เวลาที่คนไข้เริ่มเจ็บปวดและเริ่มกินยา เวลา ___:___ น.

(ชั่วโมงที่ 0)

ระดับความเจ็บปวด

ชั่วโมงที่ 1 เวลา ___:___ น.

ระดับความเจ็บปวด

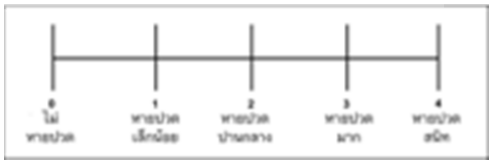


ระดับการบรรเทาความเจ็บปวด

ชั่วโมงที่ 2 เวลา ___:___ น.

ระดับความเจ็บปวด

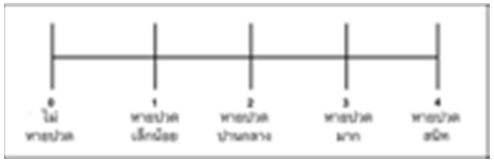
ระดับการบรรเทาความเจ็บปวด



ชั่วโมงที่ 3 เวลา ___:___ น.

ระดับความเจ็บปวด

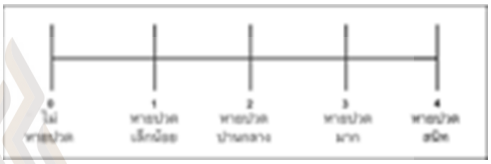
ระดับการบรรเทาความเจ็บปวด



ชั่วโมงที่ 4 เวลา ___:___ น.

ระดับความเจ็บปวด

ระดับการบรรเทาความเจ็บปวด



ชั่วโมงที่ 5 เวลา ___:___ น.

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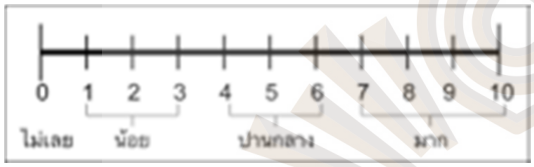

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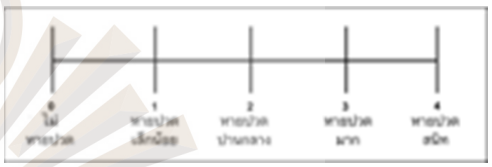

ชั่วโมงที่ 6 เวลา ___:___ น.

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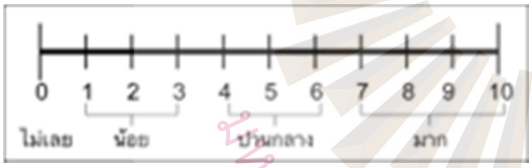
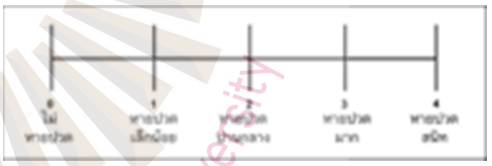


ระดับการบรรเทาความเจ็บปวด



การประเมินอาการโดยรวมของตนเอง

ผลข้างเคียงของยา

- ☐ **คลื่นไส้**
- ☐ **อาเจียน**
- ☐ **ปวดศีรษะ**
- ☐ **ปวดท้อง**
- ☐ **ท้องผูก**
- ☐ **ท้องร่วง**
- ☐ **มือสั่น**
- ☐ **ใจสั่น**
- ☐ **มึนงง**
- ☐ **ง่วงซึม**
- ☐ **หายใจไม่ออก**
- ☐ **ประสาทหลอน**
- ☐ **กล้ามเนื้อกระตุก**
- ☐ **ผื่นคันทางผิวหนัง**
- ☐ **เลือดออกในทางเดินอาหาร**

หากภายใน 6 ชม. ท่านไม่สามารถทนความเจ็บปวดได้ ท่านได้รับประทานยาเสริม ณ เวลา __:__น.

การศึกษาเปรียบเทียบผลของยาผสมทรามาดอล/อะเซตามิโนเฟน และยาไอบูโพรเฟนในการลดความเจ็บปวดเฉียบพลันหลังจากการผ่าฟันคุดกรามล่างซี่ที่สาม

Comparative study of efficacy of tramadol/acetaminophen combination tablet and ibuprofen in acute pain control after mandibular third molar surgery

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บทคัดย่อ

วัตถุประสงค์

เพื่อเปรียบเทียบฤทธิ์ระงับปวดของยาผสมทรามาดอล 37.5 มก./อะเซตามิโนเฟน 325 มก.(Tr/Ac) และไอบูโพรเฟน 400 มก.(Ibu)ในการควบคุมความเจ็บปวดเฉียบพลันหลังผ่าฟันกรามคุดล่างซี่ที่สาม

วิธีการศึกษา

การศึกษาแบบปิดบังสองทาง สุ่มตัวอย่างแบบบล๊อคในอาสาสมัครอายุระหว่าง 18-40 ปี ที่ได้รับการผ่าฟัน กรามคุดล่างซี่ที่สามที่จำเป็นต้องกรอกระดูกและแบ่งฟัน อาสาสมัครที่มีความเจ็บปวดหลังผ่าตัดในระดับปานกลางหรือมากจะถูกแบ่งเป็น 2 กลุ่มจำนวนเท่ากัน โดยได้รับยา Tr/Ac หรือ Ibu จากนั้นอาสาสมัครจะต้องให้ประเมินความเจ็บปวดโดยใช้การบอกความรู้สึกเป็นตัวเลขด้วยเลข 0-10 และประเมินระดับการบรรเทาอาการปวดโดยใช้ตัวเลข 5 ระดับ โดยประเมินทุกชั่วโมงจนครบ 6 ชั่วโมง จากนั้นทำการคำนวณผลรวมระดับการบรรเทาความเจ็บปวดเมื่อครบ 6 ชั่วโมง (TOTPAR6) และผลรวมระดับความเจ็บปวดที่เปลี่ยนแปลงเมื่อครบ 6 ชั่วโมง(SPID6) และเมื่อสิ้นสุดการศึกษา อาสาสมัครจะประเมินความพึงพอใจโดยใช้ตัวเลข 5 ระดับ

ผลการศึกษา

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) ไม่มีความแตกต่างกันอย่างไม่มีนัยสำคัญทางสถิติ(Wilcoxon rank sum test, $p>0.05$) อาสาสมัครในกลุ่ม Ibu มีความพึงพอใจมากกว่าอย่างไม่มีนัยสำคัญทางสถิติ (Chi square, $p>0.05$)

บทสรุป

ยาผสมทรามาดอล 37.5 มก./อะเซตามิโนเฟน 325 มก.มีฤทธิ์ระงับปวดเฉียบพลันหลังการผ่าตัดฟันคุดได้เทียบเท่ายาไอบูโพรเฟน 400 มก.

คำสำคัญ:

การลดความเจ็บปวดเฉียบพลัน, ยาไอบูโพรเฟน,ยาผสมทรามาดอล/อะเซตามิโนเฟน, การผ่าฟันกรามคุดล่างซี่ที่สาม

Abstract

Objective:

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 mandibular third molar.

Materials and methods:

This double-blinded, block randomized controlled study in subjects aged between 18-40 years who were underwent surgical removal of 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.

Results:

The collected data from 33 subjects for each group was 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, $p>0.05$).

Conclusion:

The analgesic efficacy of tramadol 37.5 mg /acetaminophen 325 mg in acute pain control after mandibular third molar surgery was comparable to Ibuprofen 400 mg.

Keywords:

Acute pain control, ibuprofen, tramadol/acetaminophen combination tablet, mandibular third molar surgery

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for management acute pain in oral surgery.[1,2] However, there are certain conditions that NSAIDs is contraindicated such as third trimester of pregnancy or allergy with cross reactivity to NSAIDs.[3,4] Thus, there is a need for other groups of analgesics with safety profiles.

Tramadol is a weak opioid. It centrally acts as μ-opioid agonist and inhibits reuptake of serotonin and adrenaline causing inhibitory effects on pain transmission in the spinal cord.[5]
Tramadol is used to treat both acute and chronic pain of moderate to severe intensity. Tramadol is generally considered to be a relatively safe analgesic with low potential for dependence relative to morphine. The main adverse reactions are nausea, dizziness, and vomiting, particularly at the start of the therapy.[6] Analgesic efficacy of tramadol can be improved by combination with acetaminophen. Tramadol directly acts on the central nervous system, while acetaminophen affects both the peripheral (COX inhibition) and central antinociception processes.[7] Combination of these two analgesic drugs with different mechanism of action provides better coverage of the target sites and may result in synergistic pain relief.

Although, tramadol/acetaminophen combination tablet is listed as toxic substance, which can be purchased over the counter in Thailand but has to be documented according to revised Drugs Act B.E. 2530.[8] It's considered a safe medication.[9,10] In some conditions that NSAIDs are contraindicated, tramadol/acetaminophen is an alternative available analgesics. Hence, the purpose of this study is to compare pain relief effect and overall satisfaction of the single dose of tramadol 37.5 mg/acetaminophen 325 mg combination tablet to ibuprofen 400 mg tablet in controlling acute post-operative pain after surgical removal of mandibular third molar. Consequently, we can provide this combination tablet as an alternative drug for those who have certain condition against conventional NSAIDs.

Materials and methods

Subjects

This randomized double-blinded controlled study was conducted in Department of Oral Surgery, Faculty of Dental Medicine at Rangsit University. The study protocol was approved by the Human Ethics Committee of Rangsit University in which all subjects provided had written the informed consent. The study included 66 healthy subjects aged between 18-40 years old, who were underwent surgical removal of mandibular third molar with overlying bone removal and tooth sectioning. Subjects had to be able to understand and communicate with the observer and carry out the study procedures. Also, they need to experience moderate or severe pain in order to be included in the study. Subjects who were allergic to tramadol, acetaminophen, ibuprofen or articaine, were on analgesic medications 2 weeks, had severe systemic disease and were currently pregnant or breastfeeding were excluded from the study.

Study Design

Subjects were locally anesthetized with 4% articaine with 1:200,000 epinephrine. Then, they were underwent mandibular third molar surgical removal which required overlying bone removal and tooth sectioning performed by oral surgeons with more than 10 years of experience. Following after the surgery, 66 subjects who rated their pain intensity as “moderate” or “severe” pain were included in the study. With a randomized block design, a single dose of either tramadol 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, supplement 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 supplement medication, time was recorded. `The pain relief was set to no relief and the pain intensity was set to pain intensity immediately prior to supplement 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:

PAR_t = pain relief score at $time_t$

TOTPAR $= \sum PAR_t$ x time(h) elapsed since previous observation

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:

Pain intensity difference (PID_t) = PI at baseline - PI at time t

SPID $= \sum PID_t$ x time(h) elapsed since previous observation

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 incidence 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 other 33 subjects. Most of the subjects in both groups were female (72.73% in Tr/Ac and 66.67% in Ibu group).

The age in both group range from 18-40 years old, and average age 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 TOTPAR6were 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 supplement drug within of 6-hour observation period. In each group, 29(87.88%) of subjects rated their overall global assessment for their assigned medication as good or better. While 4(12.12%) of subjects 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 different was not statistically significant(p>0.05)(Table 4).

Safety Evaluation

All enrolled subjects were included in the safety analysis. There were 12 (36.37%) of the subjects in Tr/Ac group and 7 (21.21%) 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 (24.24%) of 33 subjects in Tr/Ac group and 5 (15.15%) 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 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.[12,13,14] In many clinical situations, a lower dosage was preferred due to decreased 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 and 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 compliance in the data collection.

There are several tools used for pain assessment in post-operative 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 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 efficacy between both groups were similar.

The absence of need for supplement medication is a reliable outcome measure in the evaluation of acute pain relief.[18] In this study, supplement medication was readily available but none of subjects needed for supplement medication. That implied the sufficient of analgesic efficacy of the medications in mandibular third molar surgery.

In dental pain study of Fricke[14] the most frequent adverse effect of tramadol were dizziness, nausea and vomiting commonly reported (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(13.79%). 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 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 of serious adverse effects 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 subjected were well tolerated with their medication. 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 satified with their assigned medication.

The limitation of this study is the short-term observation period and 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 post-operative 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, but did not induce serious adverse effects in short term use. However, it should be used with caution and patients should be informed about adverse effects.

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ตารางที่ 1 ข้อมูลทั่วไปของอาสาสมัคร และระดับความเจ็บปวดเริ่มต้น

Table 1 Demographic characteristics and baseline pain intensity

Characteristics		Tr/Ac (n = 33)	Ibu (n = 33)
Sex, number	Female(%)	24(72.73)	22(66.67)
	Male(%)	9(27.27)	11(33.33)
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

Tr/Ac = tramadol37.5mg/acetaminophen 325 mg; Ibu = ibuprofen 400 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
TOTPAR 0-2 Hours	3.45 ± 1.87	4.03 ± 1.89	0.198
TOTPAR 2-4 Hours	3.85 ±1.82	4.61 ± 1.87	0.097
TOTPAR 4-6 Hours	4.30 ±1.89	4.55 ± 2.03	0.529
TOTPAR6	11.61 ± 4.61	13.18 ± 4.60	0.111

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

ตารางที่ 3 ผลรวมระดับความเจ็บปวดที่เปลี่ยนแปลงทุก 2 ชั่วโมงและผลรวมระดับความเจ็บปวดที่เปลี่ยนแปลงเมื่อครบ 6 ชั่วโมงหลังการรับประทานยา

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
SPID 0-2 Hours	5.55 ± 4.35	5.64 ± 3.54	0.832
SPID 2-4 Hours	6.64 ± 3.67	7.12 ± 4.02	0.767
SPID 4-6 Hours	7.58 ± 4.32	7.52 ± 4.46	0.908
SPID6	19.76 ± 11.43	20.27 ± 10.37	0.773

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

ตารางที่ 4 การประเมินความพึงพอใจของอาสาสมัครภายหลังที่ได้รับยา 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	12.12	4	12.12
Good	16	48.48	12	36.36
Very good	12	36.36	15	45.46
Excellent	1	3.03	2	6.06

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

ตารางที่ 5 อาการไม่พึงประสงค์ที่เกิดขึ้นซึ่งน่าจะเกิดจากการใช้ยา

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	15.15	0/33	0	0.020*
Nausea/Vomiting	4/33	12.12	1/33	3.03	0.163
Drowsiness	8/33	24.24	5/33	15.15	0.353
Headache	3/33	9.09	1/33	3.03	0.302
Tremor	1/33	3.03	0/33	0	0.314
Stomachache	1/33	3.03	0/33	0	0.314
Constipation	0/33	0	2/33	6.06	0.151
Total number of events	22	-	9	-	0.001*
Total number of subjects	12/33	36.36	7/33	21.21	0.174

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

* $p<0.05$, Chi Square test.

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