Onset of Analgesia and Analgesic Efficacy of Tramadol/Acetaminophen and Codeine/Acetaminophen/Ibuprofen in Acute Postoperative Pain: A Single-Center, Single-Dose, Randomized, Active-Controlled, Parallel-Group Study in a Dental Surgery Pain Model

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A Single-Center, Single-Dose, Randomized,

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in a Dental Surgery Pain Model

Directed by Professor Eui-Wung Lee

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Acknowledgements

LIST of CONTENTS

LIST of FIGURES

LIST of TABLES

ABSTRACT

Onset of Analgesia and Analgesic Efficacy of Tramadol/Acetaminophen and Codeine/Acetaminophen/Ibuprofen in Acute Postoperative Pain: A Single-Center, Single-Dose, Randomized, Active-Controlled, Parallel-Group Study in a Dental Surgery Pain Model

Background: The combination of tramadol and acetaminophen has demonstrated good efficacy in various clinical pain models. However, there is a need for comparisons of the onset of analgesia and other measures of analgesic efficacy with this combination and other strong combination analgesics for the management of acute pain.

Objective: The goal of this study was to compare the time to onset of analgesia and other measures of analgesic efficacy with tramadol/acetaminophen 75/650 mg (Tr/Ac) and codeine/acetaminophen/ibuprofen 20/500/400 mg (Co/Ac/Ib) in the management of acute pain after oral surgery.

Methods: This was a single-center, single-dose, randomized, active-controlled, parallel-group study in healthy subjects who had undergone surgical extraction of ≥ 1 impacted third molar requiring bone removal. When patients reported at least moderate pain after dental surgery (score ≥ 5 on a 10-point scale), they were randomized to 1 of 2 treatment groups. The time to onset of analgesia was measured using a 2-stopwatch technique. The

times to the onset of perceptible and meaningful pain relief, pain intensity, pain relief, patient's overall assessment, and adverse events were recorded for 6 hours after dosing.

Results: One hundred twenty-eight subjects participated in the study, 64 in each treatment group. The 2 groups were similar in terms of baseline pain severity and demographic characteristics (mean age, 23.7 and 23.4 years in the Tr/Ac and Co/Ac/Ib groups, respectively; mean body weight, 58.5 and 60.3 kg). The median times to the onset of perceptible pain relief were a respective 21.0 and 24.4 minutes, and the median times to the onset of meaningful pain relief were 56.4 and 57.3 minutes. Mean total pain relief and the sum of pain intensity difference were also similar in the early period after dosing (0–4 hours). However, between 4 and 6 hours, Co/Ac/Ib was associated with significant differences in both variables compared with Tr/Ac ($P < 0.05$). Although similar through the 4-hour assessment, mean pain intensity difference was significantly greater with Co/Ac/Ib at 5 and 6 hours. The proportion of the patients assessing their assigned treatment as *good* or better was significantly greater with Co/Ac/Ib compared with Tr/Ac ($P < 0.05$). The safety profile of Tr/Ac was comparable to that of Co/Ac/Ib.

Conclusions: In this small and selected group of subjects, the onset of analgesia and analgesic efficacy of Tr/Ac was comparable to that of Co/Ac/Ib. Tr/Ac provided rapid and effective analgesia for acute postoperative dental pain in this population.

Key words: onset of analgesia, analgesic combination, analgesic efficacy, tramadol/acetaminophen, postoperative pain.

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INTRODUCTION

To reduce the occurrence of adverse events (AEs) associated with the use of opioid analgesics, these agents have been combined with nonopioid agents such as

acetaminophen to lower the amount of opioid needed to produce an equivalent degree of analgesia.[1,2] Such combination products also have been claimed to produce a synergistic analgesic effect.[1,2]

Tramadol plus acetaminophen is one such analgesic combination.[1] Tramadol hydrochloride, which has weak opioid activity, produces analgesia through an opioid effect that binds mu-opioid receptors and modifies transmission of pain signals through inhibition of serotonin and norepinephrine reuptake within pain pathways of the central nervous system.[1,3,4] Clinical experience indicates that tramadol is associated with fewer adverse effects than typical opioid, notably respiratory depression, constipation, and potential for addiction.[1,3,4] Furthermore, tramadol has been reported to be effective for various types of postoperative pain, including dental pain.[5–7] Acetaminophen, on the other hand, produces analgesia by elevating the pain threshold through inhibition of N-methyl-D-asparate– or substance P–mediated nitric oxide synthesis and/or inhibition of prostaglandin E_2 release in the central nervous system.[1,8,9] Acetaminophen, which has excellent antipyretic-effectiveness and safety profiles, has been available for ~40 years.[1,8,9]

In animal models, the combination of tramadol and acetaminophen in approximately a 1:8 milligram ratio has been reported to result in synergistic analgesia.[10] Clinical studies have reported that the combination of tramadol/acetaminophen 37.5/325 mg was effective and well tolerated in patients with dental pain,[11,12] osteoarthritis flare pain,[13] chronic back and joint pain,[14,15] and fibromyalgia.[16] This combination has demonstrated comparable efficacy and tolerability to the combination of hydrocodone/acetaminophen[12] and codeine/acetaminophen.[14]

Use of the combination of codeine phosphate/acetaminophen/ibuprofen 10/250/200 mg, which is not available in the United States, has been reported to provide good pain relief with no severe AEs in patients with chronic osteoarthritis (n=25)[17] and in the dental pain model (n=25).[18] Codeine is an opioid analgesic and relieves mild to moderate pain by binding to stereospecific opioid receptors in the central nervous system, altering processes affecting perception of and emotional response to pain.[19] Codeine is converted to the more active drug morphine; however, this conversion is not equal in all patients or ethnic groups. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects.[1,19] It inhibits the activity of the enzyme cyclooxygenase, resulting in decreased formation of the prostaglandin and thromboxane precursors of arachidonic acid.[19]

In acute pain, a rapid onset of pain relief is desirable.[20,21] Comparisons of the onset of analgesia and analgesic efficacy of tramadol/acetaminophen and other strong analgesic combinations in acute pain are necessary. To our knowledge, the time of onset of the analgesic effect of codeine/acetaminophen/ibuprofen has not been reported. Therefore, the purpose of this study was to compare the time to onset of analgesia and other measures of analgesic efficacy with tramadol/acetaminophen 75/650 mg (Tr/Ac) and codeine/acetaminophen/ibuprofen 20/500/400 mg (Co/Ac/Ib) in the treatment of acute pain after oral surgery. The surgical extraction of impacted mandibular third molars, a common oral surgical procedure, induces acute moderate to severe pain and has been used as a model for the effectiveness of analgesic agents by numerous investigators.[2,12,13,18]

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

Healthy men and women aged ≥16 years with moderate or severe pain (score ≥5 on a 10-point scale with 0 signifying no pain) resulting from oral surgery involving bilateral extraction of >2 third molars, one of which was at least a partial bony mandibular impaction requiring bone removal, were eligible for participation. Bone removal was considered necessary to ensure adequate postoperative pain intensity. The procedure involved 1 day of hospitalization. Women of childbearing potential had to have a negative urine pregnancy test result on the day of receiving study medication. All patients had to be sufficiently alert to understand and communicate with the study observer and be able to carry out the study procedures.

Patients were excluded if they had received or used another experimental drug or medical device within 30 days before screening; had received any analgesic medication other than short-acting preoperative or intraoperative anesthetic agents within 12 hours before receiving study medication; had taken any long-acting NSAID within 3 days before receipt of study medication; received any other analgesic medication after completion of oral surgery; had a history of seizure; had a history of drug and/or alcohol abuse within the past 6 months; had taken monoamine oxidase inhibitors, tricyclic antidepressants, neuroleptics, or other drugs that reduce the seizure threshold within 4 weeks of study participation; had renal or hepatic dysfunction; were sensitive or allergic to tramadol, acetaminophen, codeine, ibuprofen, or other NSAIDs or aspirin; had peptic ulcer disease; had taken any selective serotonin reuptake inhibitors, diet pills, or methylphenidate within 4 weeks of study participation; or were at risk based on the

precautions, warnings, and contraindications in the package inserts for Tr/Ac[22] and Co/Ac/Ib.[19]

Before patients entered the study, the investigators obtained a medical history and performed a screening physical examination. After being informed of the nature of the study, all patients or the legal representatives of children aged <18 years signed a written informed consent form that had been approved by the institutional review board.

Study Design

This was a single-center, single-dose, randomized, active-controlled, parallel-group study. Patients undergoing >1 surgical extraction of an impacted third molar requiring bone removal were enrolled over 6 months at the Department of Oral and Maxillofacial Surgery, Dental College Hospital, Yonsei University, Seoul, Korea. The surgery was performed under local anesthesia with 2% lidocaine. The surgeon rated the surgical trauma as mild, moderate, or severe.

When patients reported moderate or severe pain after oral surgery, they were assigned to 1 of 2 treatment groups based on a randomization code. Single oral doses of the assigned study drugs were packaged in identical containers containing either Tr/Ac or Co/Ac/Ib and administered to each patient. The 2 products were not physically identical.

The study coordinator instructed patients in the use of the stopwatches and assessment scales. During the 6 hours after administration of study medication, the study coordinator recorded patients' assessments on case-report forms in the day-hospitalization ward. If the response to study drug was inadequate or there was no analgesic response, supplemental analgesia was available in the form of mefenamic acid 500 mg.

Outcome Measures

The time to onset of analgesia was measured using a 2-stopwatch technique. Two stopwatches were activated when the study drug was administered. At the onset of perceptible pain relief, the patient stopped the first watch. At the onset of meaningful pain relief, the patient stopped the second watch. The study coordinator recorded the elapsed times shown on the watches on patient's charts and case-report forms.

Additional measures of analgesic efficacy included pain intensity, pain relief, use of supplemental analgesic medication, and the patient's overall assessment. When the patient complained of moderate or severe pain (time zero), the baseline pain intensity score was recorded on the 10-point pain scale. The patient subsequently assessed his or her current pain using the same scale and pain relief from baseline at 30 minutes and 1, 2, 3, 4, 5, and 6 hours after receiving study medication. A 6-hour assessment period was used because of the dosing instructions for Tr/Ac[22] (2 tablets q4–6 h) and Co/Ac/Ib[19] (1 or 2 capsules q4h). Pain relief was rated on a 5-point scale (0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete). At the end of the observation period or at withdrawal from the study, patients completed an overall assessment of study medication using a 5-point scale (1 = excellent, 2 = very good, 3= good, 4 = fair, 5 = poor).

When patients took supplemental analgesic medication, they were discontinued from the study, and the study coordinator recorded the time, dose of rescue medication, and all other efficacy assessments at the time of withdrawal.

Further efficacy assessments included total pain relief (TOTPAR), derived from the sum of recorded pain relief scores; pain intensity difference (PID), calculated by subtracting each recorded pain intensity score from the baseline pain intensity score; and sum of pain intensity difference (SPID), computed by adding the calculated PID scores.

The safety profiles of the study treatments were assessed based on AEs reported by patients during the observation period. An AE was defined as any unfavorable and unintended sign, symptom, or disease temporarily associated with the use of an investigational product. Such surgical consequences as dry sockets, surface ostitis, ecchymosis, edema, infection, and paresthesia were not recorded as AEs, because these consequences do not appear in the immediate postoperative period. Blinded study investigators judged and recorded the relationship between the study therapies and the reported AEs.

Statistical Analysis

The study was designed to include 128 qualified patients randomly assigned to 1 of 2 treatment groups. The comparability of the demographic and baseline characteristics of the 2 treatment groups was tested using the chi-square test or Fisher exact test for categorical variables (eg, sex) and the t test for continuous variables (eg, age).

Efficacy analyses were performed using last-observation-carried-forward methodology. Time to the onset of perceptible pain relief and time to the onset of meaningful pain relief were summarized using medians (95% CIs) and means (SDs) and assessed using the Wilcoxon rank sum test and the t test. Kaplan-Meier curves were generated for the rates of pain relief and meaningful pain relief in each group and compared using the log-rank test. Mean TOTPAR and SPID scores were computed for the intervals from 0 to 2 hours, 2 to 4 hours, and 4 to 6 hours. Between-group differences were tested using the Wilcoxon rank sum test.

For the safety-profile analysis, only those signs and symptoms that emerged during the study were summarized for the 2 groups. Between-group differences in the incidence of drug-related AEs were assessed using the Fisher exact test.

RESULTS

Demographic and Baseline Characteristics

Table I.Demographic characteristics and baseline pain intensity.

Characteristic	Tr/Ac (n = 64)	Co/Ac/Ib (n = 64)
Sex		
Female	37	39
Male	27	25
Age, y		
Mean	23.4	23.7
Range	16–40	17–37
Body weight, kg		
Mean	58.5	60.3
Range	30–98	44–100
Height, cm		
Mean	166.8	167.3
Range	150–188	155–187
Baseline pain score*		
5	28	28
6	19	27
7	11	6
8	6	3
Mean (SD)	5.92 (1.00)	5.75 (0.82)

Tr/Ac = tramadol/acetaminophen 75/650 mg; Co/Ac/Ib = codeine/acetaminophen/ibuprofen 20/500/400 mg.

[*]10-point rating scale.

One hundred and twenty-eight patients were enrolled in the trial and randomized equally to the 2 treatment groups. All patients were Asian Koreans, and were similar in terms of sex, age, body weight, height, and surgical characteristics (**Tables I and II**). Mean (SD) baseline pain scores were 5.92 (1.00) in the Tr/Ac group and 5.75 (0.82) in the Co/Ac/Ib group. Bilateral extraction of mandibular third molars, not including a maxillary tooth, was the most common type of oral surgery in this trial (**Table II**). The surgical trauma rating was mainly moderate (46.8% Tr/Ac, 50.0% Co/Ac/Ib).

Two patients in the Tr/Ac group took supplemental analgesia within the 6-hour observation period and were withdrawn from the study at the time of receiving supplemental medication. Another 2 patients in the same group reported perceptible pain relief but did not experience meaningful pain relief. Last-observation-carried-forward methodology was used in these 4 patients.

Times to Onset of Pain Relief

Table III summarizes the median and mean times to the onset of perceptible and meaningful pain relief. The median times to the onset of perceptible pain relief were 21.0 minutes (95% CI, 17.1–25.0) in the Tr/Ac group and 24.4 minutes (95% CI, 21.0–27.7) in the Co/Ac/Ib group. The median times to the onset of meaningful pain relief were a respective 56.4 minutes (95% CI, 48.7–64.1) and 57.3 minutes (95% CI, 51.5–63.0). The differences between groups were not statistically significant (**Figures 1 and 2**). The mean

(SD) times to the onset of perceptible pain relief were 26.9 (16.1) minutes in the Tr/Ac group and 25.0 (13.7) minutes in the Co/Ac/Ib group. The corresponding mean times to the onset of meaningful pain relief were 66.3 (31.3) and 57.0 (23.6) minutes. Again, the differences between groups were not statistically significant.

Table II.   **Surgical characteristics.**

	Tr/Ac (n = 64)	Co/Ac/Ib (n = 64)
No. (%) of teeth extracted		
2*	37 (57.8)	36 (56.3)
3	13 (20.3)	7 (10.9)
4	14 (21.9)	21 (32.8)
No. (%) of bony extractions		
1	3 (5.7)	0
2	59 (92.2)	58 (90.6)
3	2 (3.1)	4 (6.3)
4	0	2 (3.1)
Surgical trauma rating, no. (%) of patients		
Mild	17 (26.6)	14 (21.9)
Moderate	30 (46.8)	32 (50.0)
Severe	17 (26.6)	18 (28.1)

*Bilateral extraction of mandibular third molars.

Table III.   **Summary of median and mean times to the onset of perceptible and meaningful pain relief.**

	Tr/Ac (n = 64)	Co/Ac/Ib (n = 64)
Onset of perceptible pain relief, min		
Median (95% CI)	21.0 (17.1–25.0)	24.4 (21.0–27.7)
Mean (SD)	26.9 (16.1)	25.0 (13.7)
Onset of meaningful pain relief, min		
Median (95% CI)	56.4 (48.7–64.1)	57.3 (51.5–63.0)
Mean (SD)	66.3 (31.3)	57.0 (23.6)

Figure 1.   **Kaplan-Meier curve for the cumulative probability of attaining onset of perceptible pain relief in the tramadol/acetaminophen (Tr/Ac) and codeine/acetaminophen/ibuprofen (Co/Ac/Ib) groups.**
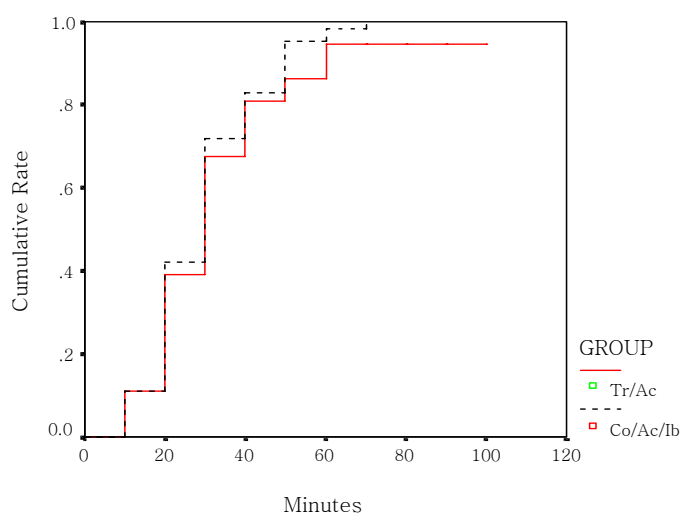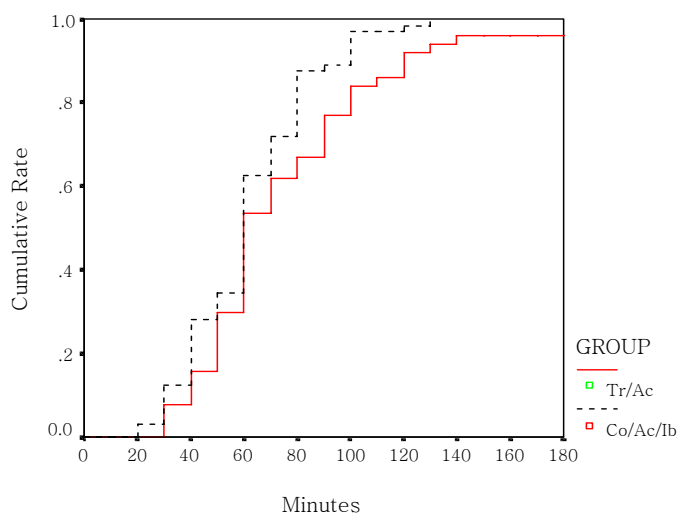
Figure 2. **Kaplan-Meier curve for the cumulative probability of attaining onset of meaningful pain relief in the tramadol/acetaminophen (Tr/Ac) and codeine/acetaminophen/ibuprofen (Co/Ac/Ib) groups.**


Other Efficacy Analyses

The time-effect curve for PID during the 6-hour observation period is shown in **Figure 3**. From 0.5 to 4 hours, the 2 drugs had similar effects. However, at the 5- and 6-hour assessments, PID was significantly greater with Co/Ac/Ib compared with Tr/Ac ($P < 0.05$).

For TOTPAR and SPID, the differences between the 2 groups were not significant during the first 2 time intervals (0–2 and 2–4 hours). However, during the last interval (4–6 hours), both values were significantly greater with Co/Ac/Ib compared with Tr/Ac ($P < 0.05$). Mean (SD) peak PID values were 4.4 (1.18) and 4.8 (0.9) in the Tr/Ac and Co/Ac/Ib groups, respectively, a nonsignificant difference. Peak pain relief values were almost identical in the 2 groups (**Table IV**).

In the Tr/Ac group, 90.6% of patients gave an overall assessment of their assigned treatment as *good* or better*,* whereas 100% of the Co/Ac/Ib group gave such an assessment ($P < 0.05$) (**Figure 4**).

Figure 3. **Time-effect curves for mean hourly pain intensity difference (PID) in the tramadol/acetaminophen (Tr/Ac) and codeine/acetaminophen/ibuprofen (Co/Ac/Ib) groups. *$P < 0.05$, Wilcoxon rank sum test.**
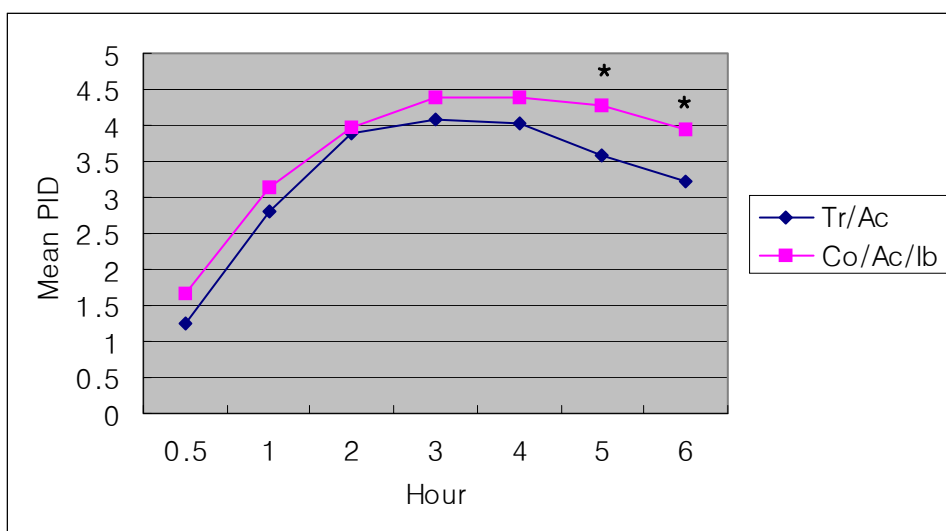

Safety Profile

Two of 64 patients (3.1%) who received Tr/Ac reported AEs (dizziness and nausea). One of these patients reported both AEs simultaneously. In the investigator's judgment, a correlation between the nausea and study medication was unlikely. The Co/Ac/Ib group reported no AEs. No severe AEs occurred in either group during this study.

Table IV. Total pain relief (TOTPAR), sum of pain intensity difference (SPID), peak pain relief (PR), and peak pain intensity difference (PID). Values are mean (SD).

Measure/Time Point	Tr/Ac (n = 64)	Co/Ac/Ib (n = 64)
TOTPAR		
0–2 Hours	6.4 (1.84)	6.9 (1.48)
2–4 Hours	5.8 (0.74)	6.1 (0.60)
4–6 Hours	5.0 (1.28)[*]	5.7 (0.77)[*]
SPID		
0–2 Hours	7.9 (2.98)	8.8 (2.79)
2–4 Hours	8.1 (2.27)	8.8 (1.92)
4–6 Hours	6.8 (2.68)[*]	8.2 (2.11)[*]
Peak PR	3.1 (0.37)	3.1 (0.33)
Peak PID	4.4 (1.18)	4.8 (0.9)

[*]$P < 0.05$, Wilcoxon rank sum test.

Figure 4. **Patients' overall assessment of study medication. The proportion of patients assessing treatment as *good* or better was significantly greater in the codeine/acetaminophen/ibuprofen group compared with the tramadol/acetaminophen group (100% vs 90.6%, respectively; *P* < 0.05, Fisher exact test).**
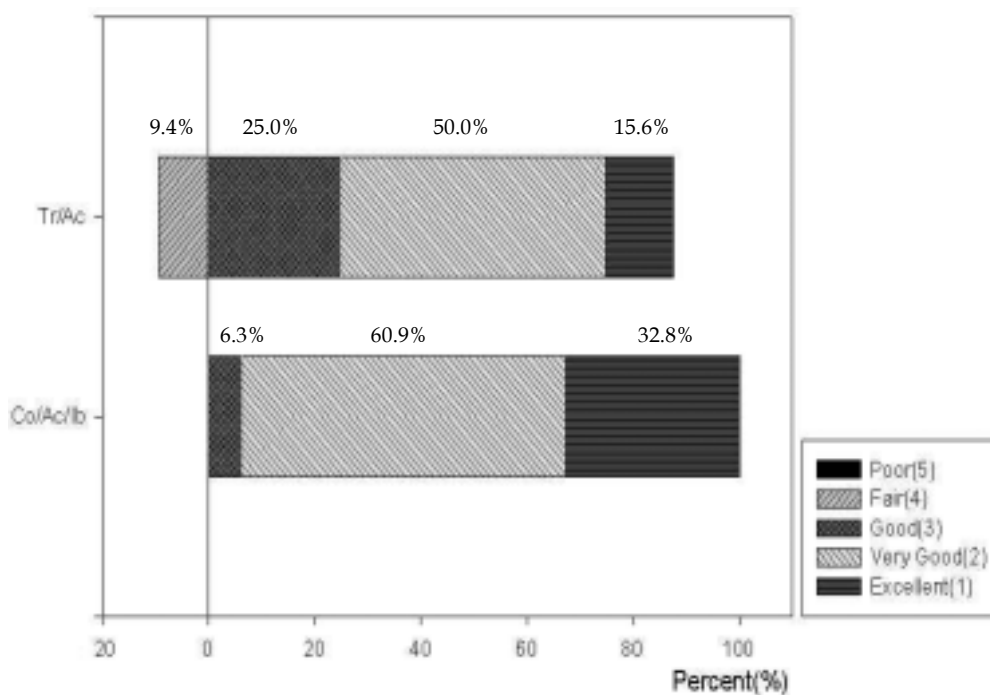
DISCUSSION

This study found no difference in the median time to the onset of perceptible pain relief between groups. The 21-minute median time to the onset of perceptible pain relief with Tr/Ac was shorter than the 34 minutes reported by Fricke et al,[12] who used the same dose of Tr/Ac in the dental pain model, and slightly longer than the 17 minutes reported by Medve et al,[11] who also reported much longer times to the onset of perceptible pain relief with ibuprofen (34 minutes) and tramadol alone (51 minutes) and a similar time of onset with acetaminophen alone (18 minutes).[11] That study and another by Moller et al[20] demonstrated that acetaminophen had a rapid onset of action. In our study, in which acetaminophen was a component in both study treatments, the times to the onset of meaningful pain relief were similar between groups.

Given a rapid onset of analgesia, other efficacy variables help characterize the early effects of a drug in the period after drug administration.[20,21] In the present study, TOTPAR, PID, and SPID values were similar between groups in the early period after administration (0–4 hours), a finding that was consistent with the onset of pain relief. Peak pain relief and peak PID were also similar in the 2 groups. However, between 4 and 6 hours after drug administration, TOTPAR and SPID values were significantly greater for Co/Ac/Ib compared with Tr/Ac ($P < 0.05$). Similarly, although there were no statistical differences in PID values until the 4-hour assessment, Co/Ac/Ib became significantly superior to Tr/Ac at the 5- and 6-hour assessment ($P < 0.05$).

The anti-inflammatory action of the ibuprofen component of Co/Ac/Ib was thought to be the reason for the latter results. Many factors in the pain that develops after surgical extraction of impacted third molars relate to the peripheral inflammatory reaction initiated by surgical trauma. Therefore, NSAIDs such as ibuprofen and ketorolac have

been reported to be effective for postoperative pain.[23–25] A 6-hour assessment was used in the present study because of the recommended dosing of the 2 drugs[19,22]; other studies of the onset of analgesia have used similar observation periods (4^{20} and 6^{21} hours). Thus, the significant between-group differences in TOTPAR and SPID from 4 to 6 hours should not be the effect of the short assessment period.

Use of Tr/Ac has been associated with dizziness, headache, nausea, vomiting, somnolence, and constipation,[11–16,24] with dizziness and nausea being the most commonly reported AEs (up to 20% and 23% of patients, respectively).[11–16] In the present study, only 2 patients (3.1%) in the Tr/Ac group reported dizziness and nausea, an extremely low incidence compared with previous reports.[11–16,24] Although a potential for seizures is known to be associated with tramadol, no severe AEs occurred during this study. Tramadol has a favorable safety profile compared with traditional opioids, and acetaminophen is useful in cases in which NSAIDs are contraindicated (eg, peptic or gastric ulcer).[1,26] Therefore, Tr/Ac may offer good efficacy with a good safety profile relative to the combination of Co/Ac/Ib, which includes a traditional opioid and an NSAID.

CONCLUSIONS

In this study, the times to the onset of perceptible and meaningful relief of acute dental pain did not differ significantly between Tr/Ac and Co/Ac/Ib. TOTPAR, SPID, and PID were similar between treatments in the early observation period (0–4 hours), although the difference in TOTPAR and SPID favored Co/Ac/Ib from 4 to 6 hours after administration, and the mean PID was significantly greater with Co/Ac/Ib at 5 and 6 hours. Both treatments were well tolerated in the population studied. Although the inclusion criteria limit extrapolation of the findings of this study to the general population or to other pain models in which bone pain is not present, the results in this population suggest that Tr/Ac provides rapid and effective analgesia in the management of acute postoperative pain.

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ABSTRACT in Korean

수술후 급성 동통에 대한
Tramadol/Acetaminophen 과
Codeine/Acetaminophen/Ibuprofen 의
효과 발현시점과 진통효과의 비교

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연구배경: tramadol 과 acetaminophen 복합제제는 다양한 통증 임상 시험에서 좋은 효과를 보여왔지만 급성 통증 상태에서 이 복합제제와 강력한 진통제라고 알려진 다른 진통제의 효과 발현 시점과 진통효과를 비교하는 것이 필요하다고 생각되었다.

연구목적: 본 연구의 목적은 구강 수술후 급성 동통의 치료에서 75 ㎎ tramadol/650 ㎎ acetaminophen (Tr/Ac) 복합제제와 20 ㎎ codeine/500 ㎎ acetaminophen/400 ㎎ ibuprofen (Co/Ac/Ib) 복합제제의 효과발현 시점과 다른 진통효과를 비교하고자 하였다.

연구방법: 이 연구는 무작위, 1 회 투여, 평행그룹 디자인으로, 단일 센터에서 실시한 비교 임상시험이었으며, 골삭제를 필요로 하는 하나 이상의 하악 매복 제3 대구치 외과적 발거 수술을 시행 받는 건강한 환자들을 대상으로 하였다. 구강 수술 후 피험자가 중등도 또는 심도의 통증을 호소하였을 때(통증 평가를 위한 10 단계 순위에서 5 점 이상), 각 피험자는 무작위 배정 방법에 따라 두 군 중의 한 군에 할당되었다. 시험 약 투여 후 6 시간 동안 지각할 수 있는 통증 완화시점과 의미있는 통증완화시점은 2 개의 stopwatch 방법을 이용하여 측정하였고, 그 외 통증 강도, 통증 완화 정도, 전반적 평가, 이상 반응 등을 기록하였다.

연구결과: 128 명의 한국인 환자가 이 시험에 등록되어 같은 수(64 명씩)로 두 군에 무작위로 할당되었는데, 성별, 나이, 체중, 신장 같은 인구통계학적 기초 자료뿐만 아니라 두 군의 수술 특징도 서로 유사하였다. 지각할 수 있는 통증 완화시점의 중간값(median)은 Tr/Ac 군과 Co/Ac/Ib 군이 각각 21.0 분과 24.4 분이었고, 의미있는 통증완화시점의 중간값(median)은 56.4 분과 57.3 분이었으며, 이들은 통계적으로 유사하였다. 전체 통증 완화정도(TOTPAR)와 최초 통증에 대한 통증 강도 차이의 합(SPID) 같은 다른 효과 변수들은 처음 2 번의 시간 구간 동안(0-2 시간과 2-4 시간)에선 두 군간의 차이가 유의하지 않았지만 마지막 시간 구간인 4-6 시간에선 통계적으로 유의 있는 차이가 발견되었다($P < 0.05$). 시간별 통증강도차이(PID)도 0.5 에서 4 시간까지 두 약제는 비슷한 효과를 보였으나, 5 시간과 6 시간째 측정치에서 Co/Ac/Ib 군이 더 좋았다. 환자의 전반적인

평가에서 "좋음" 이상으로 평가한 것도 Co/Ac/Ib 군이 Tr/Ac 군보다 유의있게 많았다. Tr/Ac 의 안정성은 Co/Ac/Ib 과 통계적으로 유사하였다.

결론: 이번 구강 수술 후 급성 통증의 치료에서 Tr/Ac 의 통증완화시점이 Co/Ac/Ib 의 통증완화시점과 차이가 없었으며 다른 진통 효과 변수들도 약물 투여 후 조기에는 유사하였다. 따라서 Tr/Ac 은 수술 후 급성 통증의 빠르고 효과적인 치료를 위해 추천할 만 하다고 사료되었다.

핵심되는 단어: 통증완화시점, 진통제 복합제제, 진통 효과, tramadol/acetaminophen, 수술후 통증