Regional Anesthesia and Pain

Effects of nabilone, a synthetic cannabinoid, on postoperative pain

[Les effets de la nabilone, un cannabinoïde synthétique, sur la douleur postopératoire]

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Purpose: Cannabinoids have been shown to have analgesic properties in animal studies, but a potential role for these drugs in acute pain management has not been established. It was hypothesized that nabilone, an oral cannabinoid synthetic tetrahydrocannabinol analogue, decreases morphine consumption, pain scores, nausea and vomiting following major surgery.

Methods: A double-blind, randomized, placebo-controlled, parallel-group pilot trial compared the effects of two different doses, 1 mg ($n = 11$) and 2 mg ($n = 9$) of nabilone, ketoprofen 50 mg ($n = 11$) or placebo ($n = 10$), given at eight-hour intervals for 24 hr. Outcomes included morphine consumption, pain scores and emesis after major surgery. Secondary outcomes included patient tolerability of the study medication.

Results: Forty-one patients (mean age 52 ± 2 yr) undergoing gynecologic (46%), orthopedic (44%), or other (10%) surgery were recruited. Cumulative 24-hr morphine consumption was not different between the four groups, but pain scores at rest and on movement were significantly higher in the 2 mg nabilone group compared to the other groups. There were no significant differences between groups with respect to episodes of nausea and vomiting, quality of sleep, sedation, euphoria, pruritus, or the number and severity of adverse events. No serious adverse event was recorded.

Conclusions: Contrary to the main hypothesis, high dose nabilone in the presence of morphine patient controlled analgesia is associated with an increase in pain scores in patients undergoing major surgery.

Objectif *: Les propriétés analgésiques des cannabinoïdes ont été démontrées chez des animaux, mais leur rôle possible sur le contrôle de la douleur aiguë n'a pas été établi. Notre hypothèse voulait que la nabilone, analogue synthétique oral du cannabinoïde tétrahydrocannabinol, diminue la consommation de morphine, les scores de douleur, les nausées et les vomissements à la suite d'une opération chirurgicale majeure.*

Méthode *: Dans une étude pilote de groupes parallèles, randomisée, à double insu et contrôlée contre placebo, les effets de deux doses de nabilone, 1 mg ($n = 11$) et 2 mg ($n = 9$), de 50 mg de kétoprofène ($n = 11$) ou d'un placebo ($n = 10$), administrés à 8 h d'intervalle pendant 24 h, ont été comparés. La consommation de morphine, les scores de douleur et les vomissements ont été notés après une chirurgie majeure. Les effets de la médication sur le patient étaient également étudiés.*

Résultats *: Quarante et un patients (moyenne d'âge de 52 ± 2 ans) subissant une intervention gynécologique (46 %), orthopédique (44 %) ou autre (10 %) ont été recrutés. La consommation cumulative de morphine sur 24 h était similaire dans les quatre groupes, mais les scores de douleur au repos et au mouvement ont été significativement plus élevés dans le groupe nabilone 2 mg. Aucune différence intergroupe significative n'est apparue quant aux épisodes de nausées et de vomissements, la qualité du sommeil, la sédation, l'euphorie, le prurit ou le nombre et la sévérité des événements indésirables. Aucun incident sérieux n'a été enregistré.*

Conclusion *: Contrairement à notre hypothèse, une forte dose de nabilone, en présence de morphine administrée comme analgésie auto-contrôlée, est associée à une hausse des scores de douleur chez les patients qui subissent une chirurgie majeure.*

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CANNABINOID compounds have potent analgesic effects and have been found active in animal models of pain.[1] However, the use of cannabis or cannabinoids in the treatment of acute pain in humans has not been as widely reported.[2] A previous clinical trial examined the acute postoperative analgesic effects of cannabinoids using *im* levonantradol,[3] a synthetic analogue of Δ^9-tetrahydrocannabinol (Δ^9-THC), the main psychoactive constituent of cannabis.[4] Since 1990, only three other clinical studies have evaluated the effects of cannabinoids in acute pain, two with human volunteers[5,6] and one in postsurgical patients.[7] The results of these trials were disappointing, as cannabinoids were no more effective than placebo in relieving pain. However, in all three trials, cannabinoids were administered as a single low dose, and failure to demonstrate efficacy may have reflected inadequate dose-response evaluation.

Postoperative nausea and vomiting is a frequent consequence of anesthesia and surgery, and remains a major concern of surgical patients.[8] Cannabinoids, and in particular Δ^9-THC, do not seem to have a role in moderating anesthetic-induced emesis,[9] although sublingually administered Δ^9-THC has been found to be effective in treating intractable postoperative nausea (Taylor E., personal communication, 1991, cited by Watcha and White, 1992). Furthermore, these drugs have been used with some success in the management of chemotherapy-induced emesis refractory to conventional treatment modalities.[10] Accordingly, the combination of anti-emetic and analgesic properties makes cannabinoids an attractive consideration for the postoperative period.

It is obvious that inhaled cannabis would not be a suitable method of drug delivery for the management of postoperative pain. In Canada, only two oral cannabinoids, synthetic analogues to THC, are available for the treatment of nausea and vomiting: nabilone and dronabinol. Nabilone was selected for evaluation.

The primary goal of this clinical trial was to assess the efficacy of an oral synthetic cannabinoid on acute postoperative pain following major surgery. The secondary objectives were to evaluate the anti-emetic properties of nabilone and to address the question of patient tolerability of the study medication. The main hypothesis of this study was that nabilone decreases morphine consumption, pain scores, nausea and vomiting following major surgery, compared to a non-steroidal anti-inflammatory drug or placebo.

Methods

This was a double-blind, randomized, placebo-controlled, parallel-group trial comparing the effects of two different doses of nabilone, ketoprofen as an "active control", or placebo. The primary outcome was cumulative (24 hr) morphine consumption via morphine patient-controlled analgesia (PCA). Secondary outcomes consisted of the following: pain intensities at rest and on movement; anti-emetic properties of nabilone; assessment of mood and euphoria; quality of sleep and incidence of side effects such as sedation and psychotic episodes.

Written informed consent was obtained from patients who agreed to take part in the study. This study was conducted according to the Declaration of Helsinki and to the Good Clinical Practice for Trials on Medicinal Products. The protocol was reviewed and approved by the Hôtel-Dieu Hospital (CHUM) Ethics Committee. The Therapeutic Products Directorate of Health Canada also gave full approval to this study (27/10/03; control number 086968).

Inclusion criteria were patients of the American Society of Anesthesiologists I, II or III; aged 18 to 75 yr, and scheduled for major surgery, using a PCA device postoperatively. Furthermore, a urine test for the detection of Δ^9-THC was performed on the day of the operation to ensure that patients had not been recently under the influence of cannabis. Excluded were patients using cannabis or subject to other substance abuse; alcoholics; patients where morphine was not the drug of choice for PCA; and patients with planned concomitant medication during the study with any of the following: non-steroidal anti-inflammatory drugs, acetaminophen, more than 300 mg acetylsalicylic acid per day, sedatives, anticonvulsants or antidepressants. Finally, patients with ischemic heart disease, cardiac arrhythmia or cardiac failure, patients with a history of gastric or duodenal ulcers, renal insufficiency or asthma, and patients with chronic pain conditions and/or receiving chronic opioid therapy, patients with a history of psychiatric illness and pregnant or lactating women were also excluded.

Randomization

Patients fulfilling all inclusion criteria were assigned a consecutive patient number which randomly assigned each patient to one of the following treatment groups: nabilone 1 mg (one capsule of 1 mg and one capsule of placebo); nabilone 2 mg (two capsules of 1 mg); ketoprofen 50 mg (one capsule of 50 mg and one capsule of placebo); placebo, (two capsules of placebo).

Nabilone (Cesamet®) was provided by Valeant Pharmaceuticals (Montréal, QC, Canada). The study pharmacist was responsible for the receipt, storage, inventory and dispensing of nabilone and maintained all accountability records as required for Schedule

1 narcotics. Nabilone, ketoprofen or placebo were administered one hour before induction of anesthesia with a sip of water, and thereafter every eight hours for 24 hr. Thus, a total of three doses were administered per patient. The two capsules administered to the patients were identically-appearing capsules given to ward nurses with patients' name and time of administration written on it. Ward and research nurses were therefore completely blinded to the study medication delivered to the patients.

Protocol

Standardized general anesthesia for all patients was administered to allow comparisons between patients undergoing different kinds of surgery. Anesthesia was induced with fentanyl (2 $\mu g \cdot kg^{-1}$), propofol and rocuronium followed by the insertion of an endotracheal tube. Anesthesia was maintained with sevoflurane 0.7 to 2% and 60% air in oxygen and the patient's lungs were mechanically ventilated. Hemodynamic goals were to maintain mean arterial pressure and heart rate within 70 to 130% of pre-induction or baseline levels. Mean arterial pressure increase to > 130% of baseline was treated by raising end-tidal sevoflurane to 2 vol% and administering boluses of fentanyl, 1 $\mu g \cdot kg^{-1}$ as needed. Incisional infiltration with local anesthetics or any regional anesthetic technique was prohibited in order to avoid a bias of unevenly applied local anesthetics across study treatment groups.

In the recovery room and before starting the PCA, morphine 3 mg *iv* boluses, separated by five minutes each, were given by a postanesthesia care unit nurse to achieve adequate analgesia: i.e., a pain score ≤ 3 on a numerical verbal scale from 0 to 10, 0 being "no pain" and 10 "intolerable pain". Thereafter, all patients were given a PCA set to deliver morphine 1 mg *iv* boluses *prn*, with a lockout interval of six minutes. The amount of morphine used as loading dose and thereafter, the hourly amount of morphine used were recorded, as well as the total amount of morphine given since the start of the PCA and up to 24 hr.

Patients were asked to grade their degree of pain using a numerical verbal scale. Pain scores were measured at regular intervals thereafter (18 evaluations in 24 hr). For all assessments, pain scores were evaluated when the patient was at rest and also on movement (specific to each surgery). If the patient was found asleep (especially at night) pain scores were not assessed so as to preserve patient comfort. In that case, the last recorded data was used.

Postoperative nausea and vomiting were measured and recorded every 30 min for the first two hours, then hourly for the next three hours and at two-hourly intervals for the next 18 hr. Nausea and vomiting were assessed using a four-point cardinal scale: 0 = no nausea or vomiting; 1 = some nausea without vomiting; 2 = severe nausea without vomiting; 3 = active vomiting ± nausea.

TABLE I Causes of exclusion criteria in 175 patients approached for the study (%)

Age > 75 yr	25.7
Cardiac problems	16.6
French not mother tongue	10.8
Treatment not compatible	6.9
Contraindication to NSAIDs	6.3
Psychiatric problems	5.7
Recruited in different protocol	4.0
Respiratory problems	3.4
Gastric problem	2.9
Anesthesia contraindication	2.3
Consumption of cannabis	1.1
Other	14.3

NSAIDs = non-steroidal anti-inflammatory drugs.

At the time of each pain assessment, the research nurse evaluated the patient's level of sedation on a four-point ordinal scale (fully awake, mildly sedated, heavily sedated, asleep). Furthermore, mood and euphoria were assessed using ten-point analogue scales.[11] Following the night's rest after the day of surgery, patients were asked to grade their quality of sleep during the previous night on a five-point ordinal scale (excellent, good, minor discomfort, major discomfort, hardly slept at all). Heart rate, respiratory rate, non-invasive blood pressure, oxygen saturation were also recorded continuously preoperatively and in the recovery room, and then on the ward each time a patient's pain scores were recorded. Finally, pruritus was monitored using a four-point ordinal scale (none, mild, moderate and severe).

A data and safety monitoring board was established, its principal mandate being to review adverse event reports, but also with the responsibility of reviewing dropouts, monitoring data collection, and protocol violations.

Statistical analysis

The primary outcome variable was the use of morphine PCA after 24 hr of treatment. It has been shown that a reduction in morphine requirements of approximately 30% would be clinically significant.[12–14] Based upon results of previous studies with comparable designs, a standard deviation of 20 mg in the placebo group was predicted.[14] A mean cumulative morphine

TABLE II Demographic data

Group	*Placebo*	*Ketoprofen*	*Nabilone 1 mg*	*Nabilone 2 mg*
n	10	11	11	9
Age (yr)	60 ± 4	44 ± 3	53 ± 2	53 ± 4
Sex (F/M)	6/4	10/1	9/2	8/1
Height (cm)	162 ± 3	160 ± 3	159 ± 2	162 ± 2
Weight (kg)	83 ± 7	67 ± 5	68 ± 4	83 ± 7
ASA 1 (n)	2	4	4	3
2 (n)	5	7	7	6
3 (n)	3	0	0	0

F = female; M = male; ASA = American Society of Anesthesiologists.

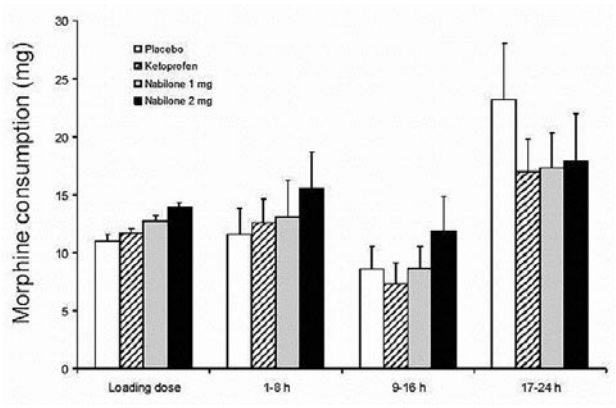

FIGURE 1 Morphine consumption (in mg) is displayed for the four groups of patients. Loading dose refers to the quantity of morphine administered to patients in the recovery room after surgery before starting the patient-controlled analgesia (PCA). Morphine consumption is separated into three periods of eight hours each from start of PCA administration until 24 hr later.

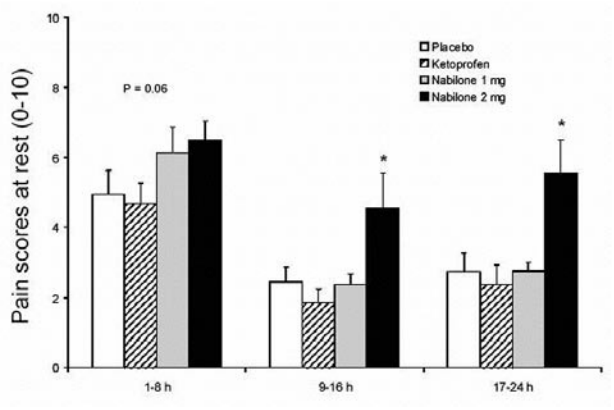

FIGURE 2 Pain at rest measured on a 0 to 10 numerical verbal scale for the four groups of patients, and separated into three periods of eight hours each from start of PCA administration until 24 hr later. *Different from the other three groups, $P < 0.05$.

requirement of 60 mg in the placebo group, and 42 mg in the active treatment group was assumed. With a significance level of 5%, a power of 80%, the number of groups being four, a clinically relevant difference of 30% and a standard deviation of 20 mg, this yielded a sample size estimate of 19 patients per treatment group (one-way ANOVA with an effect size of 0.39). The randomization list (random blocks) was generated by a computer program which assigned each patient a number in one of the four different treatment groups.

A significance level of 5% was used for all statistical tests. Sums of pain intensities of the pain scores were calculated. In case of a missing value, this was replaced by the last previous valid value ("last value carried forward option"). The sum of pain intensities and the amounts of morphine administered during each interval were compared separately between treatment groups for each time point or interval, respectively, using conventional analysis of variance (ANOVA) with post hoc Tukey tests for multiple testing to limit the overall significance level to 5%.

The levels of nausea and vomiting, sedation, quality of sleep, and the severity of adverse events possibly, probably or highly probably related to the study medication were compared using the non-parametric Kruskal-Wallis analysis to test if there was a difference between treatment groups; this was followed by a Mann-Whitney test with Bonferroni correction for multiple comparisons. The data and safety monitoring board recommended an interim analysis after every 50 patients enrolled. Statistical analysis was performed using SAS version 8.2 (Cary, NC, USA).

Results

For several reasons discussed later, this study was discontinued after 18 months (November 2003 to April 2005) following recruitment of 41 patients divided into nabilone 1 mg ($n = 11$) and 2 mg ($n = 9$), ketoprofen ($n = 11$) and placebo ($n = 10$) groups. From the 277 patients who were screened, 175 (63.2%) had exclusion criteria (Table I). Of the 102 remaining patients, 41 (40.2%) were included in the present

TABLE III Perioperative data and postoperative pain scores

Group	*Placebo*	*Ketoprofen*	*Nabilone 1 mg*	*Nabilone 2 mg*
Duration of surgery (min)	101 ± 9	107 ± 11	97 ± 11	94 ± 11
Type of surgery (n)				
Orthopedic (hip or knee arthroplasty)	5	2	5	6
Gynecology (hysterectomy or myotomy)	3	8	5	3
Urology	1	0	1	0
Plastic	0	1	0	0
General	1	0	0	0
Total fentanyl used peroperatively (μg)	335 ± 28	280 ± 55	288 ± 29	332 ± 44.4
Total morphine used via PCA (mg)	43.3 ± 8.2	36.9 ± 5.9	39.0 ± 6.8	45.4 ± 8.1
Pain at rest (24 hr) (score 0–10)	3.8 ± 0.6	3.4 ± 0.3	4.4 ± 0.3	5.9 ± 0.6*
Pain on movement (24 hr) (score 0–10)	5.9 ± 0.5	5.6 ± 0.3	6.3 ± 0.5	7.7 ± 0.5*

PCA = patient controlled analgesia. *Different from the other three groups, $P < 0.05$.

TABLE IV Secondary outcomes (number of patients, unless stated differently; % in brackets)

Group	*Placebo (n = 10)*	*Ketoprofen (n = 11)*	*Nabilone 1 mg (n = 11)*	*Nabilone 2 mg (n = 9)*
No nausea	3 (30)	2 (18.2)	4 (36.4)	3 (33.3)
Some nausea	4 (40)	2 (18.2)	3 (27.3)	2 (22.2)
Severe nausea	2 (20)	2 (18.2)	1 (9.1)	1 (11.1)
Active vomiting	1 (10)	5 (45.5)	3 (27.3)	3 (33.3)
Quality of sleep (on a scale 0–10)	6.9 ± 0.7	6.2 ± 0.3	7 ± 0.7	5.6 ± 1.2
Severity of adverse events				
Mild	0	2	1	0
Moderate	5	7	8	5
Severe	2	2	2	3

study, 29 (28.4%) refused to take part, and 32 (31.4%) were missed for various reasons (mainly those surgeries scheduled at 08:00 hr for which there was insufficient time to properly obtain informed consent).

Demographic data are presented in Table II. Thirty-three of 41 (80%) patients were women and 90% of patients underwent orthopedic or gynecologic surgery. Total morphine consumption for the 24 hr period was not different between groups ($P = 0.84$), (Table III, Figure 1). However, intensity of pain at rest and on movement was significantly different between groups ($P = 0.0073$ and 0.0187, respectively; Figures 2, 3). Furthermore, pain scores in the nabilone 2 mg group were significantly higher than in the other three groups, at rest and on movement, when compared to placebo and ketoprofen. Overall, the incidence of nausea and vomiting was not different between groups, nor was quality of sleep, euphoria, sedation, pruritus and mood (Table IV). However, sedation scores were significantly higher for nabilone 2 mg compared to the ketoprofen group during the third postoperative period (17–24 hr after starting PCA). Similarly, euphoria, although not significantly different between the four groups, was more frequent in the nabilone 1 mg and 2 mg groups, and more so in the latter group. Mean values of blood pressure, heart rate and respiratory rate were not different between groups at corresponding periods. No psychotic episodes were recorded. Ninety percent of patients (37/41) had at least one adverse event, but event frequencies were not different between groups (Table IV). The most common adverse effects were dry mouth, nausea and vomiting, respiratory depression, sedation and pruritus. No serious adverse events were observed.

Discussion

Contrary to the proposed hypothesis, this study showed that nabilone administration over 24 hr in the postoperative period was not associated with a decrease in morphine consumption in patients undergoing major surgery, using PCA morphine. Furthermore, and unexpectedly, nabilone at high doses significantly increased pain scores at rest and upon movement. No other measured variables were significantly different

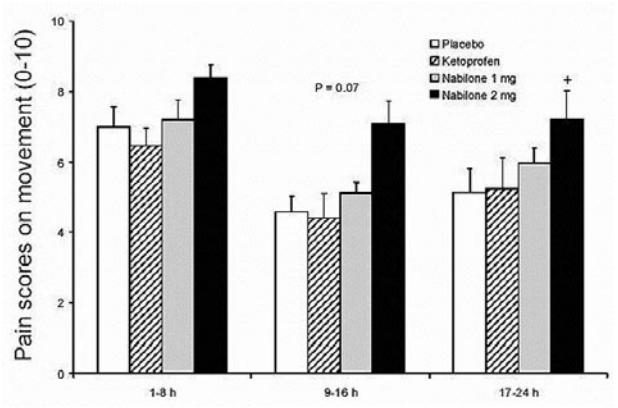

FIGURE 3 Pain on movement measured on a 0 to 10 numerical verbal scale for the four groups of patients, and separated into three periods of eight hours each from start of PCA administration until 24 hr later. + Different compared to placebo and ketoprofen groups, $P < 0.05$.

between the two nabilone, ketoprofen or placebo groups.

Jain *et al.* investigated the acute postoperative analgesic effects of cannabinoids using *im* levonantradol, a synthetic analogue of ^{9}-THC, in 56 patients. Significant pain relief was obtained with levonantradol, but commonly associated with drowsiness.[3] In 2002, Greenwald *et al.* reported the acute antinociceptive properties of inhaled cannabis in recreational drug users.[5] Only five male volunteers completed the study which consisted of three test sessions during which they smoked cigarettes containing 0% (placebo) and 3.55% THC (active). Overall, cannabis produced significant dose-dependent antinociception that was not antagonized by naltrexone. The effect was weak and only significant at the highest dose. Furthermore, the analgesic effects of oral THC, morphine or their combination were reported in healthy subjects under experimental pain conditions in a randomized, placebo-controlled, double-blind, cross-over study involving 12 healthy cannabis-naïve volunteers.[6] Each subject received orally either 20 mg THC (dronabinol), 30 mg morphine, a mixture of 20 mg THC and 30 mg morphine or placebo as a single dose. In a heat test, neither morphine nor THC produced an analgesic effect. In a cold test morphine alone and the morphine-THC combination were analgesic but not THC alone, whereas in the pressure test only morphine alone was analgesic. Taken together these results illustrate that THC provides poor pain control in this battery of acute pain tests. Finally, a randomized clinical study examining postoperative pain showed a lack of efficacy of oral THC in women undergoing elective total abdominal hysterectomy.[7] Postoperatively, all patients used a PCA with morphine for 24 hr. Afterwards the PCA was discontinued, and when the patient requested further analgesia, they were randomized to receive either THC 5 mg capsules or placebo. The primary outcome was the sum of the pain intensity differences over a six-hour period, while the secondary outcome measure was time to request rescue analgesia (oral codeine 30 mg). No differences in mean sum of the pain intensity scores were found between the THC and placebo groups (n = 20 per group). From the different studies reported in the literature, it is apparent that oral cannabinoids are poor analgesics when tested for the treatment of acute pain, and rarely are they more effective than placebo.

The explanation for the anti-analgesic effects of nabilone is not obvious. However, paradoxical effects of cannabinoids have been reported at high doses and may explain the current findings. Indeed, nabilone was used in high doses in this clinical trial. For example, chronic pain patients are prescribed doses of nabilone 0.5 mg *hs* in gradually escalating doses, according to the analgesic response and tolerance. At high doses, nabilone produces reverse effects from those predicted, especially when used in the treatment of anorexia and depression (nabilone monograph). [A] Another explanation may be the sedative effects of nabilone in higher doses, since sedatives can be anti-analgesic when administered during acute pain. Nevertheless, even at a dose of 1 mg *po*, nabilone was no better than placebo or ketoprofen.

In the present study, ketoprofen was not different from placebo in terms of morphine consumption and pain scores. This is surprising, as it is has been shown that non-steroidal anti-inflammatory drugs decrease both.[15] The relatively small number of patients may have been a factor, but recruitment was nevertheless sufficient to demonstrate the dose-dependent anti-analgesic properties of nabilone. Furthermore, patients in the ketoprofen group were, in general, younger, weighed less, with more females in this group compared to the placebo group. These factors may explain, in part, the greater 'baseline' pain in the ketoprofen group.

Limitations

The study had to be discontinued prior to enrolling the planned number of subjects. The limited recruitment of patients from a single centre can be explained

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by several factors: 1) the very strict exclusion criteria (> 60% of patients excluded at this stage); 2) use of an ambulatory surgical setting; 3) consideration of patients undergoing non-invasive (laparoscopic) surgery for which PCA was not required, and finally; 4) limitations of funding such a labour-intensive study. Despite these challenges, we were able to recruit similar numbers of subjects compared to other studies evaluating cannabinoids for postoperative analgesia.[3,7] Furthermore, in these studies, patients received only one dose of study medication compared to three doses in the present study. A practical concern is the use of oral medications during the early postoperative period which may be associated with poor patient tolerance. This is also the reason why patients undergoing major gastrointestinal surgery could not be recruited in this study. Finally, on a futility basis, there were sufficiently convincing data from 41 subjects demonstrating an anti-analgesic effect of the higher dose of nabilone, that continuing the study to answer the primary question would have little merit.

In conclusion, despite potentially promising properties, this study demonstrates that nabilone, an oral synthetic cannabinoid, does not decrease morphine consumption in the postoperative period following major surgery. In contrast, at a dose of 2 mg *po*, nabilone is associated with a significant increase in pain at rest and on movement compared to placebo, ketoprofen or nabilone 1 mg. Other clinical variables were not different between groups. Caution must be applied before generalizing these findings, as only a small number of patients were recruited in the present study. Therefore, although cannabinoids may be effective in relieving chronic pain in humans, their role in the treatment of acute postoperative pain is uncertain, and requires further clinical evaluation.

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