Comparative study between intravenous ibuprofen, intravenous tramadol alone and in combination after arthroscopic reconstruction surgery

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Background
Ambulatory anesthesia is becoming a major part of an anesthetist's workload. Inadequate postoperative analgesia can delay discharge and impair a patient's return to full function.

Aim
The aim of this study was to evaluate the analgesic efficacy of intravenous ibuprofen as a newly intravenous analgesic and tramadol when used alone and when combined.

Methods
This blind randomized study included 75 patients according to American Society of Anesthesiologists physical status I and II, aged between 19 and 46 years, and scheduled for arthroscopic reconstruction surgery. Patients were randomly allocated into three equal groups: group I received ibuprofen 800 mg intravenously, group II received tramadol 100 mg intravenously, and group III received a combination of both drugs ibuprofen 400 mg and tramadol 70 mg intravenously after induction. In all patients, anesthesia was induced with propofol (2–3 mg/kg), fentanyl (2 μg/kg), and a single dose of cisatracurium 0.15 mg/kg. Pain during rest and mobility was assessed in the immediate postoperative period, 2, 4, 6, and 8 h successively using the visual analogue scale (VAS), and opioid consumption was recorded.

Results
Group III showed significantly less consumption of morphine doses in comparison with either group I or group II. Although there was no statistically significant difference in VAS during rest among all groups, group III still had the least VAS scores during knee movement that was significant in comparison with group I or group II. Also, group I was statistically significant higher than group II. Eight hours postoperatively, there was significantly greater patient satisfaction with the postoperative pain management in group III in comparison with group I and group II.

Conclusion
A combination of intravenous ibuprofen and tramadol has been shown to provide better analgesia and higher patient satisfaction than each drug used separately. The combination of both drugs decreased the doses of each, which helped to avoid adverse effects.

Keywords:
ambulatory anesthesia, intravenous ibuprofen, postoperative analgesia, tramadol

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Introduction

Newer anesthetics and techniques allow rapid recovery and early discharge of the patients from hospital and resumption of their previous lifestyle [1]. Inadequate postoperative analgesia can delay discharge and/or impair a patient's return to full function. Opioids are effective analgesics, but their usefulness is limited by side effects such as nausea, vomiting, somnolence, constipation, and respiratory depression [2]. Tramadol (with opioid-like activity) and nonopioids, for example, paracetamol, nonsteroidal anti-inflammatory drugs (NSAID), and local anesthetics have opioid-sparing effects [3,4]. Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. It has an affinity for μ-opioid receptors and inhibits the neuronal reuptake of serotonin and norepinephrine [5]. Tramadol has central analgesic effects because of monoaminergic and μ-receptor agonistic activities. It also has local anesthetic properties, and the risk of serious adverse effects is limited [6,7]. Ibuprofen, a nonsteroidal anti-inflammatory agent belonging to the group of propionic acid derivatives, inhibits the enzyme cyclooxygenase (prostaglandin synthesis) that catalyzes the transformation of unsaturated fatty acids into prostaglandins. It is assumed that the inhibition of the prostaglandin synthesis is the cause for the analgesic, antipyretic, and anti-inflammatory action of the drug. As tramadol and NSAIDs probably have different sites of action, their combination may have an additive or a synergistic effect. The objective of this study was to compare the analgesic properties of

tramadol and the newly intravenous (i.v.) analgesic (ibuprofen) administered separately or together and to evaluate the effect of the combined drugs on patient satisfaction among patients undergoing arthroscopic reconstruction surgery under general anesthesia.

Patients and methods

A prospective, randomized, blinded, trial was conducted in Al-Azhar University Hospitals. The hospital ethics committee approved the study protocol. Seventy-five patients of American Society of Anesthesiologists physical status I and II, aged between 19 and 46 years, scheduled for arthroscopic reconstruction surgery, were enrolled to participate in this study after obtaining informed patient consent. Exclusion criteria were gastrointestinal adverse events (including bleeding, ulceration, and perforation), pregnancy, breast-feeding women, history of drug abuse, and intake of narcotic analgesics, NSAIDs, or tramadol within 24 h before the study, and operations longer than 120 min. All patients were premedicated with 5 mg midazolam tablet 1 h before surgery. In all patients, anesthesia was induced with propofol (Diprivan 1%, 2–3 mg/kg; Astra-Zeneca, Madrid, Spain), fentanyl (2 μg/kg), and single-dose cisatracurium (Nimbex 0.15 mg/kg; GlaxoSmithKline, S.A., Madrid, Spain). Laryngeal masks (classic) were used for all patients. Lungs were mechanically ventilated. Maintenance of anesthesia was achieved with sevoflurane (1.5 ± 0.5 vol%; Abbott, Abbott Laboratories, Illinois, USA). Patients were allocated into three equal groups: group I received 800 mg ibuprofen i.v. in 100 ml bottle of 0.9% saline (Caldolor ampule; Cumberland Pharmaceuticals Inc., Nashville, Tennessee, USA) over 20 min, group II received 100 mg tramadol (about 1.5 mg/kg) i.v. (Grunenthal, Aachen, Germany) in 100 ml bottle of 0.9% saline, and group III received both ibuprofen 400 mg and tramadol 70 mg (about 1 mg/kg) i.v. in 100 ml bottle of 0.9% saline, all administered after induction. Arthroscopies were carried out by the same surgeon who was blinded to the drug administered. Local anesthetics were avoided in all patients under the study. At the end of the procedure, residual paralysis was antagonized with neostigmine and atropine in all patients. After removal of the laryngeal mask, the patients were transferred to the postanesthesia care unit (PACU). Pain intensity at rest and during active knee movement was assessed every 10 min using a 100 mm visual analogue scale (VAS) (0 = no pain → 10 = worst imaginable pain) [8]. I.v. morphine boluses (3 mg) were administered and possibly repeated every 20 min with a maximum dose of 12 mg until VAS 3 or less. The number of patients complaining from nausea and vomiting was recorded postoperatively. Patients would not be discharged to the ward unless awake and oriented, able to move all extremities on command, hemodynamically stable, respiratory stable (able to breathe deeply), oxygen saturation 95% on room air, no or mild discomfort, and no or mild nausea and vomiting [9]. After leaving the PACU, pain was reassessed during rest and active movement at 2-h intervals until 8 h using VAS. Patient satisfaction with postoperative pain management was assessed at the eighth hour postoperatively using a four-point rating scale (poor = 0, fair = 1, good = 2, and excellent = 3). Morphine 3 mg i.v. was administered upon request in cases of persistent pain until VAS 3 or less. Total doses of morphine administered in the PACU and in the ward until 8 h were calculated.

Statistical analysis

Analysis of data was carried out by an IBM computer using statistical program for social science (SPSS; Chicago, Illinois, USA) as follows:

(1) Description of quantitative variables as mean, SD, and range.
(2) Description of qualitative variables as number and percentage change.
(3) Paired *t*-test was used to compare quantitative data in the same group.
(4) One-way analysis of variance (ANOVA) with the Tukey test was used to compare more than two groups in terms of quantitative variables.

Results

There were no intergroup differences in patients' characteristics or duration of surgery, but stay in PACU was statistically significantly lower in group III than the two other groups (Table 1).

Total morphine administered was significantly lower among the patients in group III compared with both groups; also, it was significantly lower in group II compared with group I by the ANOVA test (Table 2).

VAS data are presented in (Table 2) and showed that in the early postoperative period group III had the lowest pain during knee movement compared with the other groups; also, group II had less pain than group I by the ANOVA test. However, no statistically significant difference could be detected between the studied groups in terms of VAS during rest in the early postoperative period by the same test.

After 2, 4, 6, and 8 h, no statistically significant difference could be detected between the studied groups in VAS either during rest or at movement, although group III had lower pain scores compared with the other two groups at different intervals by the ANOVA test ($P > 0.05$). However, VAS was statistically significantly higher during movements compared with rest within each group by a paired *t*-test ($P < 0.0$1).

Patients in the combination group III considered pain management as good or excellent at eighth hour postoperatively, and patients' satisfaction was statistically significantly better than that in the other two groups. No statistically significant difference was found between group I and group II, but still clinical evidence of better patients' satisfaction in group II than in group I (Table 3).

Moderate to severe nausea in the recovery room was statistically significantly higher in group II compared with

Table 1 Patients' characteristics and operative data

	Group I ($n=25$)	Group II ($n=25$)	Group III ($n=25$)	*P*-value
Age (year)	31.2 ± 7.1	32.4 ± 6.8	33.6 ± 8.5	>0.05
Sex (male/female)	15/10	13/12	14/11	>0.05
Weight (kg)	80 ± 7.9	79 ± 4.3	76.8 ± 6.8	>0.05
Duration of Surgery (min)	56.8 ± 6.7	54.5 ± 6	55.3 ± 7.3	>0.05
Stay in PACU (min)	51.6 ± 9	38 ± 7.2	34.6 ± 5.6	<0.001

PACU, postanesthesia care unit.

Table 2 Visual analogue scale and total morphine consumption

	Group I ($n=25$)	Group II ($n=25$)	Group III ($n=25$)	*P*-value
Early postoperative				
Rest	4.4 ± 1.5	4.1 ± 2.2	3.1 ± 2	>0.05
Movement	6.1 ± 1.8	4.4 ± 1.9	3.7 ± 1.1	<0.001
After 2 h				
Rest	3.1 ± 1.4	2.5 ± 1.7	2.2 ± 1.5	>0.05
Movement	4.2 ± 1.9	4.3 ± 1.7	3.6 ± 1.7	>0.05
After 4 h				
Rest	3.3 ± 1.3	2.9 ± 1.2	2.5 ± 1.4	>0.05
Movement	4.1 ± 1.4	4 ± 1.3	3.5 ± 1.1	>0.05
After 6 h				
Rest	3.2 ± 1.4	3.1 ± 1.2	2.4 ± 1.2	>0.05
Movement	4.2 ± 1.2	4.1 ± 1.3	3.6 ± 1.1	>0.05
After 8 h				
Rest	2.7 ± 1.3	2.3 ± 1.2	2.1 ± 1	>0.05
Movement	3.7 ± 1.2	3.2 ± 1.1	3.1 ± 1.1	>0.05
Total morphine	10.6 ± 1.4	9.2 ± 2.8	6.6 ± 2.6	<0.001

Table 3 Patients' satisfaction

	Group I ($n=25$)	Group II ($n=25$)	Group III ($n=25$)	*P*-value
Excellent	2	5	14	<0.005
Good	7	10	8	
Fair	13	8	2	
Poor	3	2	1	

Table 4 Postoperative side effects

	Group I ($n=25$)	Group II ($n=25$)	Group III ($n=25$)	*P*-value
Nausea	4	8	1	<0.05
Vomiting	2	4	1	>0.05
Dry mouth	1	5	2	>0.05
Dizziness	1	2	0	>0.05

group III ($P<0.05$). Other side effects such as vomiting, dry mouth, and dizziness were more frequent in group II, but the difference was not statistically significant in comparison with group I and group III (Table 4).

Discussion

Tramadol 1.5 mg kg administered i.v. upon induction of anesthesia was superior to i.v. ibuprofen (800 mg) in reducing pain intensity and rescue morphine consumption after arthroscopic reconstruction surgery. Furthermore, the combination of tramadol and ibuprofen provided an additional analgesic effect, particularly during active knee movement. Patients in the tramadol–ibuprofen group had better pain relief, less morphine consumption, and higher satisfaction in terms of pain management without the undesirable effects of tramadol. NSAIDs have analgesic effects that have been attributed to their peripheral anti-inflammatory actions in inhibiting the synthesis of prostaglandins through the inactivation of cyclooxygenase. This peripheral receptor action of the NSAIDs can thus indirectly inhibit central neural sensitization and consequently reduce the amplification of pain [8,10]. Multiple studies have shown the analgesic efficacy and tolerability of orally, intramuscularly, or i.v. administered tramadol in acute pain. Meta-analysis of data from 3453 patients in 18 placebo-controlled trials established the safety and dose-dependent efficacy of tramadol in the treatment of moderate to severe dental or postsurgical knee pain [9]. Although tramadol has also been used in post-traumatic, obstetric, and renal or biliary colic pain, most studies have investigated postoperative pain. Among these, only a few studies have investigated the analgesic efficacy of tramadol in patients undergoing day-case surgery. These studies proved that the analgesic efficacy of tramadol was better than fentanyl and ketorolac [11,12]. The benefit of tramadol in day-care surgery was observed in a study of 228 patients undergoing surgery through a groin incision tramadol (100 mg) administered during and after operation and was compared with the combination of intraoperative fentanyl (100 µg) and postoperative co-codamol. In these relatively painful procedures, tramadol provided superior analgesia [9]. This study did not have to be placebo controlled as the analgesia efficacy of i.v. ibuprofen and tramadol was compared with the combination of classical NSAIDs and acetaminophen in adults and children. In gynecologic surgery, the combination of acetaminophen with diclofenac reduced postoperative morphine consumption significantly more than acetaminophen alone [13]. After tonsillectomy, in children, the

combination of ibuprofen with acetaminophen was associated with a significantly better reduction in postoperative opioid requests than the combination of the selective COX-2 inhibitor rofecoxib with acetaminophen [14].

There are limited information data on the analgesic efficacy of the combination of i.v. ibuprofen and tramadol in comparison with either drug, as i.v. ibuprofen added recently to the market. Ilias and Jansen [15] reported that i.v. lornoxicam at a dose of 8 mg is superior to placebo and at least as effective as i.v. tramadol 50 mg in relieving moderate to intolerable posthysterectomy pain. Staunstrup *et al.* [16] reported that intramuscular l6 mg lornoxicam offers a useful alterative to 100 mg tramadol for the treatment of moderate to severe pain. This is not in agreement with our result of tramadol having better analgesic effect compared with ibuprofen because they used a double dose of lornoxicam, which has several side effects such as gastrointestinal mucosal damage, renal impairment, induced asthma, serious cardiovascular thrombotic events, and myocardial infarction [17]. In the present study, the combination of i.v. ibuprofen with tramadol has been shown to exert an additional analgesic effect particularly during the stay in the PACU without increasing the doses of individual components. At the same time, the combination improved tolerability by using lower doses of each medication. Combinations are most effective when individual agents act synergistically, and data from animal studies suggest that tramadol and paracetamol have synergistic activity [18]. Further studies are required to explain the synergism between ibuprofen and tramadol. The higher morphine consumption during the PACU period in patients who received either ibuprofen or tramadol alone could explain the similarity in both the pain scores and the rescue analgesic doses during the subsequent 8 h. Side effects such as vomiting, dry mouth, and dizziness were more frequent in the tramadol group compared with i.v. administered ibuprofen and can provide an additional analgesic effect when combined with tramadol intraoperatively in patients undergoing arthroscopic reconstruction surgery under general anesthesia in comparison with either drug alone.

Conclusion

The combination of ibuprofen and tramadol has been shown to provide better analgesia, higher patient satisfaction, less dose needed, and no side effect than each drug used separately.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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