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A Single Blind Controlled Comparison of Tramadol/ Paracetamol Combination and Paracetamol in Hand and Foot Surgery. A Prospective Study

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Abstract. *The objective of this study was to compare the efficacy and effectiveness between an analgesic combination of tramadol/paracetamol (37.5+325 mg), and paracetamol monotherapy (1000 mg) for acute postoperative pain after hand and foot surgery. The study design was a single blind randomized controlled trial. A total of 114 patients who underwent hand and foot surgery under brachial plexus block were randomized to receive either paracetamol monotherapy (group P, n=57) or tramadol/paracetamol (group TP, n=57) postoperatively. The number of patients who required an extra-dose of analgesic pain score, and adverse affects were compared between the two groups. Analgesic requirement was significantly lower in those in the TP group when compared with the P group. In the TP group, the pain score after surgery was significantly lower than in the P group. Adverse effects did not significantly differ between the two groups. There were no serious adverse events in either group. The association of tramadol and paracetamol appears to have more efficacy when compared with paracetamol monotherapy for acute postoperative pain after hand and foot surgery.*

Hand and foot surgery procedures are usually performed on an ambulatory basis, and postoperative pain is a major problem (1, 2). Patient pain is commonly treated with oral medication that can be taken easily. The drugs used are nonsteroidal anti-inflammatory, paracetamol, and opioid (3). Several studies have shown that traditional analgesic drugs fail to provide adequate analgesia in many patients (1-4), and these is evidence of a better treatment with a combination of two drugs (5, 6). The use of two drugs capitalizes on their potentially differing pharmacokinetic profiles. An example is the combination of paracetamol, with a rapid analgesic onset, and an opioid, with long central analgesic characteristics.

In our study, we analyzed the pain relief and side-effects of combination of tramadol (37.5 mg) and paracetamol (325 mg) in comparison to paracetamol monotherapy (1000 mg). The aim was to evaluate the effectiveness and the tolerability of the combination, and to compare the analgesic efficacy of paracetamol monotherapy (group P) and tramadol/ paracetamol combination (group TP) for the control of pain after hand and foot surgery.

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Patients and Methods

A total of 114 patients, eligible to undergo hand and foot surgery in a period of 6 months, were recruited in the study. Inclusion criteria were diagnosis of carpal tunnel syndrome, Guyon canal syndrome, Dupuytren disease, De Quervain's tenosynovitis, hallux valgus, claw-finger and mallet-finger of the hand or foot, tarsal tunnel syndrome, necrosis of the distal phalanx by scleroderma, or hand trauma; ASA class I, II, III.

Exclusion criteria were alcoholism, drug dependency, psychiatric disease, pregnancy and lactation, history of allergy or hypersensitivity to tramadol or paracetamol; ASA IV.

Informed consent was obtained from all patients. The medical history of each patient was taken to determinate the presence of other chronic diseases. Faculty of Medicine and Ethics Committee for Human Research of La Sapienza University of Rome approved the present study. Patient characteristics are shown in Table I.

Patients were randomized for treatment allocation at 1:1 ratio, resulting in 57 patients in the P group and 57 patients in the combination tablet TP group. To maintain the single blind technique, each medication bottle was labeled with a medication code number and packaged with the study medication according to the randomization sequence. The investigator assigned medication code numbers to eligible patients in ascending sequential order.

The youngest patient included in the study was 18 years old, the oldest was 87 years old; patients had an average age of 56 years. Average height was 173 cm for men and 160 cm for women. Average weight was 81 kg for men and 67 kg for women.

Group P (n=57 patients) included 25 men and 32 women. Eleven patients were affected by hypertension, 8 by thyroid disease, 3 by sclerodermia and 12 by other chronic pathologies. Postoperatively, all patients of this group were treated with 1,000 mg of paracetamol in monotherapy.

On the other hand, the TP group (n=57 patients), included 23 men and 34 women. Eleven patients were affected by hypertension, 8 by thyroid disease, 4 by sclerodermia, and 9 by other chronic pathologies. All patients of this group received a tablet combination of 37.5 mg tramadol and 325 mg of paracetamol after surgery.

Brachial plexus block was done with 2% lidocaine 10 cc. All operations were performed between 8:00 am and 2:00 pm. Postoperatively, patients were observed for pain and drug side-effects. A Visual Analogue Scale (VAS) of 0-4 was used to assess the pain; 0 was taken as no pain, 1 was taken as mild pain, 2 was taken as moderate pain, 3 was taken as severe pain and 4 as unbearable pain. Seven records of the state of pain were performed: the first one before surgery, the second at 120 minutes, the third at 6 hours after surgery, the fourth at 12 hours and the fifth at 24 hours. The last scores were taken 3 and 7 days after the patient was discharged. After the operation, in the postanesthetic care unit, all patients were randomized to receive a single dose of study medication. Before discharge, oral and written information regarding the protocol of the study were given to patients; they also received tablets of combined tramadol/paracetamol or paracetamol alone. Patients were advised to take tablets 2 times a day for 3 days and were allowed to take an extra dose if pain persisted. No other analgesic drugs were prescribed.

Since the most common side-effects of the drugs we used are nausea and vomiting, all the patients were also observed for the occurrence of these symptoms. Moreover, we evaluated changes in liver function, alterations in the kidney, gastrointestinal reactions, and dizziness.

Patients completed the present study if they had no treatment-limiting adverse event within 72 hours after surgery.

Statistical analysis. Data was entered in Microsoft Excel format 2007. Comparison and analysis between extra dose analgesic required and VAS, in two groups, on various hours and days were done by using Chi-square test. *P*-value less than 0.01 were considered as significant.

Results

A total 114 patients were enrolled in the present study and they were randomized into two groups of 57 cases each. The patients of the P group were designated to receive paracetamol monotherapy while the TP group received tramadol/paracetamol combination. All the patients were evaluable and data was analyzed.

The two groups were evenly matched as per age, gender distribution and diagnosis (Table I), as well as severity of illness and grade of preoperative VAS seen (Table II).

Comparison between postoperative VAS, extra-dose analgesic required and adverse events, in the two groups, on various hours and days were analyzed.

In the TP group, the pain score by VAS in the first six hours after surgery was significantly less than that in the P group (Table II). The pain score within 24 hours and 72 hours later after surgery was not different between these two groups (VAS=0).

Table I. *Clinical data of study cases*.

	Group	
	P	TP
Cases	57	57
Gender		
Men	25	23
Women	32	34
Diagnosis		
Carpal tunnel syndrome	17	20
Guyon canal syndrome	3	3
Dupuytren disease	4	4
De Quervain's tenosynovitis	3	3
Hallux valgus	7	5
Claw-finger	4	4
Mallet-finger	6	6
Tarsal tunnel syndrome	3	3
Distal necrosis	3	4
Trauma	7	5
Age (years)	56.81	56.69
Weight (kg)	72.97	70.17
Height (cm)	165.23	165.66

In fact, comparison of mean VAS scores between the two groups showed that postoperative VAS scores were significantly lower in TP group (0.40) than in the P group (1.92) in the early hours. This difference was statistically significant (p-value <0.005). Thereafter, there was not much difference between the two groups up to the seventh postoperative day (Table II).

Total consumption of the extra-dose analgesic in the TP group was significantly less than in the P group in the first twelve hours after the operation (Table III). The total number of extra-dose analgesic tablets required by P group was 50, while that in TP group was 4. This difference was statistically significant (p-value <0.005).

Patients of the TP group and those of the P group did not have significantly different adverse effects. There were no serious adverse events in any group (Table IV).

Lastly, although the patients of the TP group requested to return to work earlier than those in the P group, this difference was not statistically significant.

Discussion

Effective postoperative pain management has been demonstrated to improve clinical outcome. Opioids are widely used to relieve postoperative pain due to their efficacy and effectiveness. However, their adverse effects

Table II. *Number of patients and pain score (VAS 0-4).*

	Group												*p*-Value
	P						TP						
VAS	0	1	2	3	4	Average	0	1	2	3	4	Average	
Preoperative	0	0	0	20	37	3.649	0	0	0	19	38	3.666	0.0389
Postoperative time													
0-6 h	14	8	3	32	0	1.92	44	7	2	4	0	0.40	<0.005
6-12 h	53	3	0	11	0	0.63	54	3	0	0	0	0.05	0.4386
12-24 h	50	0	0	7	0	0.36	57	0	0	0	0	-	
24-72 h	57	0	0	0	0	-	57	0	0	0	0	-	
7 days	57	0	0	0	0	-	57	0	0	0	0	-	

such as nausea, vomiting, itching, and respiratory depression are of concern. In patients who underwent upper extremity surgery under brachial plexus block, when local anesthetic was completely absorbed, the patients felt pain and required an analgesic at different doses. Multimodal analgesia, which is a combination of analgesic drugs, provides more effective pain relief than relying on one drug alone and plays an important role in reducing adverse effects (2).

In the present comparison of the efficacy and effectiveness between tramadol/paracetamol (37.5 mg plus 325 mg) combination and paracetamol (1,000 mg) for acute postoperative pain after hand or foot surgery, the combination provided better analgesia than paracetamol alone at 1,000 mg.

Tramadol is a phenylpiperione analog of codeine. It is a synthetic, centrally acting opioid analgesic, characterized by two distinct but complementary mechanisms of action. It binds weakly to μ-opioid receptors in the central nervous system and also inhibits reuptake of noradrenalin and serotonin, selectively binding the pre-synaptic transporters for these neurotransmitters (7, 8). This particular pharmacodynamic profile makes tramadol a double-action drug, inducing opioid-like effects and at the same time acting like a tricyclic antidepressant (9). Only a few studies have investigated the analgesic efficacy of tramadol in patients undergoing day-care surgery. These studies proved that the analgesic efficacy of tramadol was better than that of fentanyl and ketorolac (10-13). The benefit of tramadol in day-care surgery was seen in study of 228 patients undergoing surgery through a groin incision. Tramadol (100 mg) administered during and after operation was compared with the combination of intraoperative fentalyn (100 μg) and postoperative co-codamol. In these relatively painful procedures, tramadol provided superior analgesia. Tramadol has been used at different doses (1.5-3 mg /kg) in various procedures, depending upon the expected severity of pain (1). However, an increased incidence of side-effects, particularly postoperative nausea (24%-40%), vomiting (9%-17%), dizziness (26%-33%), headache (18%-32%), and sedation (16%-25%), has been reported in many studies (9). Reduced doses may be used in renal and hepatic impairment (14).

Paracetamol is a drug with analgesic and antipyretic effect, and a weak anti-inflammatory action. It is a cyclooxygenase

Table III. *Number of patients requiring extra-dose analgesic.*

	Group		*p*-Value
Postoperative time	P	TP	
0-6 h	32	4	<0.005
6-12 h	11	0	<0.005
12-24 h	7	0	<0.01
24-72 h	0	0	
7 days	0	0	

Table IV. *Adverse events due to combination (TP) and monotherapy (P).*

	Group	
Adverse events	P	TP
Nausea and vomiting	1	2
Itching	1	1
Erythema	2	1
Headache	0	0
Dizziness	0	0
Hot flush	0	0
Any serious event*	0	0

*An adverse event was considered as serious if it was life threatening, required hospitalization or resulted in a persistent or significant disability.

(COX) inhibitor resulting in the inhibition of prostaglandin synthesis predominantly in the central nervous system rather than in peripheral tissues. It is widely used as an analgesic. In combination with nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids, it is also used in the management of more severe pain (such as cancer pain) (2). The main mechanism of action is reducing the oxidized form of COX, preventing it from forming proinflammatory chemicals, which are important mediators of inflammation, pain, and fever (15). It has a hepatic metabolism resulting in it being conjugated with glucuronic acid. A minor metabolite *N*-acetyl-*p*-benzochinone, of paracetamol is involved in its hepato- and nephrotoxicity, is usually linked with glutathione, but in cases of overdose, the metabolite accumulates and induces hepatotoxicity.

In our study, we analyzed the pain relief activity and side-effects of combination between these two analgesics, tramadol (37.5 mg) and paracetamol (325 mg). A combination of these two drugs can reduce the dose required of each component. This reduction critically improves the tolerability of the treatment. Improvement in tolerability is caused by a reduction of 25% in daily tramadol intake.

By combining drugs with different mechanisms of action and pharmacokinetic profiles, it is possible to enhance efficacy even though lower doses of individual drugs are used. Various studies have suggested enhanced analgesic efficacy using multimodal analgesic strategies compared with unimodal analgesic treatment so that one can limit side-effects, reduce postoperative pain and analgesic requirements and facilitate an earlier return to normal activities (2, 3, 5-7, 16). The main points of treatment with a combination of these two drugs are improvement in analgesic effect, decrease of side-effects and a better tolerability for patients. The use of 25% less tramadol in the combination should reduce the incidence of tramadol-related adverse events, while the addition of paracetamol should quicken the onset of analgesia and possibly improve the degree of analgesia (16).

Combination therapy based on acetaminophen and an opioid may improve pain relief and provide faster onset and longer duration of action than either component separately (17-20). In a meta-analysis of single-dose oral tramadol plus acetaminophen in dental or gynecologic/orthopedic patients with moderate to severe pain, the tramadol/paracetamol combination was more effective than either of two components administered alone (21, 22). In addition to the potential for increased efficacy due to combined medications, adverse drug events were expected to decrease.

In the present study, the efficacy and effectiveness of tramadol (37.5 mg) plus paracetamol (325 mg) for acute postoperative pain after hand and foot surgery were significantly improved, including better pain relief and reduced pain intensity, when compared with paracetamol due to its synergistic property.

Conclusion

The combination of tramadol (37.5 mg) and paracetamol (325 mg) may enhance the efficacy and tolerability of opioid treatment. This combination improves analgesia due to the different pharmacological targets. In fact, if paracetamol is combined with lower doses of tramadol, better analgesia can be achieved due to synergism along the pain pathway. In the outpatient surgery, very often only paracetamol is given, with the risk being the need for extra doses, with more possibility of side-effects and greater cost. Our study has shown that combination of tramadol/paracetamol allows better control of the postoperative pain after hand and foot surgery.

References

1 Chung F, Ritchie E and Su J: Postoperative pain in ambulatory surgery. Anesth Analg *85*: 808-816, 1997.

2 Sawaddiruk P, Paiboonworachat S and Janthawichai K: Comparison of efficacy and effectiveness between Ultracet and tramadol/acetaminophen in acute postoperative pain after upper extremity surgery. J Med Assoc Thai *93*: 812-817, 2010.

3 Rawal N, Allvin R, Amilon A, Ohisson T and Hallen J: Postoperative analgesia at home after ambulatory hand surgery: a controlled comparison of tramadol, metamizol and paracetamol. Anesth Analg *92*: 347-351, 2001.

4 Rawal N, Hylander J, Nydahl PA, Olofsson I and Gupta A: Survey of postoperative analgesia following ambulatory surgery. Acta Anaesthesiol Scand *41*: 1017-1022, 1997.

5 Zhang WY and Li Wan Po A: Analgesic efficacy of paracetamol and its combination with codeine and caffeine in surgical pain: a meta-analysis. J Clin Pharm Ther *21*: 261-282, 1996.

6 Perrot S, Krause D, Crozes P, Naim C and GRTF-ZAL-1 Study Group: Efficacy and tolerability of paracetamol/tramadol (325 mg/37.5 mg) combination treatment compared with tramadol (50 mg) monotherapy in patients with subacute low back pain: a multicenter, randomized, double-blind, parallel-group, 10-day treatment study. Clin Ther *28*: 1592-1606, 2006.

7 Ali M and Khan FA: Comparison of analgesic effect of tramadol alone and a combination of tramadol and paracetamol in day-care laparoscopic surgery. Eur J Anaesthesiol *26*: 475-479, 2009.

8 Scott LJ and Perry CM: Tramadol: a review of its use in preoperative pain. Drugs *60*: 139-176, 2000.

9 Raffa RB, Friedrichs E, Reimann W, Shank RP, Codd EE and Vaught JL: Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an atipica opioid analgesic. J Pharmacol Exper Therap *260*: 275-285, 1992.

10 Hopkins D, Shipton EA, Potgieter D, Van derMerwe CA, Boon J, De Wet C and Murphy J: Comparison of tramadol and morphine via subcutaneous PCA following major orthopaedic surgery. Can J Anaesth *45*: 435-442, 1998.

11 Putland AJ and McCluskey A: The analgesic efficacy of tramadol *versus* ketorolac in day-care laparoscopic sterilisation. Anaesthesia *54*: 382-385, 1999.

12 Moore RA and McQuay HJ: Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol *versus* placebo, codeine and combination analgesics. Pain *69*: 287-294, 1997.

13 Bamigbade TA, Langford RM and Blower AL: Pain control in day surgery: tramadol compared to standard analgesia. Br J Anaesth *80*: 558-559, 1998.
14 Dayer P, Desmeules J and Collart L: Pharmacology of tramadol. Drugs *53(S2)*: 18-24, 1997.
15 Aronoff DM, Oates JA and Boutaud O: New insights into the mechanism of action of acetaminophen: Its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. Clin Pharmacol Ther *79*: 9-19, 2006.
16 Tallarida RJ and Raffa RB: Testing for synergism over a range of fixed ratio drug combinations: replacing the isobologram. Life Sci *58*: PL23-28, 1996.
17 Schnitzer T: The new analgesic combination tramadol/acetaminophen. Eur J Anaesthesiol Suppl *28*: 13-17, 2003.
18 Schug SA: Combination analgesia in 2. Clin Rheumatol *25(S1)*: S16-21, 2006.
19 McClellan K and Scott LJ: Tramadol/paracetamol. Drugs *63*: 1079-1086, 2003.
20 Smith AB, Ravikumar TS, Kamin M, Jordan D, Xiang J and Rosenthal N: Combination tramadol plus acetaminophen for postsurgical pain. Am J Surg *187*: 521-527, 2004.
21 McQuay H and Edwards J: Meta-analysis of single dose oral tramadol plus acetaminophen in acute postoperative pain. Eur J Anaesthesiol Suppl *28*: 19-22, 2003.
22 Bourne MH, Rosenthal NR, Xiang J, Jordan D and Kamin M: Tramadol/acetaminophen tablets in the treatment of postsurgical orthopedic pain. Am J Orthop (Belle Mead NJ) *34*: 592-597, 2005.

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