Original Article

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Comparison of Butorphanol Tartrate and Tramadol Hydrochloride for Post-Operative Pain Relief Following Abdominal Surgery: A Prospective, Randomized, Double-Blind Study

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Abstract

Background: Butorphanol tartrate is a mixed synthetic agonist-antagonist opioids analgesic used for the management of post-operative pain in minor and major surgical procedures. Tramadol hydrochloride is a centrally acting mμ receptor agonist, frequently used as an analgesic.

Aim: The purpose of this study was to compare the analgesic efficacy and side effects of equipotent moderate doses of butorphanol and tramadol.

Materials and Methods: In the present randomized, prospective, double-blind study, 60 patients of either sex, aged between 18 and 60 years, American Society of Anesthesiologists physical status Grade I and II undergoing elective abdominal surgeries under general anesthesia were enrolled in the study. Patients were randomly assigned to two groups (30 patients each); Group B received injection butorphanol 2 mg and Group T received injection tramadol 100 mg, 10 min prior to extubation. Patient's visual analog scale (VAS), duration of analgesia, the number of doses required in 24 h, and side effects were noted.

Results: In the present study, the mean duration of analgesia after the first dose was 3.42 h in Group B and 6.46 h in Group T. The mean number of doses required in 24 h was 4.3 in Group B and 2.4 in Group T. At 0-¼ h, mean reduction in VAS was 3.0 in Group B and 1.57 in Group T. Mean reduction at 0-4 h was 0.33 in Group B and 4.56 in Group T. Thus, evident that analgesic effect of butorphanol wears off after 4 h while tramadol has peak effect at 3-4 h. Side effects such as vomiting were present in 30% patients in Group B as compared to 60% patients in Group T.

Conclusion: Butorphanol was found to be an effective analgesic than tramadol and has minimal side effects.

Key words: Agonist-antagonist, Analgesic, Butorphanol tartrate, Post-operative pain, Tramadol hydrochloride

INTRODUCTION

Opioids are powerful centrally acting analgesic agents, used to provide the specific anti-nociceptive component of a balanced anesthesia technique.[1-3] Post-operative pain relief can be achieved by several methods, including the use of systemic opioids and regional anesthesia with intrathecal or epidural opioids or local anesthesia. On demand analgesia using a patient-controlled analgesia (PCA) system is regarded as the ideal option for systemic opioids analgesia. While PCA devices are not yet commonly used in all recovery units, the use of repetitive boluses on demand is still the most frequent form of administration in post-operative pain therapy. Butorphanol is mixed agonist-antagonist opioid.[4] Capable of relieving intense pain. Tramadol is an agonist at mμ opioid receptors.[5] Butorphanol has been used widely in the management of post-operative pain.[6] Receptor specificity of butorphanol has been used to limit respiratory depression, gastrointestinal side effects, and reduced risk of dependency. Theoretically, it offers

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an advantage over traditional opiates such as morphine and pethidine in the treatment of moderate pain. The analgesic activity of butorphanol is dose related.[7] Since butorphanol is not a controlled substance, its use can reduce administrative liability for abuse and lower the number of distribution records associated with Schedule II narcotics. Butorphanol injection was approved in 1978;[8] the nasal spray was approved in 1991.[9] Butorphanol is an agonist at kappa opioid receptors. The stimulation of kappa receptors seems a likely alternative action for anti-shivering action.[10,11] The purpose of present study was to compare the analgesic efficacy of intravenous (IV) butorphanol tartrate with IV tramadol hydrochloride for post-operative pain relief following abdominal surgery. Extensive Medline search revealed very limited literature regarding the IV use of butorphanol, and thus the aim of our study was to compare the analgesic efficacy of butorphanol with tramadol, their duration of analgesia and their side effects.

MATERIALS AND METHODS

After approval from the Institutional Ethical Committee and written informed consent, 60 patients of either sex, aged between 18 and 60 years, American Society of Anesthesiologists physical status Grade I and II, were included in a prospective, randomized, double-blinded study to be performed in the Department of Anesthesiology, Teerthanker Mahaveer Medical College and Hospital, Moradabad from January 2014 to December 2014. Patients undergoing elective abdominal surgeries (*viz*. urological and general surgical procedures) under general anesthesia were enrolled in the study. Patients with a history of drug abuse, not given consent, history of drug allergy, pregnant patients, and patients with coagulation disorders were excluded from the study.

A sample size calculation was done using the standard deviation of time to the first request for analgesics. To find a 30 min difference in the mean duration of a request for analgesic (two sided-alpha of 5% and beta of 10%), 22 subjects were enrolled per group. We decided to include 30 patients per group to allow for possible dropouts.

Patients were randomly assigned to two groups (30 patients each) by computer-generated randomization. In Group B, injection butorphanol tartrate (2 mg) was given IV slowly 10 min prior to extubation. In Group T, injection tramadol hydrochloride (100 mg) was given IV 10 min prior to extubation. Drugs were prepared by a blinded anesthesia technician not involved in the study in identical 2 ml syringes and were administered according to the randomization list.

A consultant anesthesiologist assessed all patients during pre-anesthetic evaluation and alprazolam (0.5 mg) was prescribed in all patients on the night before surgery and advised nil per orally from midnight. In the operation theater, monitoring devices for electrocardiogram, heart rate, oxygen saturation (SPO_2), and end-tidal carbon-dioxide ($EtCO_2$) were attached. All patients were premedicated with injection glycopyrolate (0.2 mg) and injection midazolam (0.03 mg/kg). All patients were subjected to general anesthesia using a standard technique which consisted injection propofol 2 mg/kg. Intubation was facilitated by using injection vecuronium 0.1 mg/kg (IV). Anesthesia was maintained with nitrous oxide (66%) and isoflurane (1-2%) in oxygen. Intra-operative muscle relaxation was maintained with intermittent doses of injection vecuronium. Reversal of neuromuscular blockade was performed with injection neostigmine 0.05 mg/kg (IV) and injection glycopyrrolate 0.1 mg/kg (IV). The first dose of either of the study drug was given 10 min prior to extubation by a blindfolded person. Immediately after extubation patients were monitored (zero order reading) and other vital parameters, such as pulse rate, non-invasive blood pressure, respiratory rates (RR), were recorded.

Systolic blood pressure, diastolic blood pressure, heart rate, SPO_2, and $EtCO_2$ were monitored intra operatively. The intensity of pain was assessed by visual analog scale (VAS).[12] The score was noted at 0 h, ¼ h, ½ h, 1 h, 2 h, 4 h, 8 h, 12 h, 16 h, and 24 h. Repeated doses were given when patients complained of pain (VAS >4). The side effects were recorded and vomiting score and sedation score were noted.

If satisfactory analgesia was not achieved within 30 min of administration of drug, second dose of the same drug was suggested and if even after second dose pain was not relieved, the patient was excluded from trial study and rescue analgesic (injection diclofenac 75 mg) was given. Antiemetic injection ondansetron 4 mg was given if the patient had one episode of vomiting. Respiratory depression was taken as RR <10 breaths/min. Excessive sedation with respiratory depression, hypotension, and bradycardia were taken as evidence of central nervous system depression.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS), version 19 (SPSS Inc., USA). Unpaired Student's *t*-test was used to analyze parametric data while Fisher/Chi-square test was applied for non-parametric data. A $P < 0.05$ was considered as statistically significant.

RESULTS

All patients were successfully enrolled and underwent abdominal surgeries in our study without any dropouts. The butorphanol tartrate group and the tramadol group were comparable with respect to patient's demographic data, duration of surgery (Table 1). The duration of analgesia after the first dose was 3.42 h in Group B as compared to 6.46 h in Group T (Table 2). In Group B, the analgesia lasted for 0-2 h in 13.3%. No patient in Group T had duration of analgesia of <2 h. 16.7% patients in Group B and 76.7% patients in Group T had duration of analgesia that lasted for 4-8 h. The mean number of doses required in 24 h was 4.3 ± 1.05 in Group B as compared to 2.4 ± 0.86 in Group T (Table 3). The *t* score = 7.6619, $P = 0.000$, was highly significant. The mean differences in VAS at 0-¼ h in Group B was 3.0 (standard deviation [SD] ± 1.72), whereas in Group T mean VAS was 1.57 (SD ± 0.93) ($P < 0.001$), very highly significant. Mean reduction in VAS was 0.33 (SD ± 1.92) in Group B at 0-4 h while mean reduction in VAS was 4.56 (SD ± 1.15) in Group T, $P < 0.000$, very highly significant. Thus, evident that the analgesic effect of butorphanol wears off after 4 h while tramadol has peak effect at 3-4 h (Table 4).

Table 1: Demographic profile

Characteristics	Group B	Group T	*P* value
Age (years)	40.63±12.08	40.60±10.65	0.50
Sex (male:female)	17:13	16:14	
Height (cm)	152.53±4.42	153.18±3.76	0.30
Weight (kg)	54.56±5.36	53.52±4.32	0.35
Duration of surgery (min)	120.17±26.44	121.00±24.21	0.49

Table 2: Duration of analgesia after the first dose

Time (h)	Group B *n*=30 (%)	Mean duration	Group T *n*=30 (%)	Mean duration
0-2	4 (13.3)	3.42±1.37	0 (0)	6.46±1.35
2-4	21 (70)		3 (10)	
4-8	5 (16.7)		23 (76.6)	
>8	-		4 (13.3)	
Total	30		30	

Unpaired *t*-test=8.6433, *P*<0.00 (VHS). VHS: Very highly significant

Table 3: Number of doses required in 24 h

Doses	Group B	Group T
1	0	4
2	2	13
3	3	10
4	13	3
5	8	-
6	4	-
Total	30	30
Mean±SD	4.3±1.05	2.4±0.86

Unpaired *t* value=7.6619, *P*=0.000 (HS). HS: Highly significant, SD: Standard deviation

In Group B, 70% of patients had no side effects, 9 (30%) had nausea compared to 12 (40%) patients in Group T. No patient had vomiting in Group B while 6 (20%) patient in Group T had vomiting (Table 5). In Group B, 43.3% patients were drowsy while 36.7% patients were drowsy in Group T. 7 and 3 patients in Group B and Group T were drowsy and not arousable by verbal commands. 13.4% patients in Group B were arousable by deep pain. No patients in both the groups were unarousable (Table 6).

DISCUSSION

The main aim of post-operative pain relief is to provide subjective comfort, in addition to inhibiting nociceptive impulse caused by trauma and to blunt autonomic as well as somatic reflexes to pain. Subsequently, this might enhance restoration of function by allowing the patient to breathe, cough and to be easily ambulant. Butorphanol is used to treat moderate to severe pain. It is an agonist at kappa-receptor, but it is a weak antagonist at the mμ receptor. Several clinical studies with the injectable form of butorphanol have shown effectiveness in relieving moderate-to-severe post-operative pain.[13] Tramadol, a weak opioid which acts on mμ receptor has been most commonly used for management of post-operative pain.[14] Tramadol has been chosen as a reference substance, as its effects are well-documented. Since the study used identical protocols, the results obtained were comparable, combine analysis of trial was valid.

The aim of this study was to know the efficacy of butorphanol in comparison with tramadol with regard to post-operative pain. The patient's age, gender, weight, and duration of surgery were statistically not significant in two groups. Therefore, the effect of age, gender, weight, duration of surgery would be minimized. The concept of using analgesia post-operatively before the onset of significant pain (preventive analgesia) has been used. Each of these modalities has led to decreased total pain after surgery and decreased pain intensity at fixed post-operative time intervals when measured by VAS. Sung *et al*.[15] conducted a retrospective study to compare butorphanol with morphine for use in a balanced anesthesia technique with nitrous oxide, oxygen, and neuromuscular relaxants. Neru *et al*.[11] have compared butorphanol and tramadol for analgesic efficacy and safety. The onset of analgesia is rapid as studied by Andrews[16] The mean duration of analgesia after the first dose was 3.42 h in Group B and 6.46 h in Group T. Padmasuta[5] observed 6.6 h mean duration of intramuscular (IM) tramadol. The mean duration of analgesia with Tramadol was comparable with the study of Padmasuta[5] where tramadol was used IM. Stehling and Zauder[17] observed 4-5 h mean duration of analgesia of IM butorphanol. Gilbert *et al*. found 4-5 h duration of

Table 4: Mean differences in VAS

Time (h)	0-¼	0-½	0-1	0-2	0-4	0-8	0-12	0-16	0-24
Group B	3.0±1.72	4.3±2.05	4.73±1.92	4.43±1.94	1.60±1.92	1.07±1.74	1.5±2.14	0.53±1.89	0.83±1.93
Group T	1.57±0.93	2.90±2.02	3.10±1.86	4.33±1.15	4.00±0.97	0.33±1.18	3.70±1.15	2.13±2.50	3.07±1.48
P value	0.0002	0.0001	0.0015	0.8093	0.0000	0.0614	0.0000	0.0070	0.0000

VAS: Visual analog scale

Table 5: Incidence of side effects

Side effects	Group B (%)	Group T (%)	*P* value
Vomiting			
Present	9 (30)	18 (60)	*P*<0.020
Absent	21 (70)	12 (40)	
Sedation			
Present	24 (80)	14 (46.3)	*P*<0.007
Absent	6 (20)	16 (53.4)	
Total	30	30	

Table 6: Sedation score

Score	0 (%)	1 (%)	2 (%)	3 (%)	4	Total
Group B	6 (20)	13 (43.3)	7 (23.3)	4 (13.4)	-	30
Group T	16 (53.4)	11 (36.7)	3 (10)	-	-	30

P=0.016, Pearson Chi-square test (1) χ^2: 10.3121, 0: Alert, 1: Drowsy but arousable by verbal command, 2: Drowsy but not arousable by verbal command, 3: Arousable by deep pain, 4: Unarousable

analgesia with 1-2 mg IM butorphanol. In our study, the average number of doses required in Group B were 4.3 where as in Group T were 2.4 over a period of 24 h. Carter *et al*. reported mean number of doses 3.8 in 24 h which was comparable to our study. Padmasutta[5] observed the mean dose of 2.5 per 24 h after IM tramadol. The observations of our study are comparable with the study of Padmasutta.[5] The only variation was the route of administration. In our study, comparing the mean differences in VAS scores in two groups, it was clear that there was a greater reduction in VAS score of butorphanol group compared to tramadol group. The results of Galloway *et al*.[18] and Del Pizzo[6] were comparable with our results. In Group B, sedation score was 0 in 20% patients compared to Group T, it was 53.4%.

In our study, Group B 70% of patients had no side effects, 30% had nausea while in Group T, 40% had no side effects, 40% patients had nausea, and 20% had nausea and vomiting. Butorphanol does not increase the incidence of post-operative nausea and vomiting as observed by Onake and Yamamoto[19] Nausea and vomiting were more frequent with tramadol 28% and 18% versus 81% and 51% than with pethidine. Ofoegbu[20] found that with IM tramadol the incidence of nausea and vomiting was 19%. None of the patients showed post-operative shivering. This can be due to the anti-shivering action of tramadol as has been described by Chen *et al*.[21] The stimulation of kappa receptors seems likely alternative for the anti-shivering action of butorphanol. Moreover, being a non-narcotic butorphanol has a low propensity for addiction. This was observed by study conducted by Charlton.[22]

As mentioned in previous studies, care is to be taken during the administration of injection butorphanol because of the risk of respiratory depression. However, we did not experience any episode of respiratory difficulty in any of our study group.

CONCLUSION

In this randomized, parallel group study, the following conclusions were drawn; that butorphanol has the short onset of action, better analgesic efficacy, with minimal side effects in comparison tramadol has a longer duration of analgesia with few side effects. Butorphanol appears to be a promising drug in near future, but an extensive study with more patient population would be more conclusive.

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