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SAFETY EVALUATION OF TRAMAL PLUS® (TRAMADOL HYDROCHLORIDE/ACETAMINOPHEN) FOR PAIN MANAGEMENT IN PAKISTANI REAL WORLD PRACTICE (STEP STUDY)

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ABSTRACT

Objective: The objectives of the study were to evaluate adverse effects mainly Central Nervous System (CNS) and Gastrointestinal (GI) in Pakistani subjects by using Tramal Plus® (Tramadol 37.5mg/Paracetamol 325mg) during the pain management in routine practice. **Material and methods:** This was an Observational, Prospective, multi-centre study conducted as per GCP guidelines at the leading hospitals of Karachi. The study compliances were monitored by Contract Research Organization (CRO). Total number of 310 subjects were enrolled, Tramal Plus® tablets for the duration of 2 weeks (14 days). During the course of treatment, the GI adverse effects were evaluated by valid GI AE's questionnaire (Dutch questionnaire) whereas CNS adverse effects mainly drowsiness and respiratory depression were also monitored. SPSS version 19 was used for the statistical analysis of the results. **Results:** As per results of 300 subjects', none reported respiratory depression whereas 7 subjects (2.3%) reported mild drowsiness and only 5 (1.7%) subjects reported moderate drowsiness. The subjects also reported drowsiness at baseline visit, 39 (13%) subjects had mild drowsiness and 2 (0.7%) subjects had moderate drowsiness, they were already on concomitant medications and were known case of hypertension and Diabetes Mellitus. For GI adverse effects, the most common reported adverse events were mild nausea (5, 1.7%), mild constipation (4, 1.33%), vomiting (2, 0.7%) and epigastric pain (2, 0.7%). **Conclusions:** The study data of Tramal plus results depicted the reduced incidence of AEs, improved tolerability with no serious adverse events as were reflected in global studies on tramadol and paracetamol combination when compared to Tramadol alone in pain management. It was also observed in local Pakistani population that drowsiness as an adverse effect can be associated with concomitant medications and co-morbid diseases patients while managing the pain.

KEYWORDS: Pain Management, Tramal Plus®, adverse effects, Pakistani population.

INTRODUCTION

Pain considered as one of the oldest common complaint and major reason for the patients to consult the doctors. For relieve the availability of analgesics groups, however, since the origin of humanity its management still challenges to the doctors.[1] Especially in case of managing long-term treatment of chronic pain that often associated with safety and tolerability issues and must be individualized for each patient. The goal of pain management is not only pain relief, but also need to address appropriately with the concern of adverse effects by improvements in restrictions of daily activities and quality of life of the overall well-being of the patient.[2] The traditional NSAIDs and second-generation NSAIDs (cyclooxygenase-2 inhibitors) associated with the serious adverse events (e.g. GI bleeding) along with the interaction with many other medicinal products.[3,4] It is now recommended for the special cautions and close monitoring for the patients with conditions such as gastrointestinal disorders, renal, cardiac or hepatic impairment.[5] For various etiologies, opioid analgesics are also useful agents for treating pain; however, adverse effects are potential limitations to their use with potential association of tolerance, dependence and addiction.[6] To tackle, as per recommendation by World Health Organization (WHO), the American Pain Society (APS) and the American College of Rheumatology (ACR), the combination of analgesics from different classes may provide additive analgesic effects with lesser side effects than when a single drug is used.[7,8,9]

Tramadol is considered as a type of opioid (atypical opioid), however, it is different from most other opioids because of its multiple mechanism of analgesic action (binding to μ-opioid receptors and inhibition of neuronal reuptake of norepinephrine and serotonin).[10,11] It is also proven to be equally effective in different acute and chronic pain states[12,13,14] and has fewer side effects as compared with the typical strong opioids. Paracetamol (also known as acetaminophen or APAP) is a very popular medication, has analgesic and antipyretic effects, however, its exact mode of action is still poorly understood and several mechanisms have been proposed, which seem to point to a largely central effect.[15] Tramadol with paracetamol offers an effective and well-tolerated alternative to anti-inflammatory drugs. This combination has demonstrated genuine synergy with sustained efficacy, safety and tolerability. The combination is also free of organ toxicity, associated with selective and non-selective non-steroidal anti-inflammatory drugs.[16]

The previous studies data supporting the rationale of combining Tramadol with acetaminophen for the efficacy and safety in acute and chronic pain states; however, in the local population, the study data for the adverse effects is missing. The key objectives of the study was to evaluate common Central Nervous System (CNS) and Gastrointestinal (GI) adverse effects in terms of Pakistani subjects prospective of using Tramal Plus®. The GI adverse effects were assess by the valid Dutch GI adverse events questionnaire based technique and other common CNS adverse effects like drowsiness symptom during the pain management in routine practice.

METHODOLOGY

This was a Post-Marketing-Observational, Prospective, Multicenter study conducted at different hospitals in the Karachi as per ICH-GCP guideline. The study was approved by Independent Ethics Committee and study compliances monitored by Contract Research Organization (CRO). The study period was from August 2015 to December 2015. As per study inclusion and exclusion criteria, 310 subjects with age of 18 years and above and requiring pain management were enrolled; whereas 10 subjects were drop out due to lost to follow-up in the study. All the subjects received the study drug, Tramal Plus (Tramadol 37.5mg/Paracetamol 325mg Tablets) for the duration of 2 weeks (14 ± 7 days) for follow up and to check any adverse event experienced by the subject during the course of treatment. All previous medication for pain management were stopped at the baseline visit for the duration of treatment or as per routinely prescribed by the Principal Investigator. The GI adverse effects were evaluated by Dutch valid GI questionnaire with common CNS adverse effects especially drowsiness and respiratory depression related to study drug during the treatment were monitored.

SPSS Software version 19 was used to summarize all variables using number of observations for analysis of the results. p value < 0.05 was considered significant. All variables were summarized using the number of observations, mean, standard deviation or standard error, median, minimum and maximum. ± 95% confidence intervals were provided in the inference tables where applicable. All hypothesis tests were two-sided and conducted using a 0.05 significance level unless otherwise stated.

RESULTS

In this study, out of 300 enrolled subjects' data, 178 (59%) were female and 122 (41%) were male. In demographic data, minimum age was 18 years with 47 years mean age ± 14 S.D. respectively. The descriptive statistics details for baseline visit as mentioned in the table: 1 whereas the vital signs Statistics details from baseline and visit 2 in table number 2.

Table: 1 Descriptive Statistics at Baseline visit

Characteristics	N	Mean	Std. Deviation
Age (years)	300	47.943	14.7789
Height (m)	300	1.63839	.093134
Weight (kg)	300	71.213	13.6240
BMI (kg/m2)	300	26.506	5.4289

Table 2: Vital signs Statistics at Baseline and visit 2

Characteristics	N	Minimum		Maximum		Mean		Std. Deviation	
		Baseline	Visit 2	Baseline	Visit 2	Baseline	Visit 2	Baseline	Visit 2
Temp (ºF)	300	96.4	98	100	100	99.187	99.47	0.6593	0.520
Pulse (beats/min)	300	70.0	70	100	100	78.467	78.08	2.6919	2.674
Resp. Rate (breaths/min)	300	15.0	14	30	22	18.953	18.30	1.7110	1.365
Systolic (mmHg)	300	100.0	110	135	130	119.050	118.57	3.6366	3.937
Diastolic (mmHg)	300	70.0	60	100	100	79.650	77.62	3.9598	5.286

For the above results from both baseline and visit 2 reflected that the vital sign(s) at both visits shows no effects on body temperature, pulse rate, respiratory rate and Blood Pressure during the treatment.

For the habit descriptions, out of 300, 273 (91%) were habit of taking tea otherwise more than 90% were non-smokers whereas 26 (8.7%) and 12 (4%) were habit of Pan and Gutka respectively. The details are in table: 3.

Table 3: Habit descriptions of Patients recruited for pain management

Habit descriptions		Frequency	Percent
Smoking			
No		289	96.3
Yes		11	3.7
Total		300	100.0
Pan			
	No	274	91.3
	Yes	26	8.7
	Total	300	100.0
Gutka			
	No	288	96.0
	Yes	12	4.0
	Total	300	100.0
Alcohol Intake			
	No	300	100.0
Tea Intake			
No		27	9.0
Yes		273	91.0
Total		300	100.0

As per the results of CNS adverse effects, no subject was reported respiratory depression during the 14 days' pain management treatment. For drowsiness adverse effect, at Baseline visit before the start of treatment, out of 300 subjects, 39 (13%) were had mild drowsiness and 2 (0.7%) were had moderate drowsiness whereas at visit 2 after completion of 14 days' treatment with Tramal Plus, only 7 (2.3%) were reported mild drowsiness and only 5 (1.7%) were reported moderate drowsiness (Fig 1). The subjects had drowsiness in baseline visits were mainly on concomitant medications with mainly known case of hypertension and diabetes.

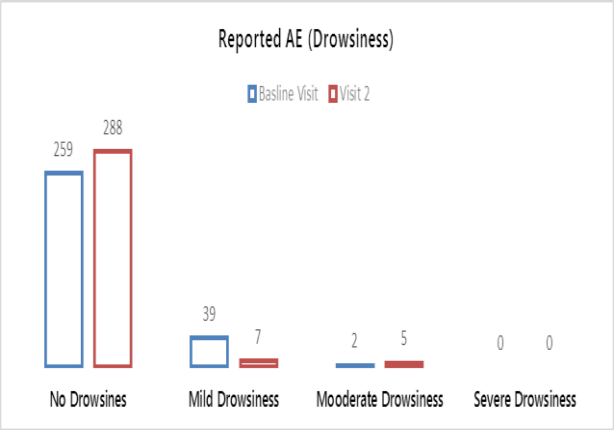

Fig 1: Reported Adverse Event (AE) Drowsiness

The Means of variable drowsiness are different at baseline with respect to drowsiness at visit 2 with $P < 0.05$ in table 4.

Table 4: Paired Samples Statistics (Drowsiness)

	Mean	N	Std. Deviation	Std. Error Mean
Drowsiness (Baseline)	0.14	300	0.370	0.021
Drowsiness (Visit 2)	0.06	300	0.295	0.017

In terms of drug GI adverse effects assess by Dutch GI questionnaire.

Out of 300 Subjects, the most common reported adverse events were mild nausea (5, 1.7%), mild constipation (4, 1.33%), vomiting (2, 0.7%) and epigastric pain (2,0.7%). The details of frequency of GI adverse event reported in table 5.

Table 5: Details for GI adverse event (as per Dutch GI adverse event questionnaire)

GI AEs Reported		None	Mild	Moderate	Quite a lot	Severe	Unbearable
1.	Abdominal pain in common	298 (99.3 %)	1 (.3 %)	1 (.3 %)	0 (0 %)	0 (0 %)	0 (0 %)
2.	Epigastric Pain in Common	297 (99 %)	2 (.7 %)	1 (.3 %)	0 (0 %)	0 (0 %)	0 (0 %)
3.	Heart Burn	299 (99 %)	1 (.3 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
4.	Bloating	299 (99.7 %)	1 (.3 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
5.	Nausea	293 (97.7 %)	5 (1.7 %)	1 (.3 %)	1 (.3 %)	0 (0 %)	0 (0 %)
15.	Vomiting	297 (99 %)	1 (.3 %)	2 (.7 %)	0 (0 %)	0 (0 %)	0 (0 %)
16.	Loss of Appetite	298 (99.3 %)	2 (.7 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
18.	Belching	299 (99.7 %)	1 (.3 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
24.	Stools Bloody	299 (99.7 %)	1 (.3 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
25.	Stools Mucous	299 (99.7 %)	1 (.3 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
26.	Stools Frequent Hard	299 (99.7 %)	1 (.3 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
27.	Stools Diarrhea	299 (99.7 %)	1 (.3 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
28.	Stools Alternate Solid or Loose	299 (99.7 %)	1 (.3 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
29.	Stools Constipation	292 (97.3 %)	4 (1.33 %)	1 (.3 %)	1 (.3 %)	0 (0 %)	0 (0 %)
30.	Stools Frequently with Pain	299 (99.7 %)	1 (.3 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)

Table 5: Frequency of GI adverse events

S. No.	Adverse Events	Frequency	Percentage (%)
3	Mild Heartburn	1	0.3
4	Mild Nausea	5	1.7
5	Moderate Nausea	1	0.3
6	Quite a lot Nausea	1	0.3
7	Mild Loss of Appetite	2	0.7
8	Mild Belching	1	0.3
9	Mild Constipation	4	1.33
10	Moderate Constipation	1	0.3
11	Quite a lot Constipation	1	0.3
12	Mild Bloody Stool	1	0.3
13	Mild Frequent Hard Stool	1	0.3
14	Mild Frequently with Pain Stool	1	0.3
15	Mild Alternately Solid or Loose Stool	1	0.3
16	Mild Mucous Stools	1	0.3
17	Mild Epigastric Pain	2	0.7
18	Moderate Epigastric Pain	1	0.3
19	Mild Bloating	1	0.3
20	Mild Vomiting	1	0.3
21	Moderate Vomiting	2	0.7

22	Mild Diarrhoea	1	0.3
23	Mild Abdominal Pain	1	0.3
24	Moderate Abdominal Pain	1	0.3
25	Moderate Shivering	1	0.3
26	Sweating	1	0.3

Table 6: Adverse Event (GI Symptoms)

Table: GI Symptoms before treatment and after treatment (Paired Sample t-Test applied)				
	Mean	**N**	**Std. Deviation**	**Std. Error Mean**
GI Symptoms (Baseline)	32.53	300	1.067	0.062
GI Symptoms (Visit)	32.15	300	0.699	0.040

Normality test (Kolmogorov) had been run to check the normality of the data and the data is found to be normally distributed.

DISCUSSION

The combination of tramadol and paracetamol (Tramal Plus) theoretically synergize the advantages both in effectiveness and safety in managing the pain. Our study was aimed to assess the safety of combination of tramadol and paracetamol, as an analgesic agent for pain in local Pakistani population. The adverse effects assessed were mainly Gastro-intestinal and drowsiness as per reported in previous studies.

For French ELZA study to assessed efficacy and safety of tramadol/paracetamol in 5495 patients presented with moderate-to-severe pain.[17] A total of 4.2% of the patients reported adverse events, most commonly gastrointestinal disorders. Similarly, the SALZA French study assessed the clinical benefits of tramadol/paracetamol in 2663 patients aged ≥65 years with moderate-to-severe pain.[18] The adverse events were reported by 4.5% of the patients, mainly gastrointestinal disorders (4.1%).

In both studies, the most common treatment-related adverse events were nausea, vomiting, constipation and dizziness.

For the study on the patients with knee or hip OA with moderate pain in 3 months' treatment comparison with celecoxib. Rofecoxib, tramadol/paracetamol and placebo.[19] For tramadol/paracetamol group safety data, no serious adverse events occurred with reported adverse events were mainly gastrointestinal AEs.

The Korean study on knee OA with moderate pain treated with meloxicam, aceclofenac and tramadol/paracetamol for 4 weeks.[20] One tramadol/paracetamol patient withdrew due to adverse events with reported adverse events related to gastrointestinal disorders. For another Korean study investigated the effect of tramadol/paracetamol titration on the development of adverse events in patients with knee OA on stable NSAID therapy for 2 weeks or titration to this dose over 7 days. The discontinuation rate due to adverse events was significantly lower in the titration group (10.5% versus 26.2% for non-titration).[21]

In all studies, the most common treatment-related adverse events were nausea, vomiting, constipation, dizziness and somnolence.

An Indian multi-centered study on 204 subjects evaluate the safety and efficacy of tramadol and diclofenac versus tramadol and paracetamol, in patients with acute moderate to severe pain the acute musculoskeletal conditions, postoperative pain and acute flare of osteoarthritis and rheumatoid arthritis. The safety evaluation results of tramadol/paracetamol group had few AEs, with more in tramadol and diclofenac combination i.e. nine (8.82%) in Tramadol/Paracetamol whereas 22 (21.78%) in tramadol and diclofenac combination. The commonest AEs were nausea, vomiting, drowsiness, epigastric pain and gastritis. The majority of the AEs were mild in intensity, requiring minimal management, without discontinuation of study drugs.[22]

In low back pain study, comparative trial to evaluate the 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. As per results, patients on paracetamol with Tramadol (84.3%) than Tramadol patients (68.8%) were better tolerate the medication treatment. Significantly fewer AEs ($P < 0.001$) were observed in patients and the overall incidence of AEs (mostly opioid-typical AEs [eg, nausea, dizziness/vertigo, sleepiness/drowsiness, constipation, vomiting]) was much lower in combination than tramadol alone. The most common AEs were nausea and dizziness.[23] Another low back pain study and Tramadol/paracetamol treatment assess reduced pain and improved quality of life and emotional and mental health. Main treatment-related adverse events in the combination group were nausea (12%), dizziness (10.8%) and constipation (10.2%).[24]

The two studies on Painful Diabetic Polyneuropathy (DPN) to assessed the efficacy and safety of tramadol/paracetamol. The adverse events were nausea, vomiting, dizziness and somnolence more common under combination treatment. Overall, the two studies suggest that fixed-dose tramadol/paracetamol is well tolerated and leads to pronounced pain relief in the treatment of painful DPN.[25,26]

For European trial to compared efficacy and safety of tramadol/paracetamol combination with tramadol alone in the treatment of postoperative pain following ambulatory hand surgery A total of 132 patients received tramadol/paracetamol combination treatment and 129 patients took tramadol. Nausea was the most common event in both groups (25.8% for tramadol/paracetamol vs 36.4% for tramadol) followed by dizziness (15.9% vs 18.6%) and somnolence (9.1% vs 14%). Overall, incidences were lower in the tramadol/paracetamol group for gastrointestinal disorders (28.8% vs 44.2% for tramadol) and nervous system disorders (21.2% vs 32.6%).[27]

The study by Stephen et al, 2003, alone in high dose tramadol with central nervous system (CNS) depressants may produce respiratory depression, a reported side effect of opioid therapy, however in low dose tramadol with combination with paracetamol not produce respiratory depression.[28,29]

Overall the Tramal Plus study results of local Pakistani is the crust of above safety studies data on tramadol/paracetamol, with the most common treatment-related adverse events were nausea, vomiting, constipation and drowsiness.

CONCLUSION

The study data of Tramal plus results depicted the reduced incidence of AEs, improved tolerability with no serious adverse events as were reflected in global studies on tramadol and paracetamol combination when compared to Tramadol alone or with other combination in pain management. It was also observed in local Pakistani population that drowsiness as an adverse effect can be associated with concomitant medications and co-morbid diseases patients while managing the pain. Therefore, Patients who require pain management and consider combination of tramadol with paracetamol should be counselled on preventive measures, i.e. use of medication at proper time and dose whereas dosage should not exceed the prescribed dose to avoid adverse effects related to Tramadol that has been minimized after combination with Paracetamol.

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CONFLICT OF INTEREST

There is no conflict of interest in publishing this study.

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