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Original Article

Novel analgesic combination of tramadol, paracetamol, caffeine and taurine in the management of moderate to moderately severe acute low back pain

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ABSTRACT

Background: Acute low back pain is one the leading cause of doctor's visit in our country with innumerable medication for treatment. Finding an ideal analgesic medication with better efficacy and least adverse effects is always a challenging task to the treating doctor. **Methods:** In this study we compared the efficacy and safety profile of a fixed dose combination of novel analgesic tramadol 37.5 mg/paracetamol 325 mg/caffeine 30 mg/taurine 250 mg with commonly used tramadol 37.5 mg/paracetamol 325 mg tablet in the treatment of moderate to moderately severe acute low back pain. Patients attending 50 clinics throughout India were enrolled in either of the above group and were asked to take one tablet every 6th hour for five consecutive days. The pain evaluation in both groups was done with verbal pain relief scale and pain intensity scale at end of treatment.

Results: Proportion of patients in novel combination group compared to tramadol/paracetamol only group responding to treatment based on treatment satisfaction (good and excellent) and mean pain intensity (no pain or mild pain), were 81% Vs 45%, ($p < 0.001$) and 83% Vs 66% ($p < 0.001$) respectively. Common expected adverse drug reaction like nausea, vomiting and dizziness occurred with far less frequency in patients under novel combination group. **Conclusion:** We conclude that significantly more patients in novel combination drug group compared to tramadol/paracetamol only group had a superior analgesic effect with lesser adverse reactions.

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1. Introduction

Low back pain affects 60–80% of the population especially between 35 and 55 years of age. The magnitude of problem in developing countries like India is high due to ignorance to see

the doctor for early treatment and occupation requiring them to carry heavy objects on the back. It is a common musculo-skeletal pain that occurs posterior in the region between the lower rib margin and the proximal thighs and that is of less than six weeks duration.¹

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The exact cause of acute low back pain patients visiting the clinic is often difficult to find in majority of cases. Muscle pull and spasms are the most common causes of acute low back pain due to lifting heavy weights at work, improper sitting posture, falls or accidents. The remaining small percentages of cases are due to fractures, *prolapsed disc*, osteoporosis and neoplasm (metastasis).

According to most published guidelines, the first line care should include reassurance as favorable outcome, analgesic medications and advice to stay active are quite sufficient.²

Clinical use of combination analgesic drugs has augmented considerably in the last few years. One such combination drug tramadol 37.5 mg/paracetamol 325 mg is an ideal combination analgesic because first, these are the most frequently used combination analgesics and second these are combination for which there is most evidences published.³

However their adverse effects such as nausea, vomiting, itching and respiratory depression are a concern for the patient particularly due to opioid component.⁴ Studies shows nausea, vomiting, dizziness and somnolence were most prominent in the tramadol groups.

As per published literature adding caffeine to pain analgesics can make pain pills work 40% more effectively. This added boost to medications pain-relieving ability allows you to take less medication, experience less potential side effects and reduce the risk of becoming addicted to the medication.⁵ Also caffeine has been found to accentuate the analgesic effects of acetaminophen and acetyl salicylic acid (ASA) in a broad collection of pain states such as dysmenorrhoea, cancer pain, post-partum pain, sore throat and dental post-surgery pain.⁶

Taurine a conditionally essential amino acid containing sulphur is found in almost all tissues in mammals.⁷ Taurine plays vital roles in a large number of physiological and pathological conditions in human body, such as the cytoprotective functions, antioxidant, anti-inflammatory and anti-apoptosis effects.⁸ Of late taurine is extensively promoted in health drinks in western countries to provide energy.

The purpose of this study is to evaluate the efficacy and safety of novel combination drug tramadol 37.5 mg/paracetamol 325 mg/caffeine 30 mg and taurine 250 mg versus standard reference drug tramadol 37.5 mg/paracetamol 325 mg in the treatment of moderate to moderately severe acute low back pain.

2. Method

Ambulatory male or female patients aged 18–60 years old with symptomatic moderate to moderately severe acute low back pain between 12th rib and buttock crease; with or without radiating pain no lower than the knee were included in the study. Acute back pain had started at least 72 h prior to inclusion in the study and not more than 6 weeks of duration. Otherwise in good health, as determined by physical examination and medical history.

The major study exclusion criteria were patients with history of inflammatory arthritis, chronic pain, metastasis, Paget's disease, or other diseases known to cause pain. Patients known to be allergic or contraindicated to tramadol, caffeine, paracetamol and taurine. Have not used any other

prescription or over the counter medications for pain within 24 h of the first dose of study medication.

3. Study design

This was an open label, active control, multi clinic parallel group study carried throughout India from July to November 2012. After patients fulfilled the study inclusion and exclusion criteria, they were enrolled randomly at a ratio of 1:1 in either of tramadol/paracetamol group or novel combination drug group. The patients were asked to take one tablet every 6th hour for five consecutive days. All patients in both groups ($n = 250$ in each group), were advised to attend the out-patient clinic on morning of day 6 for clinical evaluation. At the follow-up visit, the patient's responses to the study drug were recorded in a standardized patient pain form. The patients were advised not to use any other analgesic medication, local gel, heat, massage etc. Patients who could not get enough pain relief with the given drug were asked to attend the clinic for review and issue of other prescription analgesic and withdrawn from the study.

4. Outcome variables

Primary efficacy variable was the rate of patients responding to treatment based on treatment satisfaction as recorded on the 6th day using a 4 point verbal pain relief scale (0 = poor response, 1 = fair, 2 = good, 3 = excellent). A patient was pre-defined as responder with rating of 2 or 3 with no intake of rescue medication during the study period.

Secondary efficacy variable was assessment of the pain intensity score, recorded at baseline and again on 6th day using a 6 point pain intensity scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = very severe pain and 5 = worst possible pain). A patient treatment was predefined as effective with pain intensity rating of one and below (no pain or mild pain).

Safety and tolerability assessment throughout five days of study period was evaluated. Analysis of adverse reactions including incidence and frequency of the adverse reactions were recorded by the doctor in patient pain form.

5. Statistical analysis

Mann–Whitney test was used to compare the pain intensity scores at baseline before start of treatment. Post treatment the proportion of patients in both groups with pain response score of 2 & 3 (good and excellent) and the pain intensity score of 0 & 1 (no pain or mild pain) were evaluated with Z-test. In order to find out whether any association existed between the two groups with regard to the presence/absence of adverse effects, chi-squared test was used. The treatment difference were considered significant at $p < 0.05$.

6. Results

A total of 520 patients were enrolled in the study, 260 patients in each group. 6 patients in tramadol/paracetamol group and 8

Table 1 – Comparison of pain intensity score at baseline in both groups.

Drug	Mean	Std dev	SE of mean	Mean difference	Z	P-value
Tramadol/paracetamol caffeine/taurine (novel analgesic)	3.04	0.79	0.05	0.079	–0.906	0.365
Tramadol/paracetamol	2.96	0.85	0.05			

Table 2 – Comparison of response to treatment (good & excellent) in both groups.

Pain relief	Tramadol/paracetamol/caffeine/taurine (novel analgesic) (N = 252)		Tramadol/paracetamol (N = 254)		Difference in proportion	95% CI for difference	Z	P-Value
	n	%	n	%				
Good & excellent	203	81%	115	45%	0.35	0.10,0.25	8.21	<0.001*

patients in novel combination drug group were lost to follow-up. Hence 506 patients completed the study without major deviations and were evaluated. The baseline characteristics of patients with regard to sex (M:F-1.3:1), age in years (average 43 yrs) and pain intensity were comparable in both groups. Though patients with severe pain intensity at study entry were slightly higher in the novel combination drug group compared to tramadol/paracetamol group, but the overall mean pain intensity was not statistically significant ($p = 0.365$) between the groups at baseline (Table 1).

7. Efficacy outcome

- Treatment satisfaction:** the proportion patients responding to the medication based on treatment satisfaction or responders (2 = good or 3 = excellent) in novel combination drug group were significantly higher compared to tramadol/paracetamol group ($p < 0.001$) (Table 2 & Fig. 1).
- Pain intensity:** the proportion of patients with mean pain intensity measured using a numerical scale, who had no pain or mild pain at end of the treatment were significantly higher in novel combination group compared to tramadol/paracetamol group at the end of treatment (Table 3 & Fig. 2).

8. Safety outcome

Common expected adverse drug reaction like nausea, vomiting and dizziness occurred in both the study groups. The

Fig. 1 – Treatment satisfaction recorded on 6th day (post-treatment). ■ Tramadol/paracetamol/caffeine/taurine (novel analgesic), □ Tramadol/paracetamol.

incidence of treatment related adverse drug reactions were significantly higher in tramadol/paracetamol group compared to novel combination drug group (Table 4). The most common adverse drug reaction noted in both group was nausea with lesser frequency in novel combination group compared to tramadol/paracetamol group. All adverse reactions noted in this study were minor in nature (Table 5); there was no reported serious adverse drug reaction in either of the patients groups. None of the patients pulled out of the study due to adverse drug reactions.

9. Discussion

Worldwide, 37% of low back pain was attributed to occupational risk factor.⁹ In each region, the attributable risk factor was higher for men than women, largely because of men's higher participation in the labor force and occupation with heavy lifting. The natural history of back pain is favorable overall; studies show that 30–60% of patients recover in one week, 60–90% recover in six weeks and 95% recover in 12 weeks.¹ Acute low back pain is usually self limited and has no serious underlying pathology.

The most commonly used medicines for acute low back pain are paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), skeletal muscle relaxants and opioid analgesics. A challenge when choosing pharmacological therapy for low back pain is that each class of medicine is associated with its own risks and benefits.

In recent years, pain management has focused on the therapeutic potential of combining analgesic medications with complementary pharmacodynamic actions so that the components of the combination should provide synergistic analgesia; reduce the dosage of each ingredient with a better safety profile.

Tramadol and acetaminophen is a rational combination of analgesic, in that their mechanisms of action do not overlap and various clinical studies prove this combination acts synergistically.

Tramadol is a synthetic codeine analog that is a weak μ -opioid receptors agonist. Part of its analgesic effects is produced by inhibition of uptake of norepinephrine and serotonin in central pain pathways.

Table 3 – Comparison of pain intensity score at end of treatment in both groups.

Pain intensity	Tramadol/paracetamol/caffeine/taurine (novel analgesic) (N = 252)		Tramadol/paracetamol (N = 254)		Difference in proportion	95% CI for difference	Z	P-value
	n	%	n	%				
No pain and mild	210	83%	168	66%	0.17	0.27, 0.43	4.45	<0.001*

Fig. 2 – Pain intensity as recorded on visit day 6 (post-treatment). ■ Tramadol/paracetamol/caffeine/taurine (novel analgesic), □ Tramadol/paracetamol.

Paracetamol is a non-opioid, non-salicylate analgesic with an unclear mechanism of action. It appears to have some central actions including inhibition of N-methyl-D-aspartate, substance P mediated nitric oxide synthesis and release of prostaglandin E2.¹⁰

Literature review has shown that the combination of tramadol/paracetamol was effective in pain relief to patients with moderate- to-severe low back pain, to increase function at three months. Compared to placebo, this combination was also effective in sub acute low back pain patients and enabled a 25% reduction in the tramadol dose, which considerably reduced the incidence of adverse effects and improved tolerability. One of the major drawbacks of this combination is nausea, vomiting, dizziness mainly due to the opioid component.¹¹

Caffeine, a mild CNS stimulant mitigates the protein synthesis of COX-2.⁶ In this way, caffeine combination enhances the inhibition of COX-2 activity and enhances analgesia in combination with paracetamol. Studies show caffeine accelerated acetaminophen absorption, resulted in enhanced and prolonged analgesic activity of acetaminophen.¹²

Literature review shows number of clinical studies evaluating caffeine as an analgesic adjuvant from patients with postpartum uterine cramping or episiotomy pain, oral surgery, headache, backache to abdominal cramping. To obtain the same amount of response from an analgesic without caffeine requires a dose that is approximately 40% greater than one with caffeine.¹³

Studies have determined the anti-nociceptive effect of tramadol and caffeine administered separately or in combination, as well as their synergistic interaction and concludes that this is a synergistic combination useful in treatment of pain. A 2010 study published in "Pharmacology, Biochemistry and Behavior" looked at the effects of caffeine and tramadol on the reduction of pain sensitivity when administered alone or in combination. The researchers discovered that caffeine and tramadol administered together had a much greater effect on pain management than the administration of either product alone. They determined that a combination of tramadol and caffeine created a useful therapy for pain management.⁵

Caffeine strengthens not only the analgesic effect of NSAIDs, acetyl salicylic acid and paracetamol, but also eliminates possible sedative effects that can be evoked by various analgesics. Together with its light mood-elevating effects, this contributes to the completeness of the desired therapeutic effect for patients suffering from pain and is thus useful.⁶

Taurine, a vital amino acid influences the membrane structure and the function of tissues and cells and exhibits antioxidant and anti-aggregative effects. Taurine is also known to have an effect on cell proliferation, inflammation and collagenogenesis.¹⁴ The role of taurine in the clinical management of wide range of medical and surgical problems is promising.¹⁵

In this current study we have evaluated the analgesic efficacy of tramadol/paracetamol/caffeine/taurine compared with tramadol/paracetamol only in treatment of acute low back pain. The analgesic efficacy in terms of proportion of patients responding based on treatment satisfaction (good and excellent) and measurement of pain intensity (no pain or mild pain) at end of treatment were significantly higher in the novel combination drug group with taurine and caffeine.

The incidence of adverse reactions was also statistically low in the group that had caffeine and taurine, with nausea the most common adverse effect, similar to other studies. Common expected adverse drug reaction like nausea, vomiting and dizziness occurred with far less frequency in patients under novel combination group. This could be attributable to caffeine resulting in enhanced analgesic action and decreased incidence of adverse reactions.

Table 4 – Comparison of Adverse drug reactions in both the study groups.

Adverse reaction	Tramadol/paracetamol/caffeine/taurine (novel analgesic) (N = 252)		Tramadol/paracetamol (N = 254)		Total	χ^2	P-value
	n	%	n	%			
	42	16.67%	167	65.75%	209	125.694	<0.001*

Table 5 – Adverse drug reactions in both the study groups.

Adverse reaction	Tramadol/paracetamol/caffeine/taurine (novel analgesic) (N = 252)	Tramadol/paracetamol (N = 254)
Nausea	11.90% (n = 30)	44.09% (n = 112)
Dizziness	7.93% (n = 20)	40.15% (n = 102)
Vomiting	3.96% (n = 10)	30.70% (n = 78)

10. Conclusion

This novel combination of tramadol/paracetamol with caffeine and taurine had a superior analgesic effect to tramadol/paracetamol only tablet, with less adverse reactions in patients with moderate to moderately severe acute low back pain.

11. List of study doctors in alphabetical order

Dr. A. K. Sharma (Uttar Pradesh); Dr. A. V. Shivayogi (Karnataka); Dr. A.N. Dinesh Shankar (Kerala); Dr. Anandamay Sain (West Bengal); Dr. Anil Mahajan (Madhya Pradesh); Dr. Ardendu Narayan Ghosh (West Bengal); Dr. Arun Bajaj (Rajasthan); Dr. Ashok Vaishnavi (Gujarat); Dr. Atul Patil (Maharashtra); Dr. Benu Gopal Das (West Bengal); Dr. Brian S. Coutinho (Maharashtra); Dr. C.T. Kiruba (Tamil Nadu); Dr. D. Balaji (Karnataka); Dr. D. Maheshwar (Andhra Pradesh); Dr. Dev Kumar Chauhan (Delhi); Dr. Dilip Palange (Maharashtra); Dr. G. P. Bhargava (Uttar Pradesh); Dr. Gurdeep Singh (Uttar Pradesh); Dr. H. P. Shobha (Karnataka); Dr. K. S. Anand (Bihar); Dr. M. Vishweswara Rao (Andhra Pradesh); Dr. M. Murali Mohan (Andhra Pradesh); Dr. M. Murugappan (Tamil Nadu); Dr. Mangesh Panat (Maharashtra); Dr. Milind D. Modak (Maharashtra); Dr. Mohit Kumar (Bihar); Dr. N. Passam Laloo (Assam); Dr. Nemi Chand (Rajasthan); Dr. Nimish V. Relan (Maharashtra); Dr. Omvijay B. Chaudhari (Maharashtra); Dr. P.K. Padmapati (Assam); Dr. R. B. Mishra (Uttar Pradesh); Dr. Rajeev B. Potdar (Maharashtra); Dr. Rajeev Pathak (Maharashtra); Dr. Rupraj M. Pawar (Maharashtra); Dr. S. Chandrasekar (Tamil Nadu); Dr. S. P. Srivastava (Uttar Pradesh); Dr. S.V. Sathyanarayana (Tamil Nadu); Dr. Sandeep Sharma (Rajasthan); Dr. Sanjay Gupta (Madhya Pradesh); Dr. Satish Chandra Mathur (Rajasthan); Dr. Shyam Gohil (Gujarat); Dr. Sudhir Gupta (Uttarakhand); Dr. U. G. Nachinolcar (Goa); Dr. Uma Shankar S.N (Andhra Pradesh); Dr. V. Braha-deeswaran (Tamil Nadu); Dr. Ved Prakash (Andhra Pradesh); Dr. Vikram Jeet Singh (Delhi); Dr. Vinod Shankar Chouhan (Bihar); Dr. Yusuf K. Bagasarwala (Maharashtra).

Conflicts of interest

The author has none to declare.

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