

ANALGESIC EFFICACY OF TRAMADOL/ ACETAMINOPHEN COMBINATION WITH DICLOFENAC SODIUM IN MODERATE TO SEVERE LOW BACK PAIN

Faiza Fakhar¹, Farzana Sadaf^{2*}, Imran Shah³ & Ishrat Younus²

¹Pharmacy Services, Department of Health, Government of Sindh, Karachi

²Department of Pharmacology, Faculty of Pharmacy, Hamdard University Karachi.

³Department of Planning and Warehouse Management, Getz Pharma, Karachi.

*Corresponding author: Farzana.Sadaf@hamdard.edu.pk

ABSTRACT: This prospective randomized cohort study was conducted in two parallel groups to compare the analgesic effects in conventional use of oral Diclofenac tablet, 50 mg tablet three times daily or 75 mg tablet twice daily (DIC group) with oral combination of Tramadol 37.5 mg and Acetaminophen (Paracetamol) 325 mg (T-APAP group) one tablet twice daily. The number of patients n= 150 in each group. Study data of total 300 patients of age 20 - 60 years, with moderate to severe Low back pain (LBP) was collected from the public and two private setup OPDs in Karachi, Pakistan. Patient demographic data of gender, age, BMI and socioeconomic status were collected. Numeric Pain Rating Scale (NPRS) was used to measure pain intensity and overall pain intensity at the baseline 0, 1st, 2nd, 3rd and 4th week of the treatment. The results indicated that the incidence of Low back pain (LBP) is highest 41.0 % (n = 123) in 30-39 years age group. According to Body Mass Index (BMI) classification most of the patients 63.6 % (n = 191) patients are overweight. In socioeconomic classification 47.3 % (n = 142) are from lower socioeconomic status. The duration of perceived pain was found to be shorter with 58.6 % (n = 88) recovery within one week of the treatment in the T-APAP Group, compared to 35.3 % (n = 53) recovery in DIC group (p< 0.05). Oral combination of Tramadol plus Paracetamol is found to be more effective than the use of oral Diclofenac alone. 79.4 % Overall Pain Relief with 5.8 scores of Overall Pain Relief (p< 0.05) were observed in the T-APAP Group. It is concluded that the oral combination of Tramadol 37.5 mg and Acetaminophen (Paracetamol) 325 mg is more effective analgesic than oral use of Diclofenac sodium alone in moderate to severe LBP.

KEYWORDS: Diclofenac, Tramadol and Acetaminophen, Low back pain

INTRODUCTION

The Global Burden of Disease Study of year 2010 indicated that LBP is one of the top 10 high-burden diseases and injuries [1]. In 2013 Global Burden of disease indicated that in 188 countries, LBP in terms of pain is the

first ranking cause of pain in people who live with disability, among all the acquired or congenital conditions [2]. In United States National Ambulatory Medical Care Survey 2017 reported LBP is one of the most common symptoms for patients' visits at

primary care setting [3]. Moreover, overall burden and in terms of disability, Global Burden of Disease Study reported that in 310 conditions, back pain was at highest rank, from year 1990 till 2015 [4]. In general lifetime prevalence of LBP is 60- 85% and about 15% of adults experience LBP at any one time in their lives. Most cases of LBP are non-specific, and only 5- 10% of cases are caused by specific condition [5]. The exact cause of LBP is unclear. It is considered that a muscle sprain, a minor ligament injury or synovitis of the facet joint could have given the nociceptive impulses in patients who usually recover within two to three weeks. Although, patients suffered for four to eight weeks have ligament or tendon injury to a greater extent. The healing time for a disc injury is longer when compared with muscular injury [6]. It was observed that the prevalence of LBP is high in adults [7]. Studies showed that elderly population experience Acute Low Back Pain (ALBP) less frequently rather they experience severe, chronic, and disabling episodes of Chronic Low Back Pain (CLBP) [8].

In recent studies it was indicated that obesity in individuals is associated with LBP [9]. The incidence of LBP is higher in obese people [10]. Many psychosocial factors such as anxiety, depression, lower social status etc. have been associated with LBP but their role is uncertain. It is reported that these psychosocial factors have impact on transition of acute, sub-acute and chronic LBP [11]. In the treatment of non-specific LBP, short term use of NSAIDs is recommended. Weak opioid analgesics can be added to the therapy. Muscle relaxants can be added when there is no improvement in the symptoms. Antidepressants are prescribed

when the patient has been diagnosed with depression, while the use of Gabapentin is not recommended [12]. Diclofenac sodium is a phenylacetic acid derivative which inhibits COX-2 more than that of COX-1 enzyme. It is metabolized and excreted in kidney and accumulated in the synovial fluid. The average adult daily dose of Diclofenac sodium is 25-75 mg; maximum daily dose is 150 mg [13].

European guidelines recommended that the use of weak opioid analgesic like Tramadol is preferable in patients of nonspecific low back pain NSLBP who are not responding to other analgesics [12]. The mechanism of action of Tramadol is mainly through inhibition of the reuptake of nor epinephrine and serotonin. It is a weak μ receptor agonist. Duration of action is 4-6 hours. The average adult dose is 50-100mg [14] with a maximum daily dose of 400mg [15]. At therapeutic dose it is tolerated well. Nausea and vomiting are the most common side effects. The mechanism of action is not defined, the pharmacological effect is suggested that it inhibits PG synthesis in the CNS as well as it is a selective inhibitor of COX-2 enzyme. It also inhibits the COX-3 enzyme in the brain cells. Average daily adult dose is 500-1000 mg. The maximum dose is 4g daily [16]. An oral combination of Tramadol and Acetaminophen is used to achieve maximum analgesic effects, specifically in moderate to severe pain. Therefore, with all these perspectives, the present study was conducted to compare analgesic effects of oral Diclofenac (DIC group) with Tramadol-Acetaminophen (T- APAP) combination drug in moderate to severe low back pain.

MATERIAL AND METHODS

Study Design

This is a prospective randomized cohort study which conducted in two parallel groups to evaluate and compare the efficacy of early prescription of opioid analgesics in fixed oral dose combination of Tramadol hydrochloride 37.5mg plus Acetaminophen 325mg versus oral Diclofenac sodium for pain management in the patients of acute LBP for period of 4 weeks with a follow up until the condition subsides. Study data was collected in the Outpatient Departments of government and private setup in Karachi, Pakistan. Study data was collected from January 2020 till December 2020. Before studying, an informed consent form was given to all the participants to document their willingness to participate in the study. The consent form was written in Urdu language, and it contains the study topic, objective of the study, data collection method, confidentiality of participant identity and collected data, participant's agreement, and signature. Patients were also informed and counseled verbally. The study was approved by the Ethical Review Board of Hamdard University prior commencement.

Sample Size

Sample size was calculated by sample size calculator Open Epi website [17]. The sample size of the study was calculated as 300.

Treatment Groups

Post inclusion the participants were divided into two treatment groups, the Tramadol plus Acetaminophen (T-APAP Group) and the Diclofenac (DIC Group). Patients in T-APAP Group were prescribed the fixed

dose combination tablet of Tramadol hydrochloride 37.5 mg plus Acetaminophen 325 mg. The dose was adjusted according to patient condition and intensity of pain from one tablet twice daily up to maximum dose of 8 tablets per day that is two tablets four times daily. Patients in DIC Group were prescribed oral Diclofenac sodium in dose of 50 mg tablet three times daily or 75 mg tablet twice daily up to maximum dose of 150 mg per day [18]. Patient consumption of prescribed analgesics was confirmed by counting empty pockets in tablet strips as patients were asked to bring used tablet strips along with them at each visit in the OPD.

All selected patients were counseled not to use other analgesics and topical analgesic preparations during the study period. Massage therapy with oil, exercise and hot compression were allowed. Patients who were already receiving physiotherapy before the study initiation continued the therapy throughout the study period; otherwise, physiotherapy was not encouraged to be started during the study period. Patients who were on anti-hypertensive treatment were monitored for clinically significant drug interactions with NSAIDs throughout the study period.

Patients' Inclusion Criteria

Following are the criteria for patient included in the study.

• Patients who signed the consent form prior to study initiation and those who were willing to participate and cooperate during the study period.

• Patients who had been suffering from acute LBP (with or without leg pain) and those who had been diagnosed with Non-specific LBP after physical examination and conformational tests.

- Patients from age 20 to 60 years
- Postmenopausal females and those were using effective contraceptive methods were included in the study.

Patients' Exclusion Criteria

Following are the criteria for patients excluded from the study.

- Patients who completely refused to participate in the study before initiation.
- Participants who did not give complete follow up data.
- Patients who had been experiencing LBP due to specific underlying pathologies such as spinal infection, spinal tumor, cancer, osteoporosis, gout, arthritis, vertebral fracture, disc slip, hernia, or spinal stenosis
- Patients who had been diagnosed with psychiatric illness, epilepsy, hepatic failure, or renal dysfunction.
- Patients who had a history of alcohol abuse, substance abuse or other drug abuse including opioids
- Patients who were taking antidepressants, antipsychotic drugs, antiepileptic therapy, sedative and hypnotics or corticosteroids
- Patients who had undergone back or spinal surgery.
- Patients who had received acupuncture and chiropractic treatment three months before the study initiation were excluded from the study. During the study period such treatments are discouraged.
- Children under 18 years of age and elderly patients over 60 years of age were excluded from the study.
- Pregnant females and females of childbearing age who were not

using any effective contraceptive methods.

Pain Assessment Tools

A questionnaire was designed to provide complete data about patients' demographics (Age, Body Weight, and Socioeconomic Status), medical history, medication history, duration of condition. If the pain is radiating towards the leg, previous usage of other analgesics and Numeric Pain Rating Scale (NPRS) were measured for assessment of current pain and overall pain. The designed questionnaire was filled in by all patients with the help of physician and pharmacist on 0, 1st, 2nd, 3rd and 4th week of the treatment until the patient condition subsided.

Pain Intensity

Numeric Pain Rating Scale (NPRS) of total 11 scores from 0 to 10 was used in assessment of pain intensity. NPRS is reliable, valid, and easy for subjects to quantify the intensity of acute and chronic pain and analgesic effect [19] in adults and children [20, 21]. In the designed questionnaire the patient has to encircle the score which defines his current pain as well as overall pain in two NPRS [22] of total 10 scores whereas,

- 0 – equals to no pain
- 1 – pain is very much improved
- 2 – much improved pain
- 3 – minimally improved pain
- 4 – no change in pain
- 5 – moderate pain
- 6 – moderate to worse pain
- 7 – minimum worst pain
- 8 – much worse pain
- 9 – very worse or severe pain
- 10 – worst possible pain

Duration of Perceived Pain: Time period of the treatment was noted from the initial day on which patient has started taking the

prescribed analgesic till the date on which patient felt no pain or if they felt that the pain is tolerable enough that there is no need to continue the use of the prescribed analgesic.

Pain Intensity Difference

Pain Intensity Difference (PID) at specified time is calculated using the formula,

$$PID_t = P_b - P_t$$

Where, PID_t is the Pain Intensity Difference after a specified time, P_b is the Baseline Pain Intensity and P_t is the Pain intensity at that specific time.

Overall, Pain Relief

Overall, Pain Relief is calculated using following formula.

$$PID_{0-4} = P_b - P_4$$

Where PID_{0-4} is the Overall Pain Intensity Difference after 4-week treatment, P_b is the Baseline Pain Intensity and P_4 is the Pain intensity at that 4th week of the treatment.

Percentage Overall Pain Relief

Overall, Pain Relief Percentage is calculated using following formula.

$$\%PID_{0-4} = [(P_b - P_4) / P_b] \times 100$$

Where, $\%PID_{0-4}$ is the Percentage Overall Pain Relief after 4-week treatment, P_b is the Baseline Pain Intensity and P_4 is the Pain intensity at that 4th week of the treatment.

RESULTS

Patient Demographic Data

Age Group: Following are the patient demographic data observed and calculated during the study. The number of cases and their respective percentages of age groups 18 – 29 years, 30 – 40 years, 41 – 50 years and 51 – 60 years, are mentioned in the Table 1. **Body Mass Index Classification:** Based on measured weight in kilograms and height in meters of the selected cases, it is calculated

that 9.0 % (n = 27) patients were underweight, 17.3 % (n = 52) patients were normal, 63.6 % (n = 191) patients were overweight, and 10.0 % (n = 30) patients were obese as per Body Mass Index classification by the World Health Organization [23].

Socioeconomic Status

It was observed that 47.3 % (n = 142) patients belonged to lower class, 34.6 % (n = 104) patients belonged to middle class and 18.0% (n = 54) patients were from upper socioeconomic status.

Exclusion Cases: In our study 35 patients were excluded due to noncompliance and failed follow-ups in OPDs. 11 patients out of 35, changed to homeopathic treatment, chiropractic care, home remedies and other methods. 3 patients refused to continue the treatment due to some minor side effects including dizziness, nausea and abdominal pain.

Duration of Perceived Pain: In the DIC Group, out of 150 patients of LBP, 64.6 % (n = 53) patients had almost complete pain relief in the first week of the medication use; 46.6 % (n = 80) of patients had pain relief in the second week of the medication use; 90.0 % (n = 15) patients had pain relief in the third week of the medication use and 98.6 % (n = 2) patients had complete pain relief on the fourth week of the medication use. In the T - APAP Group, out of 150 patients of LBP, 41.3 % (n = 88) patients had almost complete pain relief in the first week of the medication use; 70.6 % (n = 44) of patients had pain relief in the second week of the medication use, 88.0 % (n = 18) patients had pain relief in the third week and 100.0 % (n = 0) patient experienced pain relief on fourth week of medication use.

Treatment Effect on Pain Intensity: Pain Intensity Scores of 150 selected cases of LBP were measured on Numeric Pain Rating Scale, for each treatment group. Patients were asked to rate the Pain Intensity on 0, 1st, 2nd, 3rd and 4th week of the treatment or until the patients felt no need to take more doses because the pain is manageable or no pain at all. The Average Pain Intensity Scores of 150 patients of the T-APAP Group (Tramadol plus Acetaminophen Treated Group) was 7.3 on the initial examination, 3.2 after the first week, 2.0 after two weeks and 1.5 after three weeks of treatment.

The Average of calculated Difference in

Pain Intensity Scores of 150 cases of the T-APAP Group were 4.1 from initial examination till first week of the treatment, 1.2 from first week till second week of the treatment and 0.5 from second week till third week of the treatment.

The Average Pain Intensity Scores of 150 patients of the DIC Group (Diclofenac Treated Group) was 6.6 on the initial examination, 3.6 after first week of treatment, 2.7 after two weeks of treatment, 2.3 after three weeks of treatment and 3.0 after four weeks of treatment with Diclofenac tablet which was prescribed on as per need basis.

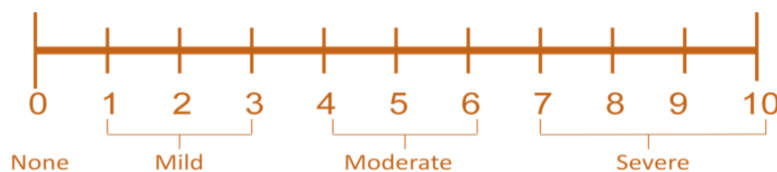


Fig 1: Numeric Pain Rating Scale from Scores 0 – 1

Table 1: Distribution of LBP cases according to Age Group

Age Group (Years)(n = 300)	Number of Cases	Percentage (%)
20- 29 Years	87	29.0
30- 39 Years	123	41.0
40- 49 Years	70	23.3
50- 60 Years	20	6.6

Table 2: Distribution of LBP cases according to Body Mass Index (BMI)

BMI Classification (Asia- Pacific) (n = 300)	Number of Cases	Number of Cases in Percentage (%)
Underweight <18.5	27	9.0
Normal 18.5 – 22.9	52	17.3
Overweight 23 – 24.9	191	63.6
Obese ≥ 25	30	10.0

Table 3: Duration for Perceived Pain

Treatment Groups	Pain subsided (no. of Patients)			
	(0-1 week)	(1-2 weeks)	(2-3 weeks)	(3-4 weeks)
DIC Group (n = 150)	53	80	15	2
	64.6 %	46.6 %	90.0 %	98.6 %
T - APAP Group (n = 150)	88	44	18	0
	41.3 %	70.6 %	88.0 %	100.0 %

Table 4: NPR Scores of Pain Intensity and Pain Relief

Treatment Groups	Pain Intensity (NPR Score)					Pain Intensity Difference PID = P _b - P _t			
	0 Week	0 - 1 Week	1-2 Weeks	2 - 3 Weeks	3 - 4 Weeks	0-1 Week	1-2 Weeks	2-3 Weeks	3-4 Weeks
	P _b	P ₁	P ₂	P ₃	P ₄	P ₀ - P ₁	P ₁ - P ₂	P ₂ - P ₃	P ₃ - P ₄
DIC Group (n = 150)	6.6 ± 0.105	3.6 ± 0.105	2.7 ± 0.105	2.4 ± 0.105	2.1 ± 0.105	3.0 ± 0.49	0.9 ± 0.49	0.3 ± 0.49	0.3 ± 0.49

T- APAP Group (n = 150)	7.3 ± 0.102*	3.2 ± 0.102*	2.0 ± 0.102*	1.5 ± 0.102*	Nil	4.1 ± 0.05*	1.2 ± 0.05*	0.5 ± 0.05*	Nil
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*p < 0.05

Table 5: Overall Pain Relief and Percentage Overall Pain Relief

Treatment Groups	Pain Intensity (NPR Score)		Overall Pain Relief $P_{b-4} = P_b - P_f$	% Overall Pain Relief
	0 Week / Initial Pain Scores P_b	4th Week / Final Pain Scores P_f		
DIC Group (n = 150)	6.6 ± 0.105	2.1 ± 0.105	4.5 ± 0.122	68.1 ± 1.3
T- APAP Group (n = 150)	7.3 ± 0.10*	1.5 ± 0.10*	5.8 ± 0.08*	79.4 ± 0.9*

*p < 0.05

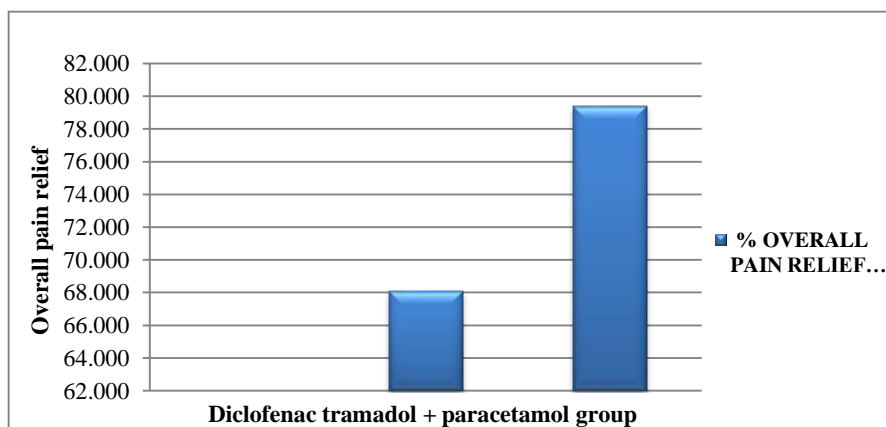


Figure 2- Comparison of Average Pain Intensity (0-4 Weeks)

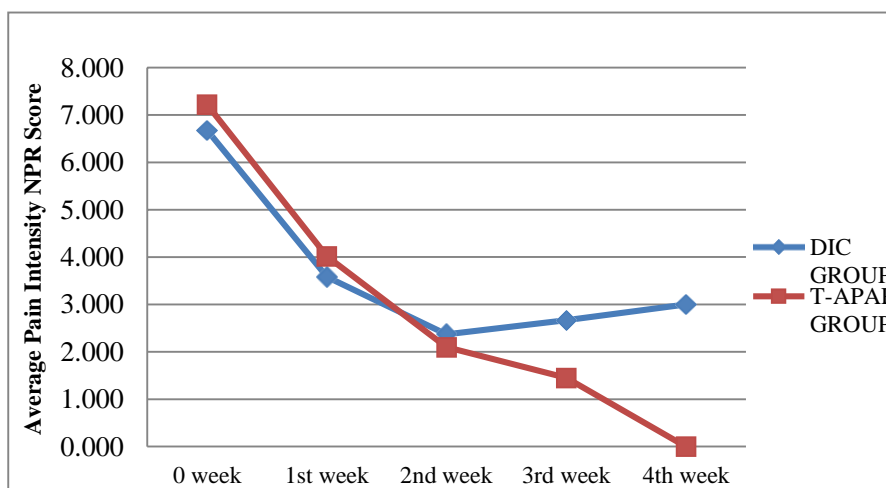


Figure 3-Comparison of Percentage Overall Pain Relief

The Average of calculated Difference in Pain Intensity Scores of 150 cases of the DIC Group were 3.0 from initial examination till first week of the treatment, 0.9 from first week till second week of the treatment, 0.3 from second week till third week and 0.3 from three weeks till four weeks of the treatment. (Diclofenac Treatment Group) and the T-APAP Group (Tramadol + Acetaminophen Treatment Group) from 0-1, 1-2, 2-3 and 3-4 weeks of the treatment.

Treatment Effect on Overall Pain Intensity

Overall, Pain Intensity Scores of 150 selected cases of LBP were calculated as differences of pain scores measured on 4th week of medication use from the baseline pain scores. Whereas Pain Intensity was measured on Numeric Pain Rating Scale from Scores 0 – 10 (Fig-1).

The average value of the Overall Pain Relief of 150 patients from the initial examination time till the complete course of treatment (up till four weeks) was calculated as 4.8 and the Percentage Fall in Overall Pain Relief was 27.4 %. The average value of the Overall Pain Relief of 150 patients from the initial examination time till the complete course of treatment (up till three weeks) was calculated as 5.6 and the Percentage Fall in Overall Pain Relief was 20.8 %. Percentage Pain Relief of DIC Group (Diclofenac Treatment

Group) and T APAP Group (Tramadol + Paracetamol Treatment Group) was calculated from the difference between the pain intensity scores observed at the end of the treatment from the pain intensity scores observed on initial assessment.

DISCUSSION

Pain is a subjective sensation which depends upon the individual characteristics of physiological as well as psychological functions. In this study the efficacy of conventional oral combination of Tramadol and Paracetamol were compared versus oral Diclofenac in selected cases of non-specific pain of the lower back region. Selection of the cases was carried out at the OPD of public and two private clinic setups located in Karachi.

Numeric Pain Rating Scale was used to obtain the subjective data of low back pain perception from 0 to 10 scale, in which 0 indicated no pain while 10 represented the worst pain felt. Difference of Pain Intensity Scores (the pain felt by the subject at the time of weekly follow ups) and the Overall Pain Relief (the difference in pain felt by the subject on the fourth week of medication use from the baseline pain scores) were used as tools to compare the primary outcomes of the both treatment groups. The secondary outcome which is the effect of oral combination of Tramadol and Paracetamol and Diclofenac use on the Disability Index was measured through

the scores obtained from Oswestry Low Back Pain Disability Questionnaire.

According to this study 41.0 % adults mostly suffered from LBP in 30 to 39 years age group, followed by 29.0 % young adults of 20 to 29 years of age and 23.3 % of older adults of 40 to 49 years age. With 6.6 % the least affected group of much older people who were aged from 50 to 60 years. The main reason is that acute LBP is more common in adult population, while chronic LBP is observed most in elderly population with increasing severity of disabilities due to degeneration [8]. A systematic review conducted in 2015 which included 28 studies with inclusion criteria irrespective of the year of publications and age of the study population concluded that the incidence of chronic LBP increases with age till 60 years [24].

Obesity and being overweight are considered as risk factors causing LBP. In this study it was observed that 63.6 % of the selected cases of LBP were overweight according to the WHO Asia-Pacific BMI classification. 10.0 % of studied subjects were found obese, low percentage is indicative that the selected individuals with LBP belonged from lower socioeconomic class. A meta-analysis of 10 cohort research studies, conducted in 2018, concluded that being overweight and obese are factors contributing to LBP among total 29,748 included subjects [25]. In 2017, a study concluded that high body fat percentage is a major factor associated with LBP [26]. In another meta-analysis systematic review in 2015, reported that out of 11 included research studies, 5 studies

concluded that obese and overweight people have double risk of having LBP when compared with individuals of normal weight [27].

Study conducted in 2017 reported that the rate of unemployment, low-income status and poor health insurance increased the length of disability among the U.S. population who were suffering from occupation related LBP [28]. However, in a baseline study with six months follow up method published in 2017, concluded that among 352 included German subjects of 18 to 65 years of age, job status is not directly related with pain intensity in chronic LBP [29]. It is observed in this study that a higher percentage, that is 47.3 % of the selected patients of LBP are from lower socioeconomic class.

This study results indicate that highest number, 88 selected LBP patients in the T- APAP Group who were taking oral combination of Tramadol plus Paracetamol have experienced almost complete pain relief earlier in first week of the medication use, than the patients from the DIC Group who were taking oral Diclofenac tablets for analgesia. It is also observed that the highest number, 80 patients in the DIC Group have experienced almost complete pain relief in second week of the treatment. This difference is clinically significant; however, the estimated p-value is statistically non-significant ($p > 0.05$). The results are comparable to a study conducted in 2020 on 82 Italian adult populations [30].

The average values of Pain Intensity Scores, Pain Intensity Differences during four weeks of medication use, Overall, Pain Relief and the Percentage Overall Pain

Relief in the DIC and the T- APAP Groups were compared, and it was observed that the analgesic effect on oral Tramadol plus Paracetamol use is more effective than oral Diclofenac alone. The results of Pain Intensity Scores, Pain Intensity Differences, Overall, Pain Relief and the Percentage Overall Pain Relief in the T- APAP Group are found to be statistically significant ($p < 0.05$) when compared with the average values of Pain Intensity Scores, Pain Intensity Differences, Overall, Pain Relief and the Percentage Overall Pain Relief in the DIC Group (Fig 3). The results are similar with study conducted in 2020; it was a comparison of analgesic effects between Diclofenac sodium and Tramadol hydrochloride use in traumatic orthopedic pain. (Fig-2) The study concluded that Tramadol hydrochloride is a more effective and better option in orthopedic pain than Diclofenac sodium [31]. According to double blind randomized crossover study was carried out with an aim to compare analgesic effect of 50 mg Diclofenac sodium plus 500 mg Paracetamol with 50 mg Tramadol plus 375 mg of Paracetamol on healthy individuals by using three different human pain models namely cold stress test, radiant heat model and blood pressure cuff inflation method. Fixed dose combination of 50 mg Tramadol with 375 mg Paracetamol was found to be more effective than 50 mg Diclofenac sodium plus 500 mg Paracetamol combination [32,33].

Conclusion

Combination of Tramadol plus Acetaminophen is found to be more effective than oral Diclofenac alone in LBP. Moreover, the duration of perceived pain is shorter in patients who were taking oral

combination of Tramadol plus Acetaminophen as most of the recovery or pain relief occurred in the early period of treatment.

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