

Research Article

Effectiveness of Orphenadrine & Paracetamol Combination (Searle Generic) in Myalgia with Anti-Pyretic Benefit in General Pakistani Practice (Nub-Effect): An Observational Study

Abaidullah Sajid^{1#} and Ali Qazi Masroor^{2#}

¹King Edward Medical University, Pakistan

²Quaid e Azam Medical College (QAMC), Pakistan

[#]Both the authors contributed equally

***Corresponding author**

Abaidullah Sajid, Professor of Medicine, King Edward Medical University, Lahore, Tel: 0092300 848403889;

Email: sajidabaidullah@kemu.edu.pk

Ali Qazi Masroor, Professor of Medicine, Quaid e Azam Medical College (QAMC), Bahawal Victoria Hospital (BVH), Civil Hospital, Bahawalpur, Pakistan, Tel: 0092300-9683228; Email: drqazimasroor@qamc.edu.pk

Submitted: 28 June 2018

Accepted: 31 July 2018

Published: 31 July 2018

ISSN: 2379-089X

Copyright

© 2018 Sajid, Qazi

OPEN ACCESS

Keywords

- Viral infections
- Myalgia & fever
- Orphenadrine/Paracetamol combination
- Effectiveness
- Pakistani population

Abstract

Objective: This study was conducted across 17 sites in nine major cities of Pakistan, to evaluate the safety and effectiveness of orphenadrine/paracetamol combination (Nuberol) in managing the viral symptoms like myalgia and fever among the local population.

Study design: In this observational, prospective, multicenter study, 300 patients with known prescreened viral infections having myalgia and fever were recruited. While patients with hypersensitivity to the formulation, contra-indication and pregnant, or breastfeeding women were excluded.

Interventions: The safety evaluation was done as per prescribing information for Nuberol. Myalgia was assessed through the Visual Analogue Scale (VAS), fever was monitored by recording temperature on 24 hourly monitoring chart and safety evaluation started on day 1 of the treatment. As per physician discretion, the treatment therapy was planned (5-10 days) with 2 follow-up visits, screening (visit 1), and after 6-10 days of treatment (visit 2).

Results: Of 300 recruited patients, 168 (56%) were males and 132 (44%) were females with a mean age of 36.79 ± 13.65 (S.D). According to the results, flu was the most prevalent viral infections 244 (81.3%), among the study sample followed by Chikungunya 36 (12%) and 9 (3%) patients with dengue. The pain intensity and fever were decreased using the therapeutic combination, on visit 1, 203 (67%) patients had mild-moderate pain (VAS, 3-6) and 12 (4%) patients reported severe pain (VAS, 7-8). Upon the follow-up visit (visit 2- after 5-10 days treatment), 239 (80%) patients were having no pain, whereas 59 (19%) patients reported mild pain (VAS, 1-2). While the fever was subsided in almost 297(99.6%) patients in 4-6 hours by visit 2.

Conclusion: The combination of Orphenadrine/Paracetamol (Nuberol) showed effective and safe in the symptomatic management of myalgia and fever in viral conditions among Pakistani population.

INTRODUCTION

Acute viral infections are contagious and can be easily transmitted from person to person for e.g.: Seasonal Influenza [1]. It is estimated that an Influenza epidemic affects 500 million people worldwide [2]. According to WHO, each year approximately 5 to 10 percent of adults are globally affected with flu [3]. Pakistan, despite being the developing country with tropical to temperate and rapid climate change; there is little information about Influenza among the Pakistani population [4].

Overall 146,914 cases of Chikungunya were reported to the Pan American Health Organization (PAHO) regional office in the year 2016 [5,6] and 3.2 million cases of Dengue in 2015 were reported worldwide [7,8]. As for Pakistan, in 2011 a most

horrific outbreak of dengue occurred in Lahore with more than 300 deaths, and 21,314 cases whereas in 2016 outbreak of Chikungunya took over Karachi, 30,000 were estimated to have Chikungunya out of which only 803 cases were reported [6,9,10].

Whereas Fever and myalgia were the main reasons of reducing the quality of life in above mentioned cases [11] and according to one report, along with high-grade fever, myalgia is the most common intensive symptom that occurs in patients affected with viral infection [7]. In Pakistan the incidence of these viral infections have greatly increased during the past few years [6]. In general practice, the most challenging is to treat myalgia and improve the quality of life in patients suffering from specific viral conditions, for example; Dengue, Influenza, Chikungunya etc.

Myalgia is described as persistent muscular pain, stiffness, cramping sensation and functional impairment [6]. Most of the etiological reasons are benign and self-limited as myalgia is usually triggered by either excessive exertion, traumatic event or any viral infection [12]. Hence, the severity can be severe, mild or moderate depending upon the cause and its intensity [12]. As the etiology is multi-factorial, the diagnosis and treatment of myalgia along with fever become challenging and varies with the severity and chronicity of the disease because the progression is widely diversified and unpredictable [13].

The treatment for these viral conditions to improve patients' quality of life, are mostly focused on treating symptoms. Thus, includes the use of NSAIDs, anti-histamines and paracetamol (alone) is usually preferred for the symptomatic relief [14]. While, Aspirin is contraindicated due to its effect on platelet activity and anti-histamines use is now prohibited because of their side effects due to non-selectivity of receptors [14,15]. According to the previous evidence, the use of corticosteroids, antibiotics, or antiviral drugs in the management of viral fevers are not supportive, and its indiscriminate use can be hazardous [16].

Orphenadrine was found to be more useful therapeutic agent for muscle spasm because of its role as a muscle relaxant, either alone or in combination with paracetamol [17]. The combination therapy is perceived, as a logical way to attain greater clinical efficacy [13], avoid polypharmacy, and unnecessary adverse effects due to multiple drug interaction [16]. Although Orphenadrine and Paracetamol, both are clinically useful individually but the combination produces more significant outcomes as compared to their pharmacological actions separately [18,19]. According to many recent studies, the reputation of polypharmacy has become disputed as it involves multiple drugs with a variety of mechanism of actions that not only involve multiple drug interactions but also reduces the patient compliance [20,21]. While there are some studies supporting the viewpoint that the side effects of the combination product can be managed by adjusting therapeutic dose levels [18].

Global and local data have suggested an increase in occurrence of endemic viral infections, where myalgia and fever were most often reported in affected patients [7-11], therefore, the current study was conducted to determine the efficacy and safety of a single-dose drug Nuberol, which is the combination of both Orphenadrine and Paracetamol. Moreover, this combination may be useful for the management of acute pain, for the long-term relief comprehensive treatment of the underlying cause is necessary.

METHODOLOGY

Study design

The Observational, Prospective, cohort study was designed as a multicenter. The investigators as per the study protocol prescribed Nuberol (combination of Orphenadrine/Paracetamol) for 5-10 days during their clinical practice. The patients' status was, prescribed known case of viral infections with associated

symptoms of fever and myalgia at the time of screening visit. Nuberol (combination of Orphenadrine/Paracetamol) was administered orally as per physician discretion.

Study population

As per the study inclusion/exclusion criteria, patients with known prescreened viral infections with the complaint of myalgia and fever were recruited. Pain intensity is not easily recorded, however, the visual analogue scale is the most sensitive method and is widely recommended for clinical studies [19]. The study assessed myalgia by VAS scale, fever by monitoring the temperature and overall safety and tolerability of the combination drug was evaluated from the day 1 of the treatment, as per physician discretion for the treatment therapy (5-10 days) with 2 patient visits, screening - visit 1 and visit 2 after 6-10 days treatment.

INSTRUMENTATION

Primary end point

The primary efficacy endpoint was myalgia management response measured by the VAS scale in 5- 10 days treatment. The VAS scale measured the pain intensity as no pain (0), mild pain (1-2), moderate pain (5-6) and severe pain (7-10). Patients were asked to mark the number of pain intensity given in a VAS. While the fever was monitored by recording the temperature each hour for 5-10 days through a monitoring chart where 98°F was considered afebrile, <100°F is mild grade, 101° < 104°F moderate grade and 104<°F high-grade fever.

Description of study visits and timing of assessments

Entry visit (V1) (baseline): All patients were informed about the nature and purpose of the study and informed consents were obtained. The patients were evaluated and the selection was made on the basis of inclusion/exclusion criteria. The details regarding patient demographics, vital signs (Including body temperature, respiratory rate, and blood pressure), relevant medical history, systemic examination, temperature, VAS scale scoring, concomitant medications, study medication were recorded in the case report form (CRF).

Visit (V2): A follow-up visit was planned for all enrolled patients, 5-10 days after the baseline visit. These subjects were evaluated for clinical response after 1-2 weeks treatment with the study drug, all the parameters were re-recorded in the follow-up visit and effectiveness and safety was assessed and adverse event (AE) were also evaluated through AE form available in CRF.

Statistical analysis

Data entry and analysis was done through the Statistical Package for Social Sciences (SPSS) version 21. P value < 0.05 was considered significant. Calculated means and relative risks were presented. Subjects were observed and the overall clinical response as effectiveness and safety before and after drug consumption was assessed.

Study oversight

This study was approved by the independent ethics committee at each participating site and conducted in compliance with Good

Clinical Practice guidelines, and local regulatory requirements. The study is supported and funded by Searle. The Searle research unit in collaboration with the principal investigators facilitated the study sponsor in preparing the documents. To maintain the GCP compliances, the sponsor assigned the CROs to monitor the study and performed the statistical analysis. The IEC reviewed the progress of the study. The confidentiality of the data was maintained. A Searle research department in collaboration with the study sponsor and others PIs were involved in the manuscript preparation.

RESULTS

In this study, a total of 300 patients were recruited out of which 168 (56%) were males and 132 (44%) were females (Table 1) while 298 patients successfully completed the study. 2 patients (0.7%) failed to visit for follow-up (Visit 2). The recruited patients reported mild pain along with other comorbidities like hypertension (4.2%), Diabetes Mellitus (5.6%) and others (4.3%).

Figure 1 shows the predominant viral infections among the study population. According to the results, the most commonly reported viral condition was Flu (81%), followed by Chikungunya and Dengue (12% and 3% respectively).

On visit 1, 203 (67.7%) patients had mild-moderate pain as indicated by the VAS score 3-6 and 12 (4%) patients had severe pain, VAS score 7-8. Upon follow-up, visit 2 (after 1-2 weeks treatment) 239 (80%) patients reported no pain, whereas 59 (19%) patients had mild pain with the VAS score 1-2 (Table 2). These patients reporting mild pain were mainly suffering from Chikungunya (61%) followed by and Dengue fever (15.2%).

The antipyretic effects of the combination drug at visit 1 and visit 2 is shown in Table 3. On visit 1, 227 (75.6%) patients were having a mild fever, 62 (20.6%) patients reported moderate fever and 11 (3.6%) patients had a high-grade fever. Whereas, on visit 2, 297 (99.6%) patients became afebrile and only 1 case was reported with a mild fever. The fever was subsided on average in 4-6 hours, monitored by the patient on daily basis on the designed fever monitoring chart.

Adverse events were recorded from the first dose of the study drug, 11 (3.9%) patients reported adverse events during

the course of the treatment (Table 4), mainly dryness of mouth, sedation, nausea, and constipation. However, this did not affect the results as no serious adverse event was reported.

DISCUSSION

The study results indicate that flu was the most prevalent viral condition among the participants (Figure 1). Secondary to flu, Chikungunya, and dengue were also prominent viral infections among the study subjects with associated symptoms of fever and myalgia (Figure 1). It is greatly noticeable that Chikungunya virus is actively circulating in Pakistani population [15]. Although it is self-resolving but may become fatal with increasing severity [15]. Viral diarrhea and HCV were the less common threats as reflected by the results (Figure 1).

Patients with above mentioned viral infections were prescribed a combination of Orphenadrine/Paracetamol and a significant pain-relieving effect was clearly observed as indicated by the VAS score in visit 1 that majority of the patients (67.7%) reported the presence of mild pain whereas in visit 2 only 19.6% of the patients had mild pain (Table 2). The similar effect has also been supported by a previous study showing a significant decline in the VAS score by Orphenadrine/Paracetamol combination [13]. But paracetamol when used individually, lacks in effective pain management and the subject usually request an increased rescue dose [17]. Hence, the literature suggests that Orphenadrine/Paracetamol combination is more effective in pain management and results in significantly quicker recovery [13].

The study drug produced clinically significant improvement in fever as well. It was observed that on an average follow-up after 5 days, 0.3% of the study population showed mild fever i.e. below 101°F (38.3°C) whereas it was observed that the fever subsided in 99.6% of the patients after the administration of Nuberol (Orphenadrine/ Paracetamol combination) (Table 3).

Previous data suggest that NSAIDs are mostly prescribed in flu and have analgesic, anti-inflammatory, and antipyretic effects [12]. The analgesic effects of the drug are achieved at lower doses, while the anti-inflammatory effects can be observed at higher doses. However, these NSAIDs can result in gastrointestinal irritation that is lower than that reported with the use of aspirin. NSAIDs have a reversible effect on platelets that may, in turn, increase the bleeding risk, longer in case of aspirin use i.e. up to

Table 1: Demographics.

| | Mean ± SD | | | |
|-----------------|-----------------|---------------------|--------------------------------|---------------|
| Age | 36.7 ± 13.65 | | | |
| Height | 5.34 ± 0.421 | | | |
| Weight | 69.71 ± 11.84 | | | |
| BMI | 20.81 ± 4.86 | | | |
| Gender | Male | | Female | |
| | N (%) | | N (%) | |
| | 168 (56.0) | | 132 (44.0) | |
| Comorbid | Diabetes | Hypertension | Hypertension + Diabetes | Others |
| | N (%) | N (%) | N (%) | N (%) |
| | 12 (4.2) | 16 (5.6) | 4(1.5) | 11(4.3) |

*SD: standard deviation, BMI: Body mass index

Table 2: Measurement of pain intensity by VAS at visit 1 & visit 2.

| Pain Intensity (VAS) | Visit 1 | Visit 2 | p-value |
|----------------------|------------|------------|---------|
| | N (%) | N (%) | |
| No Pain | 0 (0) | 239 (80.3) | .000* |
| Mild pain | 203 (67.7) | 59 (19.6) | |
| Moderate pain | 85 (28.3) | 0 (0) | |
| Severe pain | 12 (4.0) | 0 (0) | |

VAS: Visual analogue scale, No pain: 0, Mild pain: 1-2, Moderate pain: 5-6, Severe pain: 7-10,

*Significance at $p < .05$ **Table 3:** Measurement of antipyretic activity of Nuberol at Visit 1 & visit 2.

| Antipyretic effect | Visit 1 | Visit 2 | p-value |
|--------------------|------------|------------|---------|
| | N (%) | N (%) | |
| Afebrile | 0 (0) | 297 (99.6) | 0.00* |
| Mild | 227 (75.6) | 1 (0.3) | |
| Moderate | 62 (20.6) | 0 (0) | |
| Severe | 11 (3.6) | 0 (0) | |

Afebrile: 9, Mild grade: $<101^{\circ}$, Moderate grade: $101^{\circ}<104^{\circ}$, Severe grade: $104^{\circ}<$ * = significant at $p < .05$ **Table 4:** Details of the Adverse Events reported.

| Adverse Events | The Frequency of Patients (N) |
|--------------------|-------------------------------|
| Distaste for mouth | 1 |
| Dizziness | 1 |
| Dry mouth | 2 |
| heartburn | 1 |
| Lightheadedness | 1 |
| Nausea | 1 |
| Sedation | 3 |
| Constipation | 2 |

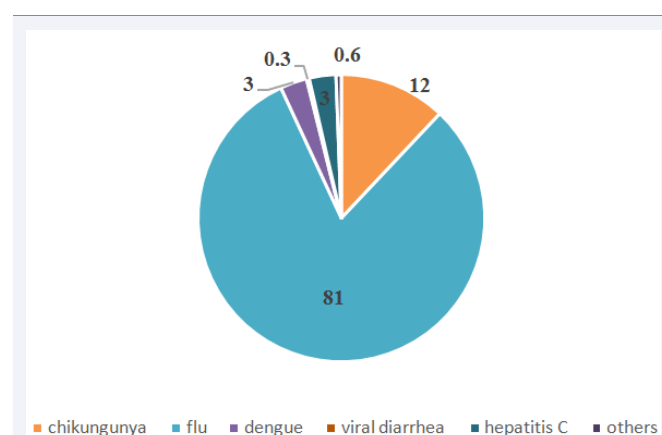
seven days [22]. Patients with aspirin hypersensitivity reaction must also use NSAIDs with caution, since cross-sensitivity may occur [23-25].

It is clearly indicated by the study objective that increase in prevalence of infectious diseases in the underdeveloped countries, has become a public health concern [16]. Pakistan lies among these underdeveloped world countries where majority of the population is suffering from viral infections including Dengue, Chikungunya, flu, hepatitis, measles etc. Particularly substantial climatic changes provide suitable medium to these viral illnesses resulting in frequent outbreaks [8,16]. Whereas the prevalent factor in elderly population is because of frail immune system impairing protective functions [8].

Therefore, the study focuses on the effective use of the combination drug (orphenadrine/paracetamol) to treat symptoms of viral infection. Although, the use of paracetamol results in the symptomatic management of fever [18], while using Orphenadrine alone have evidence-based results of showing sedative characteristics [24]. Hence, in order to avoid multiple drug regime and their adverse effects along with drug-drug interaction, the study agent Nuberol proved to be

more applicable as it effectively lowered fever and reduced pain intensity. Although the two salts are individually effective, polypharmacy leads to medication errors, multiple adverse drug reactions, drug-drug interactions, and decreases patient compliance [14]. Elderly population is sensitive to viral infection as well as polypharmacy [7,8] therefore, to avoid further drug interactions, adverse effects and risking patient's amenability it is suggested to use a combination of these agents. While the limitation of the study include no involvement of the control group and less number of viral diseases when there are various other viral illnesses with myalgia and fever as major symptom.

In addition to the efficacy of the drug, no serious life-threatening adverse event were observed as the drug was administered according to the dose prescribed while other non-serious adverse events included dry mouth, dizziness, lightheadedness, nausea, constipation, and sedation (Table 4). None of these side effects interfered in the study results.

**Figure 1** Recruited patients suffering from viral infections with associated symptoms of myalgia and fever.

CONCLUSION

The study focuses on the symptomatic management of myalgia and fever by administration of a single drug Orphenadrine/Paracetamol combination (Nuberol) among Pakistani patients suffering from the common viral infections that affect their normal routine activity. In conclusion, Nuberol at therapeutic doses is well-tolerated by most patients and effective in the management of both myalgia with fever with lesser adverse effects.

ACKNOWLEDGMENT

Contributors

NUB-EFFECT Study Investigator's List²

Karachi: Hameed Abdul², Shafi Khalid², Usman Asif²

Bahawalpur: Abbas Muhammad², Bhatti M. Ajmal², Masroor Sadia²

Lahore: Rasheed Humayun², Aftab Usman², Shahab Shahid²

Islamabad: Mahmud Muhammad Rizwan², Fazil Imran², Saeed Irfan²

Peshawar: Iqbal Naveed², Shah Nazeer²

Swat: Ali Anwar², Swati Zeb Amir²

Thanking note: We are thankful to all patients for being the vital part of the study

Study support team: The Searle Company Limited, Clinical Research Unit Team

Dr. Asif Mahmood, Dr. Ali Yasir (Manuscript writer) and Ms. Yasmeen Fazal, (Clinical Research Associate)

Contract Research Organisation (CRO):

Advanced Educational Institute Research Centre (AEIRC), (CRO)

Services for Site Feasibility, assistance with Study Documents Preparation, Ethics Committee document submission and Site Management

Dr. Nazish Urooj: Project Manager.

Mr. Raza (CRA, Bahawalpur Region), Mr. Talha (CRA, Lahore Region), Mr. Mohsin (KPK, CRAs)

Data Management Team (AEIRC): Ms. Yusra Saleem, Ms. Nida Khan & Mr. Shamooun Noushad (Biostatistician)

FOOTNOTES

Funding

This Investigator-Initiated Study (IIS) was funded by "The Searle Company Limited" (TSCL), Pakistan. The interventions for this study were provided by TSCL, Karachi, Pakistan.

Competing interests

The team of AEIRC (CRO) and Clinical Research Unit of TSCL are employed by the study Sponsor.

Patient consent

Obtained

Ethics approval

The study protocol and follow-up analysis were approved by the Ethics Committee of the Pakistan Medical Association (PMA), Karachi, Pakistan (registration number 0165).

Provenance and peer review

Not commissioned; externally peer reviewed.

REFERENCES

1. World Health Organization. Influenza (Seasonal) factsheet. 2009.
2. Taubenberger JK, Morens DM. 1918 Influenza: the mother of all pandemics. *Emerg Infect Dis.* 2006; 12: 15-22.
3. World Health Organization. Seasonal Influenza. 2018.
4. Badar N, Aamir UB, Mehmood MR, Nisar N, Alam MM, Kazi BM. Influenza virus surveillance in Pakistan during 2008-2011. *PLoS One.* 2013; 8: e79959.
5. World Health Organization. Chikungunya. 2017.
6. Rauf M, Fatima-tuz-Zahra, Manzoor S, Mehmood A, Bhatti S. Outbreak of chikungunya in Pakistan. *Lancet Infect Dis.* 2017; 17: 258.
7. Murray NE, Quam MB, Wilder-Smith A. Epidemiology of dengue: past, present and future prospects. *Clin Epidemiol.* 2013; 5: 299-309.
8. Staples JE, Breiman RF, Powers AM. Chikungunya Fever: An Epidemiological Review of a Re-Emerging Infectious Disease. *Clin Infect Dis.* 2009; 49: 942-948.
9. Mallhi TH, Khan YH, Khan AH, Tanveer N, Qadir MI. First chikungunya outbreak in Pakistan: a trail of viral attacks. *New Microbes New Infect.* 2017; 19: 13-14.
10. Rasheed SB, Butlin RK, Boots M. A review of dengue as an emerging disease in Pakistan. *Public Health.* 2013; 127: 11-17.
11. Rigau-Pérez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vorndam AV. Dengue and dengue haemorrhagic fever. *Lancet.* 1998; 352: 971-977.
12. Byrne E, Trounce I, Dennett X. Chronic relapsing myalgia (? Post viral): clinical, histological, and biochemical studies. *Intern Med J.* 1985; 15: 305-308.
13. Patterson J, Sammon M, Garg M. Dengue, Zika and Chikungunya: emerging arboviruses in the new world. *West J Emerg Med.* 2016; 17: 671-679.
14. World Health Organization. Dengue/Severe dengue frequently asked questions. 2017.
15. Hunskaar S, Donnell D. Clinical and pharmacological review of the efficacy of orphenadrine and its combination with paracetamol in painful conditions. *J Int Med Res.* 1991; 19: 71-87.
16. Rozenfeld S, Fonseca MJ, Acurcio FA. Drug utilization and polypharmacy among the elderly: A survey in Rio de Janeiro City, Brazil. *Rev Panam Salud Publica.* 2008; 23: 34-43.
17. Kapoor AK, Raju SM. *Illustrated medical pharmacology*, 1st edn. JP Medical Ltd: JP Medical publishers. 2013; 30: 253-254.
18. McGuinness BW. A Double-Blind Comparison in General Practice of a Combination Tablet Containing Orphenadrine Citrate and Paracetamol ('Norgesic') with Paracetamol Alone. *J Int Med Res.* 1983; 11: 42-45.
19. Høivik HO, Moe N. Effect of a combination of orphenadrine/

- paracetamol tablets ('Norgesic') on myalgia: a double-blind comparison with placebo in general practice. *Curr Med Res Opin.* 1983; 8: 531-535.
20. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf.* 2014; 13: 57-65.
21. Colley CA, Lucas LM. Polypharmacy. *J Gen Intern Med.* 1993; 8: 278-283.
22. Józwiak-Bebenista M, Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. *Acta Pol Pharm.* 2014; 71: 11-23.
23. Revill SI, Robinson JO, Rosen M, Hogg MI. The reliability of a heat analogue for evaluating pain. *Anaesthesia.* 1976; 31: 1191-1198.
24. Doña I, Blanca-López N, Cornejo-García JA, Torres MJ, Laguna JJ, Fernández J, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. *Clin Exp Allergy.* 2011; 41: 86-95.
25. Thiessen B, Portenoy RK, Argoff CE. *Pain Management Secrets.* 2009. Chapter 37 - Adjuvant Analgesics. 274-286.

Cite this article

Sajid A, Masroor AQ (2018) Effectiveness of Orphenadrine & Paracetamol Combination (Searle Generic) in Myalgia with Anti-Pyretic Benefit in General Pakistani Practice (Nub-Effect): An Observational Study. *J Drug Des Res* 5(2): 1069.