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AN OPEN LABEL, NON-RANDOMISED, CLINICAL STUDY TO EVALUATE THE EFFICACY OF HOMEOPATHIC FORMULATION OF ANACOSINUM PELLETS IN PATIENT WITH FLU AND FLU LIKE SYMPTOMS

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ABSTRACT

BACKGROUND: Influenza is a highly infectious, but relatively benign viral disease which is particularly common in the winter months. Influenza is a highly infectious and prevalent viral disease that is particularly common in the autumn and winter months in temperate regions of the world. Flu symptoms include fever between 38° C and 40° C (about 100-104 °F) or higher, muscle and joint pain throughout the entire body (myalgia and arthralgia), headache, severe fatigue, dry cough, stuffy and/or runny nose, lack of appetite and extreme tiredness. The common cold is distinct from flu, associated with the influenza virus. A fever greater than 38°C and generalized aches and pains are the best predictors of a diagnosis of the flu. The primary outcome of this study is to assess efficacy Anacosinum pellets in the condition of Flu and overall compliance to the drug treatment. The secondary outcome is to assess the efficacy of Anacosinum Pellets by Symptomatic relief from clinical symptoms of Flu and mean change in Visual Analog Scale (VAS) Chart score.

METHODS: This study was an open Label, non-randomized, clinical study to evaluate the efficacy of homeopathic formulation of "Anacosinum tablet" in a patient with Flu and Flu like symptoms. The inclusion criteria were adult above 18 years to below 60 years, both male and female. All eligible subjects who meet the Inclusion and Exclusion was enrolled into the study were visiting the study site on Screening, Day 0 (Baseline Visit) and Day 7. The 200 Subjects were enrolled in this study. The primary endpoint was percentage change (increase/ decrease) in baseline as compared to day seven was analyzed using chi- square with Pearson's test. The secondary endpoint of Anacosinum Pellets was the symptomatic relief from clinical symptoms of Flu and improvement in the health status. The secondary endpoint was analyzed using descriptive statistics. The p- value (p=NS) for vital measures was found not to be statistically significant.

RESULTS: A total of 200 samples was included in this study among them, 78 (39%) were female and 122 (61%) were male patients. The average age was 29.61± 10.45 (range, 18-60) years. The mean change in vital measure was found statistically significant (≤0. 05). A summary of adverse events, was not occurring during the treatment. The results show that significant decrease in body temperature, Sore throat, Sneezing/ Nasal irritation. Headache, Cough, Runny Nose, Malaise. The Efficacy results of this study had shown more significant results with Anacosinum pellets.

CONCLUSION: Anacosinum pellets at a dose of 1 vial thrice a day Before food for 7 days was more efficacious. The adverse event and also the serious adverse event were not found in this study. This particular data is much in need, due to which it will bring the positive effects of this medicine to worldwide physicians so that more patients of flu and flu like symptoms are benefitted. The body temperature and the Flu related symptoms were not worsened during the treatment. The incidence rate of serious adverse event and adverse event were not reported. Hence, it's proven the tolerability of this drug Anacosinum pellet.

KEYWORDS :

BACKGROUND:

Flu is a common and viral condition and it is felt that it should be managed through multiple approaches viz., Pharmaco logical, non- pharmacological, and or vaccination. All these treatment modalities have a range of effects and their availability and cost over- burdened, apart from this the unexpected or unusual eventualities range from mild to moderate and sometimes even severely observed. The World Health Organization (WHO) estimates that the average global burden of interpandemic influenza is approximately 1 billion cases of influenza, 3-5 million cases of severe illness and 300,000-500,000 deaths annually. Complicating the global influenza burden is the recent recognition of a novel quad-reassortment swine origin influenza A virus which is the agent associated with the WHO declared influenza pandemic. Flu symptoms include fever between 38° C and 40° C (about 100-104 °F) or higher, muscle and joint pain throughout the entire body (myalgia and arthralgia), headache, severe fatigue, dry cough, stuffy and/or runny nose, lack of appetite and extreme tiredness. The common cold is distinct from flu, associated with the influenza virus. A fever greater than 38°C and generalized aches and pains are the best predictors of a diagnosis of the flu. The Conventional management options are limited to bed rest and treatment of complications such as secondary bacterial infections. The major objective while treating the Flu and Flu like symptoms is to achieve the efficacy, safety and tolerability of the drug and also triggering the lower most amount of morbidity of the patients.

There are various other modalities for treating the flu and flu like symptoms are taking plenty of bed rest, drink fluids, and also sit in a steamy bathroom or try some lozenges etc.

METHODS

This study was an open label, non-randomized, clinical study to evaluate the efficacy of homeopathic formulation "Anaco sinum pellets" in patients with Flu and Flu like symptoms. The Inclusion criteria were adult-Above 18 years to 60 years, both male and female. Patients recently diagnosed with muscle and joint pain throughout the entire body (myalgia and arthralgia), headache, severe fatigue, dry cough, stuffy and/or runny nose, lack of appetite and extreme tiredness was included in the study. While the confirmation of the flu symptoms was also included in the study. The exclusion criteria were Upper Respiratory Tract Infections (URI or URTI) including rhinitis, sinusitis, pharyngitis, tonsillitis, laryngitis, tracheitis and otitis media and the Lower Respiratory Tract Infections (LRI or LRTI) including pneumonia and acute bronchitis. Which also include the Chronic obstructive airway

disease (COAD) including chronic bronchitis and emph yse ma. The patients with known history of Bronchial Asthma, Pulmonary Tuberculosis, tumors of the larynx, bronchi, and lungs, DM and HTN, H/o renal, hepatic or blood disorder or severe cardiac insufficiency, and also the subjects with hypersensitivity to herbal extracts or dietary supplements and pregnant women, lactating women and women of childbearing potential not following adequate contraceptive measure, women who were found positive for a urine pregnancy test was not included in the study. All eligible subjects who meet the Inclusion and Exclusion was enrolled into the study had visited the study site on screening, Day 0 (Baseline visit), Day 7. The 200 subjects were enrolled in this study. Subjects in the study had received the active Investigational Product and advised to take one vial thrice a day before food for 7 days. The physical examination and demographics were recorded at screening time physical examination and monitoring was continuing on Day 7. Vitals were recorded on all visits and the VAS at baseline and final visit Visual Analog Score (Intensity of pain will be graded from 0-9. Pain intensity will be assessed in each case). Adverse events were monitored up to 7 days and were recorded on Day 1 and Day 7. A buffer period of ±1 days was being allowed for every visit and beyond which it was considered as a protocol deviation. All the subjects who meet the eligibility criteria and have received at least one dose of study medication and had post baseline efficacy data was included in the efficacy analysis. All subjects who were receiving at least one dose of study drug was also included in the safety analysis. Patient data from all the centers were pooled together and analyzed.

STUDY RATIONAL:

Flu is a common and viral condition and it is felt that it should be managed through multiple approaches viz., Pharma cological, non- pharmacological, and or vaccination.

All these treatment modalities have a range of effects and their availability and cost over- burdened, apart from this the unexpected or unusual eventualities range from mild to moderate and sometimes even severely observed.

As a substitute, other novel treatment options such as Homoeopathy can be considered as a cost effective replacement for the treatment strategies. There have been clinical studies conducted in various parts of the world which have assessed the effects of the Ana Barbariae extract against treatment of Flu and Flu like symptoms to positive results. Homeopathic clinicians are using these medicines for treatment of Flu for years. However, there is a paucity of the clinical studies which have assessed their effects in treatment of Flu.

STATISTICAL ANALYSIS:

Demographic data such as age, gender was analyzed using descriptive statistics. Out of 200 subjects all the 200 subjects have complete data. Categorical data were represented in the frequency form and continuous data were presented as the Mean±SD or median (IQR). The vital measures and changes in Flu and Flu like symptoms from baseline to end of treatment was analyzed using Non- parametric Wilcoxon signed-rank test. The primary outcome of the study is to assess the efficacy of Anacosinum pellets in the condition of Flu and overall compliance to the drug treatment and the endpoint was percentage change (increase/ decrease) in baseline as compared to day seven using chi- square with Pearson's test. The secondary efficacy of Anacosinum pellets by sympto matic relief from clinical symptoms of Flu and improvement in the health status and endpoint reduction in symptoms of Flu and mean change in Visual Analog Score. The secondary endpoint was analyzed using descriptive statistics. A p-value≤0. 05 in a two-tailed test was considered statistically significant. Statistical analyses were performed using SPSS (the statistical package for social sciences) IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

RESULTS

A total of 200 samples was included in this study among them, 78 (39%) were Female and 122 (61%) were male patients. The average age was 29.61± 10.45 (range, 18-60) years. The change over the time in vital measure in the table and figure [1]. The median Systolic BP (mmHg) at baseline was 120 (120-130) and on day 7th was 120 (120-120). The p-value was found out not to be statistically significant. Hence, treatment effect was not shown significant change at day 7th as comparable to baseline. Diastolic blood pressure at baseline was 70 (70-80) and at visit day, seven 80 (70-80), this shows that not more changes in baseline to day 7th visit. Heart rate, respiratory rate, and body weight do not have any changes at the baseline and day, seven visits are shown in Figure [1]

Body temperature of patient trend was shown a significant decrease. The p-value was <0.001 which was found to be statistically significant. The median 37.8 (37.5-38) at baseline and day, seven visits, was found to be 37 (37-37). Hence, it concludes the effect of the treatment on body temperature. This result shows significant decrease in body temperature in table [2] and Figure [2].

Body weight (kg) has not shown any significant changes over the baseline to 7th day. The median at baseline was 59 (54-68) and on 7th day 59 (54-68) not statistically significant changes. The p-value was found to be not statistically significant. This was shown no significant changes over the time as comparable to baseline. Hence, the results show that there were no significant changes over the time in body weight.

Results were not statistically significant, but not clinically meaningful mean decrease or increase in vital measure observed in the after treatment. In addition to the key results reported below, further results (including efficacy, safety and tolerability results) are reported.

EFFICACY

The primary endpoint of the study was the percentage change in the VAS Visual Analog Scale table [3]. The Visual Analog Score (VAS) Chart Score for symptoms was shown in table [3]. The Friedman test was performed to see the difference between related time points i.e., Baseline till day 7 on the sum of the ranks of Flu parameters. There was significant difference between scores was observed for different related time points (baseline till day 7) with p-value being <0.001 which is Moderate than 0.05. The intensity of the VAS rating for all the symptoms were reported in percentages along with 95% Confidence Interval (CI) at Baseline (Day 0) and at Day 7 for each of the VAS ratings**.** The change in percentages from 'Severe' discomfort to 'Mild' or 'Moderate' discomfort and 'No pain/Normal' was seen for all the symptoms of body temperature. The p-value was found out to be statistically significant (p=<0.001).

The Visual Analog Score (VAS) chart scores for sore throat was shown in table [3]. The score for Mild sore throat patients were 11 (37.9%) as compared to baseline Moderate sore throat, while those patients with No pain/Normal sore throat on visit day seven was 72 (42.1%) as compared to baseline. Patients with Mild on the visit day, seven were 0 (0%) and No pain/Normal was due to sore throat was 89 (52%) as compare to baseline. It has shown most of the patients with No pain/Normal. Moreover, patients with No pain/Normal 10 (5.8%) and 18 (62.1%) as Mild compare with the baseline Severe sore throat. It has shown that those patients with Severe sore throat at baseline were Mild at visitation day

seven and No pain/Normal not more. The p-value was found to be <0.001 which was statistical significant. Hence, it concludes that there was statistical significance difference between proportions. This result shows significant decrease in Sore throat graph [1].

The Visual Analog Score (VAS) was observed at day seven with No pain/Normal 80 (42.8%) and Mild 3 (23.1%) of Sneezing Nasal Irritation as compared to Moderate Sneezing Nasal Irritation at baseline. Patients with Mild 0 (0%) and 88 (47.1%) as compare to Sneeze Nasal Irritation at baseline. Moreover 19 (10.2%) patients with No pain/Normal and Mild 10 (76.9%) as compared to Severe Sneezing Nasal Irritation at baseline. The p-value was found to <0.001 which was statistically significant. Hence, conclude that there was statistically significant difference between proportions. This result was shown that significantly decrease (p=<0.001) graph [2].

The Visual Analog score (VAS) in patients with headache was observed with No pain/Normal 33 (18.4%) and Mild 6 (28.6%) at day seven visits as compared to Moderate headache at baseline. Moreover, patients with headache, No pain/Normal 134 (74.9%) and Mild 5 (23.8%) at day seven visit headache as compare to baseline. Whereas, patients with No pain/Normal 12 (6.7%) and Mild 10 (47.6%) headache as compare to baseline. The p-value was found to be statistically significant, (p=<0.001). Hence, conclude that the difference between the proportion of baseline and day seven visits. Since, this was shown that headache was significantly decreased at day seven visits as compared to baseline. This result shows that a significant decrease (p=<0.001) in graph [3].

The Visual Analog score (VAS) in patients with Moderate cough, No pain/Normal 68 (51.5%), Mild 42 (68.9%) and 0 (0%) cough at day seven visits as compared to Moderate cough at baseline. Moreover, patients with No pain/Normal 54 (41.3%), Mild 8 (13.1%) and Moderate 0 (0%) cough at day seven visits as compare to Moderate cough at baseline. However, patients with No pain/Normal 1 (0.8%) and Moderate with more Moderate 0 (0%) were observed at day seven visits as compare to no comfort at the baseline. Lastly, patients with No pain/Normal 8 (6.1%), Mild 11 (18%) and Moderate 7 (100%) cough at day seven visits was observed as compared to Severe cough at baseline. The p-value was <0.001, which was considered as statistically significant. Hence conclude that those patients had Severe cough at baseline, those were significantly decreased at day seven visits. This result shows that a significant decrease (p=<0.001) in graph [4].

The Visual Analog Score (VAS) in patients with No pain/Normal 90 (62.1%) and Mild 21 (38.2%) runny nose as compared to the Moderate runny nose at baseline. No pain/Normal due to runny nose. Moreover, those patients with No pain/Normal 30 (20.7%) and 1 (1.8%) runny nose as compare patients with Mild runny nose at baseline. Those patients were No pain/Normal 25 (17.2%) and Mild 33 (60%) runny nose at day seven as compared to patients had a very Moderate runny nose at baseline. The p-value was <0.001, which was considered as statistically significant. Hence the results show more significantly decrease at day seven visits as compared to baseline. This result shows that a significant decrease (p=<0.001) in graph [5].

The Visual Analog Score (VAS) in patients with No pain/Normal 173 (86.5%) with or without low grade fever at day seven visits as compared to patients with or without low grade fever at baseline. Those patients with No pain/Normal 7 (3.5%) with or without low grade fever at day seven visits as compared to patients with or without low grade fever at baseline. Moreover, patients with No pain/Normal 20 (10%) with or without low grade fever at day seven visits as compared to patients with or without low grade fever at baseline. This result shows that a significant decrease (p=<0.001) in graph [7].

In the remaining all categorizes at 7th day as compare to baseline was showing the decrease in the test. Hence the results were showing that more significant decrease as compare to baseline. This shows that the treatment effect was more significant.

SAFETY

All subjects received at least one dose of study drug was included in the safety analysis. All subjects in the study were monitored for any adverse events and serious adverse events. Adverse events were recorded during and at the end of study treatment, and the investigator was allowed to assess the various parameters like severity, seriousness, expectedness, relationship to study medication (causality) outcomes. A summary of adverse events, adverse events that were occurring or not worsened during treatment table. Most of the patients were reported with Fever, Sore Throat, Sneezing Nasal Irritation, Headache, Cough Runny Nose, Malaise and With or Without Low Grade Fever however, a smaller number of the patients expressed with worsening Flu and flu like symptoms. At follow-up the patients with Fever, Sore Throat, Sneezing Nasal Irritation, Headache, Cough Runny Nose, Malaise and With or Without Low Grade Fever, pain was shown more significant decrease in the symptoms during the treatment. Moreover, patients with Sore throat has shown decrease during the treatment. A patient with Mild and very Mild cough, Runny Nose, Headache, sneezing/Nasal irritation was decreased during the treatment. Most of the patients were reported with Fever, Runny Nose, Headache and Sneezing/ nasal irritation was seen changes over the time.

The incidence rate of adverse events and serious adverse events were not reported, hence demonstrating the favorable tolerability profile for Anacosinum Pellets.

DISCUSSION:

Anacosinum is a homeopathic product which is being marketed already for the treatment and condition of Flu and Flu like symptoms. Though the physicians are using it on patients with success and content, there is no study conducted which has tapped these effects. This is needed as this will help in bringing forward the positive effects of this medicine to worldwide physicians so that more patients of Flu and its Symptoms can be benefitted. The perspective observational study of Indian population, no more study was done on this drug. The previous literature shows that no more evidence available for this drug. The study was conducted on Indian population with 200 sample size. In this study the symptoms pertaining to Flu were assessed at baseline and at day 7th. Numerous studies have evaluated the efficacy of Anacosinum pellets in Flu and Flu like Symptoms and overall compliance to the drug treatment. The World Health Organization (WHO) estimates that the average global burden of interpandemic influenza is approximately 1 billion cases of influenza, 3-5 million cases of severe illness and 300,000-500,000 deaths annually. The symptoms pertaining to Flu were assessed before and after treatment. Fever, Sore Throat, Sneezing Nasal Irritation, Headache, Cough Runny Nose, Malaise and With or Without Low Grade Fever were graded as per their severity of complaints.

The symptom score at baseline and at day 7th was found out to be statistically significant (P<0.001). Patients had more follow-up as compare to this study.

In our study 1 vial thrice a day was a treatment regimen. Anaco sinum study shows more efficacy and Moderate symptom score. While the Anacosinum study was conducted on male

and female patients. It has shown a better results during the treatment. The change over the time in vital measure was found not statistically significant (p=NS). The result is shown that the Anacosinum pellets was not more affected on the vital measure. The Visual Analog Score (VAS) Chart Score in fever, Sore throat, Headache, Sneezing/ Nasal irritation in patients on day 7th was approximately decreased. Hence, it showed the treatment effect more significant. Similarly the moderate and severe Sore throat, Headache, Sneezing/ Nasal irritation was significantly decreased. All results have shown that the treatment effect more significant in reducing the symptoms for the flu. The score in patients with no Malaise was more, while the results was shown more relevant. Because the data was skewed. Similarly, those patients with mild, moderate and severe sneezing/ Nasal irritation, Cough, Sore throat were shown more significant reduction after the treatment. The number of the patients with No pain/Normal was increasing the trend. The primary endpoint was achieved. Treatment effect was shown more significance. Moreover, those patients have one, two and more than two symptoms those patients were showing the decreasing trend over the time. Since, the treatment is more effective. No patient was found with adverse and serious adverse event. The tolerability of the treatment was favorable.

CONCLUSION:

Anacosinum pellets at a dose of 1 vial thrice a day Before food for 7 days was more efficacious. The adverse event and also the serious adverse event were not found in this study. This particular data is much in need, due to which it will bring the positive effects of this medicine to worldwide physicians so that more patients of flu and flu like symptoms are benefitted. The body temperature and the Flu related symptoms were not worsened during the treatment. The incidence rate of serious adverse event and adverse event were not reported. Hence, it's proven the tolerability of this drug Anacosinum pellet.

SUPPLEMENTARY RESULTS:

Table 1: Pair wise comparison of SBP, DBP, Heart Rate, Respiratory Rate, Temperature and Weight after7 days follow-up compared to baseline.

Vital measure	n	Baseline	Day 7	p-value
Systolic BP (mm Hg)	200	120(120-130)	120(120-120)	*NS
Diastolic BP (mm Hg)	200	70(70-80)	80(70-80)	*NS
Heart Rate (bpm)	200	82(82-84)	82(82-84)	*NS
Respiratory Rate (beats/mins)	200	16(16-18)	16(16-18)	*NS
Body Temperature (Degree Celsius)	200	37.8(37.5-38)	37(37-37)	*NS
Body Weight	200	59(54-68)	59(54-68)	*NS

Table 2: Pair wise comparison of Baseline vs Day1 till Day 7 using Wilcoxon Rank Sum Test

Body temperature	n	Median(25th percentile to 75th percentile)	p-value
Baseline	200	37.8(37.5-38)	
Day 1	200	37.7(37.5-37.8)	<0.001
Day 2	200	37.5(37.4-37.7)	<0.001
Day 3	200	37.5(37.3-37.5)	<0.001
Day 4	200	37.2(37.2-37.4)	<0.001
Day 5	200	37.1(37-37.2)	<0.001
Day 6	200	37(37-37)	<0.001
Day 7	200	37(37-37)	<0.001

Table 3 : Efficacy, safety and tolerability assessment of the Anacosinum drug.

Anacosinum pellets											
		Baseline					Day 7 visit				
VAS					95 % CI					95 % CI	
Symptom	Type	n	n'	%	LL	UL	n	n'	%	LL	UL
Sore Throat	Moderate	200	83	41.50	0.31	0.52	200	173	86.50	0.81	0.92
	Mild	200	89	44.50	0.34	0.55	200	7	3.50	-0.10	0.17
	Severe	200	28	14.00	0.01	0.27	200	20	10.00	-0.03	0.23
Sneezing Nasal Irritation											
	Moderate	200	83	41.50	0.31	0.52	200	29	14.50	0.02	0.27
	Mild	200	88	44.00	0.34	0.54	200	171	85.50	0.80	0.91
	Severe	200	29	14.50	0.02	0.27	200				
Headache											
	Moderate	200	39	19.50	0.07	0.32	200	13	6.50	-0.07	0.20
	Mild	200	139	69.50	0.62	0.77	200	187	93.50	0.90	0.97
	Severe	200	22	11.00	-0.02	0.24	200				
Cough											
	Moderate	200	110	55.00	0.46	0.64	200	7	3.50	-0.10	0.17
	Mild	200	63	31.50	0.20	0.43	200	61	30.50	0.19	0.42
	No pain/Normal	200	1	0.50	-0.13	0.14	200	132	66.00	0.58	0.74
	Severe	200	26	13.00	0.00	0.26	200				
Runny nose											
	Moderate	200	111	55.50	0.46	0.65	200	55	27.50	0.16	0.39
	Mild	200	31	15.50	0.03	0.28	200	145	72.50	0.65	0.80
	Severe	200	58	29.00	0.17	0.41	200				
Malaise											
	Moderate	200	5	2.50	-0.11	0.16	200	200	100.00	-	-
	Mild	200	41	20.50	0.08	0.33	200				
	No pain/normal	200	154	77.00	0.70	0.84	200				
With or Without Low Grade Fever											
	Moderate	200	173	86.50	0.81	0.92	200	200	100.00	-	-
	Mild	200	7	3.50	-0.10	0.17	200				
	No pain/Normal	200	20	10.00	-0.03	0.23	200				

Figure 1: Box plot shows comparison change over the time

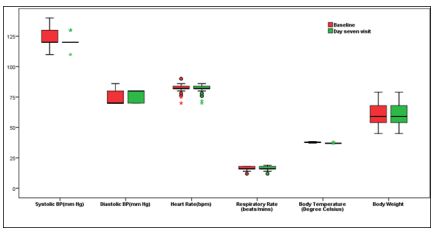
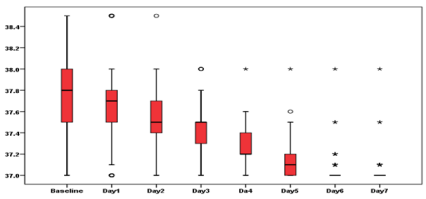
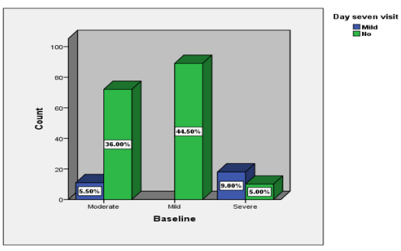


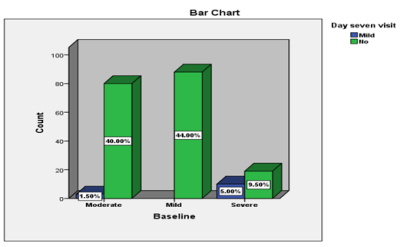
Figure 2: Box plot for body temperature of patients at baseline to day 7 visit.



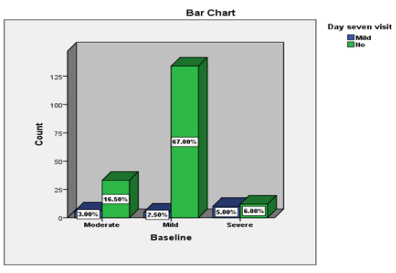
Graph 1: Percentage bar for Visual Analog Score (VAS) in Sore Throat



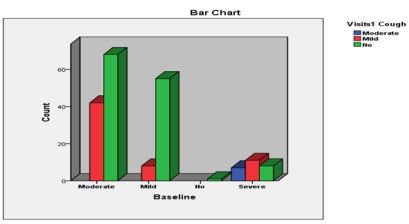
Graph 2: Percentage bar for Visual Analog Score (VAS) with Sneezing/ Nasal Irritation.



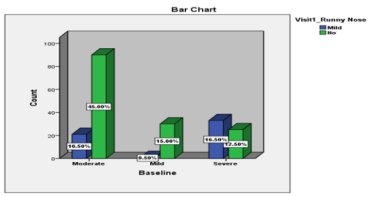
Graph 3: Percentage bar for Visual Analog Score (VAS) for Headache



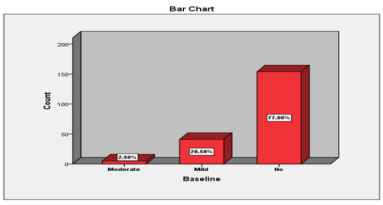
Graph 4: Percentage bar for Visual Analog Score (VAS) for cough at baseline.



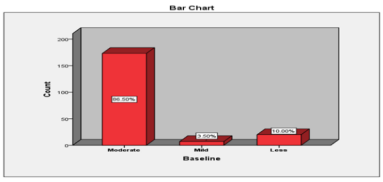
Graph 5: Percentage bar for Visual Analog Score (VAS) for runny nose.



Graph 6: Percentage bar for Visual Analog Score (VAS) for Malaise at baseline



Graph 7: Percentage bar for Visual Analog Score (VAS) for with or without low grade fever.



AUTHOR CONTRIBUTIONS

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