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Original Research Article

Analysis of Rupatadine in Reduction of Dengue Haemorrhagic Fever among the Patients with Acute Dengue

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Abstract:

Introduction: In dengue hemorrhagic fever (DHF), patients may have organ damage and endothelial dysfunction that results in vascular leak. The dengue NS1 protein, several inflammatory cytokines including IL-1β as well as TNF-α, inflammatory lipid mediators like platelet activating factor (PAF). Rupatadine, an oral second-generation antihistamine, competitively inhibits both histamine and PAF receptors and has not been associated with any negative cardiac consequences in people from Europe and Asia.

Aims and Objectives: To analyze the efficacy of Rupatadine in reduction of dengue haemorrhagic fever by alleviation of clinical and laboratory parameters, as compared to the controls.

Methods: This is a randomized double-blind, placebo-controlled trial which was carried out on 55 patients with a suspected dengue infection. The study has two groups in which one group was given 40 mg of oral rupatadine (Rupatadine group) and the other group "Control group" for a duration of 5 days. Both the groups was given the conventional supportive care therapy in accordance with national recommendations. Baseline characteristics were determined and after 5 days, the end-points were determined in each group for analyzing the efficacy of Rupatadine as compared to the control.

Results: the control group showed high abdominal pain (44%), vomiting (36%), diarrhea (52%), ascites (48%), liver tenderness (28%0 compared to rupatadine group. Bleeding manifestations (13.3%) and platelet counts are high in the rupatadine group compared to controls. Duration of the fever was significantly lesser in Rupatadine group than control group ($p<0.05$). The study also found that the vomiting and hepatic tenderness were significantly reduced in patients who received Rupatadine ($p<0.05$).

Conclusion: The study has concluded that Rupatadine is efficacious in reducing the fever duration, vomiting, hepatic tenderness and Dengue shock in the patients with DHF.

Keywords: Rupatadine, dengue hemorrhagic fever, dengue, ns1 protein.

Introduction

There were 104 million dengue infections worldwide in 2017 compared to 23 million in 1990 [1], making it one of the most quickly spreading vector-borne viral illnesses. Parallel to this growth, the age standardized demise rate worldwide

climbed since 0.31 per 100,000 people in 1990 to 0.53 per 100,000 people in 2017 [1]. This increased burden is assumed to be caused by a number of causes, including urbanization, increased mobility, and climate change-related global warming [2, 3]. In Sri Lanka, dengue is a significant communal wellbeing concern, India, in addition to numerous additional reserve underprivileged nations, where it accounts for 70% of dengue illnesses [4, 5].There have been apparently no particular therapies for dengue; instead, fluid administration and close observation for complications are the cornerstones of dengue therapy [6]. There isn't currently a treatment or cure aimed at this infectious disease; instead, cautious observation in addition to hydration management is the primary options [1]. It is obvious that there is a critical clinical need for a secure, approved drug that can be used in resource-limited areas, in which the bulk of outbreaks originate.

Even while the most of Dengue Virus (DENV) infections are asymptomatic or mild, some people experience problems like organ damage and dengue hemorrhagic fever (DHF). The primary cause of DHF is endothelial dysfunction that results in vascular leak [7]. The dengue NS1 protein, several inflammatory cytokines including IL-1β as well as TNF-α, inflammatory lipid mediators like platelet activating factor (PAF), besides a defective immunological response to the DENV are all likely to have a role in the vascular leak [8–10].

Rupatadine, an oral second-generation antihistamine, is reported to demonstrate longer action of double histamine-1-receptor inhibiting actions as well as PAF receptor inhibiting actions for the treatment of severe allergic disease besides prolonged urticarial [11, 12].Rupatadine has been proven towards be well accepted in numerous clinical trials in patients cured aimed at allergic rhinitis [11–13], in addition to off-label doses of up to 40 mg/day have demonstrated towards be well handled in prolonged urticarial [14]. Rupatadine competitively inhibits both histamine and PAF receptors. Even at 100mg doses, rupatadine has not been associated with any negative cardiac consequences in people from Europe and Asia [14–16]. We evaluated the possibility that rupatadine could be repurposed for usage throughout severe dengue disease considering the PAF receptor inhibiting action. It has the benefits of being taken orally and being reasonably priced, and could therefore provide a significant useful function in clinical settings with limited resources.

In the past, we demonstrated how PAF affected endothelial function in a dose-dependent manner. ZO-1 expression and endothelial electrical resistance were both considerably raised by PAF receptor inhibition and were both decreased by sera from individuals with a dengue shock syndrome [17]. Rupatadine was discovered to be effective and well accepted in individuals with acute dengue, and it also dramatically decreased the amount of fluid leakage and the decline in platelet counts [18]. Rupatadine appeared to lower the percentage of people who developed ascites and pleural effusions when administered early (3 days after the onset of the illness), but this was not statistically significant since the trial had sufficient power to determine this [18].

Materials and Methods

Research design

This is a randomized double-blind, placebo-controlled trial was carried out on 55 patients during the period of one year, in the outpatient department of our hospital. The study has two groups in which one group was given 40 mg of oral rupatadine (Rupatadine group) and the other group “Control group” for a duration of 5 days. A computerized random number generator was used to randomly assign dengue patients presenting to the hospital's OPD in a 1:1 ratio to either of the two groups. After

the randomization process was complete, the patients were allocated to a study group (or Rupatadine group) who received rupatadine 40mg, once a daily every morning for 5 days. There were no additional variations between the groups and both the groups was given the conventional supportive care therapy in accordance with national recommendations. Baseline characteristics were determined and after 5 days, the end-points were determined in each group for analyzing the efficacy of Rupatadine as compared to the control.

Inclusion and exclusion criteria

Following given written agreement, patients with a suspected dengue infection who visited the OPD of the hospital with a febrile illness lasting for less than three days and who tested positive for the dengue point of care, NS1 antigen test, were included in the study.

Also, expectant mothers, people who have adverse responses to antihistamines or pertinent excipients, people who abuse alcohol or other drugs, and people who have had hepatic or renal impairment previously diagnosed were all eliminated.

Statistical analysis

Non-parametric statistical tests were applied, and Graph PRISM version 8.3 was used for the statistical analysis. Multiple unpaired non-parametric t-tests were used to compare differences between the serial values of the platelet counts and white cell counts in patients on the two treatment arms. The Holm-Sidak technique was used to correct for multiple comparisons, and 0.05 was chosen as the statistically significant value (alpha). 2-way repeated measures ANOVA was used for longitudinal analysis. S1 Data contains de-identified patient data.

Ethical approval

The patients were given thorough information about the study by the authors. The patient's permission has been gotten. The concerned hospital's ethical committee has accepted the study's methodology.

Results

Table 1 shows the baseline characteristics of participants. The patients were divided into two groups rupatadine (n=30) and control (n=25) groups. The mean age of participants is 28 years. Males are more in number compared to females. The platelet count is hight in rupatidine group compared to control.

Table 1: Baseline characteristics of patients

Characteristics	**Rupatadine N = 30**	**Control N = 25**	***p*-value**
Duration of illness at time of presentation (median, IQR)	3 (2 to 3)	3 (2 to 3)	0.21
Day of illness at time of recruitment			
Day 1	5	7	
Day 2	37	38	
Day 3	89	75	
Age (median, IQR)	28 (21 to 38)	28.5 (22 to 39)	0.64
Gender male: female	49:17:00	57:11:00	
Infecting DENV serotype			
DENV1	31	33	
DENV2	53	55	
DENV3	13	20	

DENV4	0	0	
negative	18	9	
Viral loads at presentation (copies/ml)	227,717 (9,242 to 5,484,384)	280,992 (4,727 to 5,132,283)	0.61
Wellness score at the time of recruitment (median, IQR)	7 (6 to 9)	6 (5 to 7)	0.35
WBC (median, IQR)	4.67 (4.5 to 6.77)	4.7 (3.1 to 5.7)	0.6
Platelet counts (median, IQR)	179 (133 to 222.5)	161 (126 to 210.5)	0.35

Table 2 shows that participants in the control group showed high abdominal pain (44%), vomiting (36%), diarrhea (52%), ascites (48%), liver tenderness (28%0 compared to rupatadine group. Bleeding manifestations (13.3%) and platelet counts are high in the rupatadine group compared to controls. Duration of fever is 4 to 6 days in controls compared to rupatadine 1 to 2 days. Duration of the fever was significantly lesser in Rupatadine group than control group ($p<0.05$). The study also found that the vomiting and hepatic tenderness were significantly reduced in patients who received Rupatadine ($p<0.05$). Also, Dengue shock was reduced in Rupatadine group as compared to the control group ($p<0.05$).

Table 2: Clinical and laboratory findings in both groups

Clinical and Laboratory Characteristics	**Rupatadine N = 30**	**Control N = 25**	**Relative risk (95% CI)**	***p*-value**
Abdominal pain	8 (26.7%)	11 (44)	1.9 (0.73 to 2.13)	>0.99
Persistent vomiting	2 (6.7%)	9 (36%)	0.69 (0.32 to 0.95)	0.047
Headache	25 (83.3%)	23 (92%)	0.86 (0.52 to 0.97)	0.06
Diarrhoea	9 (30%)	13 (52%)	0.91 (0.72 to 1.3)	0.98
Reduced appetite	23 (76.7%)	21 (84%)	1.4 (0.82 to 1.9)	0.62
Hepatic tenderness	1 (3.33%)	7 (28%)	0.47 (0.38 to 0.73)	<0.0001
Admission to hospital	14 (46.67%)	19 (76%)	0.81 (0.69 to 1.13)	0.59
Development of DHF	3 (10%)	6 (24%)	0.78 (0.51 to 1.14)	0.09
Ascites	3 (10)	12 (48%)	0.78 (0.51 to 1.14)	0.09
Pleural effusions	5 (16.6%)	1 (4%)	1.4 (0.66 to 2.1)	0.78
Bleeding manifestations (excluding cutaneous bleeding)	4 (13.33%)	2 (8%)	0.98 (0.56 to 1.37)	>0.99
Dengue shock	1 (3.34%)	4 (16%)	0.71 (0.14 to 1.5)	0.048
Dextran given	4 (13.33%)	5 (20%)	0.77 (0.21 to 1.5)	0.82
Normal saline boluses given	2 (6.67%)	4 (16%)	0.77 (0.21 to 1.5)	0.82
Blood given	0 (0)	2 (8%)	0.0 (0. to 1.03)	0.49
Platelet counts (nadir of thrombocytopenia) <20,000 <50,000	11 (36.6%) 17 (56.6%)	6 (24%) 3 (12%)	1.4 (0.73 to 1.9) 0.74 (0.53 to 0.97)	>0.99 0.01

Duration of fever (median, IQR)	2 (1 to 2)	5 (4 to 6)		0.95
Duration of illness (median, IQR)	3 (2 to 4)	7 (5 to 8.25)		0.0003

The total number of patients included in the study are 55 and those underwent randomization are 55. The patients are divided into two groups rupatadine (30) and control group (25). The patients who lost the followup are 3 in rupatadine and 1 in the control group (table 3).

Table 3: Recruitment of the patients and their follow up in the study

Total no. of patients	55	
No. of patients underwent randomization	55	
Groups	**Rupatadine**	**Control**
No. of patients	30	25
Patients who lost the followup	3	1
Patients who completed the follow up	272	24

Discussion

Rupatadine's effectiveness in the management of acute dengue infection was examined and reported by Malavige et al. in 2016. Three treatment groups—placebo, rupatadine 40 mg daily, and rupatadine 10 mg daily were utilized in the study. On day 4.8 of their illness, 138 patients were included; 44 of them received rupatadine 40 mg day, 44 received rupatadine 10 mg daily, and 44 received a placebo. Both the 10mg and 40mg doses of rupatadine were deemed safe and did not result in any worsening of adverse reactions were contrasted to the placebo. In all 3 groups, the percentage of all who progressed pleural effusions or ascites (22.7%) was the same. When given rupatadine 40 mg, none of the patients experienced bleeding symptoms, although 2 (4.5%) of the 10 mg patients and 5 (11.4%) of the placebo patients did. While 1 (2.3%) patient in the 10mg arm and 3 (6.8%) individuals in the placebo arm both experienced liver dysfunction, no patients in the rupatadine 40mg arm did. But contrasted to the 10mg rupatadine and the placebo group, those who received rupatadine 40mg daily showed less of a decrease in platelet counts and less of an increase in liver transaminases. In patients with an acute dengue infection, rupatadine seems to be safe. However rupatadine did not decrease the percentage of patients who have fluid leakage when administered on days 4-5 of sickness, it does seem to lessen dengue-related complications. It will be crucial to confirm these results in larger research, though [19].

A systematic examination of rupatadine's efficiency in the therapeutic management of dengue infection was conducted and reported by Malavige et al. in 2018. In 183 adult patients with acute dengue in Sri Lanka, they performed a randomized, placebo-controlled trial. The results revealed that rupatadine up to 40mg daily seemed effective and very well accepted, with comparable rates of side incidences involving control with rupatadine. Post-hoc research revealed small but significant variations in a variety of measures on particular sickness days, despite the fact that key end-point of a massive decrease in extravasation (formation of pleural effusions) was not fulfilled. Greater platelet amounts as well as lesser aspartate-aminotransferase stages on day 7 in the rupatadine cohort in comparison towards the control cohort, as well as narrower effusions on day 8 in the subgroup of patients with pleural effusions were among the findings. Rupatadine was demonstrated to prevent fluid leakage in a DENV-2

model in vivo as well as the impacts of PAF with severe dengue sera on HUVEC cells in vitro. Patients with acute dengue appeared to tolerate and respond well to rupatadine 40mg. The primary endpoints we looked at did not show any direct indication of benefit, although post-hoc analysis showed tiny but major differences in a number of indicators on specific illness days. To determine the relevance of these putative effectiveness signals, a bigger clinical trial with an early enrollment focus is required [20].

An investigation and report on a randomized, double-blind, placebo-controlled experiment were done by Malavige et al. in 2022. Patients who had had symptoms for less than three days were assigned to receive oral rupatadine 40 mg for five days as part of the treatment arm (n = 123) or a placebo (n = 126). Daily measurements of clinical and laboratory parameters were taken to monitor the progression of DHF and other comorbidities. Although this was not statistically significant, 12 (9.7%) participants in the treatment arm and 22 (17.5%) in the placebo arm experienced DHF (p=0.09, relative risk). Additionally, rupatadine significantly decreased (p=0.01) the percentage of patients with platelet counts below 50,000 cells/mm3, as well as persistent vomiting, headaches, and hepatic pain in patients (p0.0001). Although there was a difference in the proportion of patients including both treated groups who needed hospital admission, the length of illness was significantly different (p=0.0002). Only 2 patients receiving rupatadine or 3 patients receiving a placebo had shock, but 6 patients receiving rupatadine as well as 7 patients receiving a placebo experienced bleeding symptoms [21].According to the results of the three trials mentioned above, rupatadine is a promising treatment for serious dengue infections and will be important in future research including a sizable population.

Conclusion

The study has concluded that Rapatadine is efficacious in reducing the fever duration, vomiting, hepatic tenderness and Dengue shock in the patients with DHF. Rupatadine was also efficacious in patients with platelet counts less than 50,000 but not in the patients with platelet counts less than 20,000. The authors also suggest to carry out more similar studies on multi-centre approach. However, this study has brought forward an important finding which would contribute clinically in the overall management of DHF.

Reference

1. Zeng Z, Zhan J, Chen L, Chen H, Cheng S. Global, regional and national dengue burden from 1990 to 2017: A systematic analysis based on the global burden of disease study 2017. E Clinical Medicine. 2021; 32:100712.
2. Xu Z, Bambrick H, Frentiu FD, Devine G, Yakob L, Williams G, et al. Projecting the future of dengue under climate change scenarios: Progress, uncertainties and research needs. PLoS neglected tropical diseases. 2020; 14(3):e0008118.
3. Yang X, Quam MBM, Zhang T, Sang S. Global burden for dengue and the evolving pattern in the past 30 years. Journal of travel medicine. 2021.
4. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013; 496(7446): 5 04–7.
5. Malavige GN, Jeewandara C, Ghouse A, Somathilake G, Tissera H. Changing epidemiology of dengue in Sri Lanka-Challenges for the future. PLoS neglected tropical diseases. 2021; 15(8): e0009624.
6. WHO, editor. Comprehensive guidelines for prevention and control of dengue fever and dengue haemorrhagic fever. SEARO, New Delhi, India: World Health Organization; 2011.

7. Malavige GN, Ogg GS. Pathogenesis of vascular leak in dengue virus infection. Immunology. 2017; 151(3): 261–9.
8. Hottz ED, Lopes JF, Freitas C, Valls-de-Souza R, Oliveira MF, Bozza MT, et al. Platelets mediate increased endothelium permeability in dengue through NLRP3-inflammasome activation. Blood. 2013; 122(20): 340 5–14.
9. Glasner DR, Ratnasiri K, Puerta-Guardo H, Espinosa DA, Beatty PR, Harris E. Dengue virus NS1 cytokine-independent vascular leak is dependent on endothelial glycocalyx components. PLoS pathogens. 2017; 13(11):e100 6673.
10. Malavige GN, Jeewandara C, Ogg GS. Dysfunctional Innate Immune Responses and Severe Dengue. Front Cell Infect Microbiol. 2020; 10:5900 04.
11. Nettis, E. et al. Rupatadine for the treatment of urticaria. Expert opinion on pharmacotherapy. 2013; 14: 1807–1813.
12. Mullol, J. et al. Rupatadine in allergic rhinitis and chronic urticaria. Allergy. 2008;63(Suppl 87): 5–28.
13. Merlos, M. et al. Rupatadine, a new potent, orally active dual antagonist of histamine and platelet-activating factor (PAF). Te Journal of pharmacology and experimental therapeutics. 1997; 280: 114–121.
14. Abajian, M. et al. Rupatadine 20 mg and 40 mg are effective in Reducing the Symptoms of Chronic Cold Urticaria. Acta Derm Venereol. 2016; 96:56–59.
15. Donado, E. et al. No cardiac effects of therapeutic and supratherapeutic doses of rupatadine: results from a 'thorough QT/QTc study' performed according to ICH guidelines. British journal of clinical pharmacology. 2010; 69: 401–410.
16. Taubel, J., Ferber, G., Fernandes, S., Santamaria, E. &Izquierdo, I. Cardiac Safety of Rupatadine in a Single-Ascending-Dose and Multiple-Ascending-Dose Study in Healthy Japanese Subjects, Using Intensive Electrocardiogram Assessments-Comparison With the Previous White Caucasian Torough QT Study. Clin Pharmacol Drug Dev. 2017.
17. Church, M. K. Efficacy and tolerability of rupatadine at four times the recommended dose against histamine- and platelet-activating factor-induced fare responses and ex vivo platelet aggregation in healthy males. Te British Journal of dermatology. 2010; 163: 1330–1332.
18. Jeewandara C, Gomes L, Wickramasinghe N, Gutowska-Owsiak D, Waithe D, Paranavitane SA, et al. Platelet activating factor contributes to vascular leak in acute dengue infection. PLoS neglected tropical diseases. 2015; 9(2):e0003469.
19. Malavige GN, Wijewickrama A, Fernando S, Madushanka P, Punchihewa C, Ginneliya A, Samarasekara S, Paranavitana S, Idampitiya D, Wanigatunga C, Dissanayaka H. Efficacy of rupatadine in the treatment of acute dengue infection. 2016.
20. Malavige GN, Wijewickrama A, Fernando S, Jeewandara C, Ginneliya A, Samarasekara S, et al. A preliminary study on efficacy of rupatadine for the treatment of acute dengue infection. Sci Rep. 2018; 8 (1):3857.
21. Malavige GN, Jeewandara C, Wijewickrama A, Gunasinghe D, Mahapatuna SD, Gangani C, et al. Efficacy of rupatadine in reducing the incidence of dengue haemorrhagic fever in patients with acute dengue: A randomised, double blind, placebo-controlled trial. PLoSNegl Trop Dis. 2022; 16(6): e0010123.