

Assessment of Analgesic Activity of Two Antihypertensive Drugs

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Abstract Inflammation is an important part of the body's defense system, since it helps to remove and repair damaged tissue as well as neutralize poisonous compounds. The cascade includes increased permeability in microvessels, the attachment of circulating cells to vessels near the damage site, migration of various cell types, and the formation of new tissue and blood vessels. The analgesic and anti-inflammatory effects of rosuvastatin and telmisartan were examined in albino rats and Swiss mice. The hot plate approach regarded licking and leaping as response points. The combo group and rosuvastatin had similar analgesic efficacy. Its analgesic efficacy was significantly lower than that of a normal analgesic aspirin. Telmisartan, too, showed no analgesic effect. In this experiment, the percentage of inhibition at 120 minutes revealed that rosuvastatin and telmisartan given alone had a favourable impact on acute inflammation. Furthermore, the decrease of acute inflammation in the combination group was equivalent to that of aspirin. The data demonstrated that the capacity of the combination group to reduce chronic inflammation is equivalent to that of aspirin as an anti-inflammatory drug.

Keywords Rosuvastatin and Telmisartan, Inflammation, Micro Vessels, Hot Plate Method

1. Introduction

In contemporary medicine, a variety of pharmaceuticals,

such as nonsteroidal anti-inflammatory agents and corticosteroids, are used to manage pain and inflammation. These drugs have the drawback of simply providing symptomatic relief, and long-term use has been related to serious adverse effects. The researchers intensively search for safe cum effective drug candidates against analgesic and anti-inflammatory diseases. The hypertension induces most of the auto inflammatory diseases through the inflammatory cascades [1] and plays vital roles in pathogenesis of several metabolic syndromes such as cardiovascular defects [2, 3] diabetic mellitus [4, 5], myocardial ischemia and infarction [6]. As people become older, vascular stiffness and decreased compliance induce isolated systolic hypertension. Those pathophysiological factors also elevate the artificial stiffness in aged and cardio vascular disease patients [7]. It's also been noted that obese folks are more likely to have many chronic inflammatory disorders. Obesity has been related to an increased risk of developing rheumatoid arthritis. Obesity has had a considerable influence on the incidence of rheumatoid arthritis, and it may account for a significant percentage of the recent increase in the incidence [8]. Currently existing drugs against, osteoarthritis suffers a major drawback, since they are only oriented towards symptomatic relief and severely, associated adverse effects [9-10]. As a result, the search for a better and safer osteoarthritis treatment continues. Elderly people are almost invariably afflicted with one or more major ailments. If a single medicine can be given to a patient with several comorbid illnesses for more than one reason, the patient's drug load and toxicity may be reduced. It will be a

major assistance to aged patients suffering from a range of comorbidities if lipid-lowering pharmaceutical Rosuvastatin and anti-hypertensive drug Telmisartan are revealed to have analgesic and anti-inflammatory properties [11-12]. As a result, the goal of this research was to compare and evaluate the pain-relieving and anti-inflammatory effects of telmisartan and rosuvastatin in a variety of animal models.

2. Materials and Methods

Experimental Animals

Adult Wistar albino rats (*Rattus norvegicus*) weighing 200 to 240 g and Swiss mice (*Mus musculus*) weighing 25 to 30 g were used in the investigation. Female animals that were not pregnant were employed. Animals were procured from the King Institute of Preventive Medicine in Guindy, Chennai, and maintained at the Central Animal House (approved by Committee for Control and Supervision on Animal Experiments, CPCSEA) of the Bharath Institute of Higher Education and Research in Chennai, India. The animals were kept in a regulated temperature and hygiene conditions in polypropylene cages with 12-hour light and dark cycles and fed with a conventional pellet diet and water. The study was approved by Institutional Animal Ethics Committee (Letter no. 001/01/IAEC/2013).

3. Evaluation of Analgesic Activity

Hot Plate method

The nociceptive responses to thermal stimulation were measured using the hot plate technique and the drug was given before 30 minutes, before the commencement of the experiment. After that, the animals were placed on Eddy's Hot plate analgesia metre set to 550.2 degrees Celsius. They were taken from the hot plate without being harmed after a 15-second cut-off time if they did not react. Licking was identified as a nociceptive reflex in response to unpleasant thermal stimuli, while leaping was classed as an emotional-component of escape. The reaction time is defined as the duration between the hot plate placement and any responses (licking or jumping) of the experimental animal. The response times of control and experimental animals were tested at a base time point (zero point), 30, 60, and 120 minutes after treatment.

Acetic acid induced writhing

The nociceptive reactions to chemical stimuli were studied using acetic acid-induced writhing. Oral gavage was used to administer the experimental drugs 30 minutes before the commencement of the experiment. Intraperitoneally, 0.1 ml of 1% acetic acid solution was

injected with a 27 gauge 12-inch needle. The mice were kept in a glass beaker for five minutes for observation, during which time the start of writhes was recorded. After that, the animals' writhes were counted for 10 minutes. For scoring criteria, writhing is defined as straining the abdomen while concurrently extending at least one hind limb [13].

Evaluation:

The data for 'onset of writhes' in seconds and 'number of writhes for 10 min' and their mean and Standard error of mean (S.E.M) calculated is documented Percentage inhibition of writhing:

Formula:

$$\text{Percentage Inhibition (W \%)} = \{ (W_c - W_1) / W_c \} \times 100$$

Where,

No. of writhes in control group W_1 ,

No. of writhes in test group

Percentage inhibition of writhing will be tabulated.

Evaluation of analgesic activity

- Physical (Thermal) method:
- Chemical Method:
- Eddy's Hot Plate method Acetic acid induced writhing

Groups in each experiment:

Hot plate method: Each group consists of six rats each.

Group I: Control group (Normal saline 2mg/kg orally in CMC)

Group II: Aspirin (100 mg/kg orally in CMC)- Standard

Group III: Rosuvastatin (5 mg/kg orally in CMC)

Group IV: Telmisartan (2 mg/kg orally in CMC)

Group V: Combination group Rosuvastatin (5 mg/kg orally) and Telmisartan (2 mg/kg orally) in CMC.

Acetic acid induced writhing: Each group consist of six mice each.

1% acetic acid is used as pain inducing agent.

Group I: Control group (Normal saline 2mg/Kg orally in CMC)

Group II: Aspirin (100 mg/kg orally in CMC) - Standard

Group III: Rosuvastatin (5 mg/kg orally in CMC)

Group IV: Telmisartan (2 mg/kg orally in CMC)

Group V: Combination group Rosuvastatin (5mg/kg orally) and Telmisartan (2 mg/kg orally) in CMC

4. Statistical Analysis

The findings are expressed using the mean and standard error of the mean (SEM) and statistically analysed with one-way analysis of variance (ANOVA) and Tukey's post hoc test (IBM SPSS Version 20). The p value (< 0.05) was considered statistically significant.

5. Results and Discussion

Table 1. Showing reaction time of control group animals in seconds

Group I: Control				
Animal	Basal	30Min	60Min	120 Min
I	5	6	6	5
II	4	5	6	4
III	5	6	5	4
IV	4	7	7	6
V	5	5	5	5
VI	5	5	5	5
Mean±SEM	4.7 ±0.52	5.7 ±0.82	5.7 ±0.82	4.8 ±0.75

Table 2. Showing reaction time of Aspirin group animals in seconds.

Group II: Aspirin (Standard)				
Animal	Basal	30Min	60Min	120Min
I	6	8	11	14
II	5	9	12	14
III	4	6	9	15
IV	5	9	11	14
V	4	10	12	13
VI	5	9	12	15
Mean±SEM	4.833±0.307	8.500±0.563	11.167±0.477	14.167±0.307

Many inflammatory diseases have been related to difficulties with the cardiovascular system. As a result of today's sedentary lifestyle, cardiovascular disorders such as dyslipidemia, hypertension, and others are known to appear in tandem [14–15]. Angiotensin receptor blockers are also used to treat hypertension, a frequent concomitant condition with anti-inflammatory qualities. The hot plate method is used to determine how sensitive an animal is to pain. It is used in basic pain research as well as to evaluate the efficacy of analgesics by looking at the reaction to

heat-induced pain. It was initially presented by Woolfe and MacDonald [16], although it is now most widely used in the version modified by Eddy and Leimbach in 1953 [17]. This is a nociception behavioural model that may be used to predict centrally acting analgesic effectiveness and potency. This was confirmed in this study, when all treatment groups' pain thresholds grew dramatically during the experiment. The increase is smaller when rosuvastatin and telmisartan are taken individually than when they are taken combined. The findings also show that, if there is any synergistic analgesic efficacy in the combination group, it is negligible. Telmisartan has no pain-relieving effect and can only be compared to a placebo. Data is collected on each animal at a baseline time point, which is shortly before medication delivery, as well as 30 minutes, 60 minutes, and 120 minutes afterwards. To summarise the data at each time point, the mean and standard error of the mean is employed (SEM).

6. Hot Plate Method

The average and standard deviation of response times in all research groups. All groups exhibited no apparent increase in mean reaction time after 30 minutes, except aspirin, which showed a considerable increase. This had a P value of 0.001 not just in the control group, but also in the other research groups. Telmisartan showed no increase in reaction time as compared to its baseline reaction time. Furthermore, as demonstrated by their mean reaction time, the combination of Rosuvastatin and Telmisartan exhibited a stronger analgesic effect than either medication alone. However, there is no statistically significant difference in analgesia production between the combination group and Rosuvastatin, showing that telmisartan plays a little to non-existent function in creating analgesia. Telmisartan's effect on mean response time was only equivalent to the control group's.

Table 3. Showing mean and Standard error of Mean (SEM) of reaction time in seconds of all comparative groups at different time points in Hot Plate method

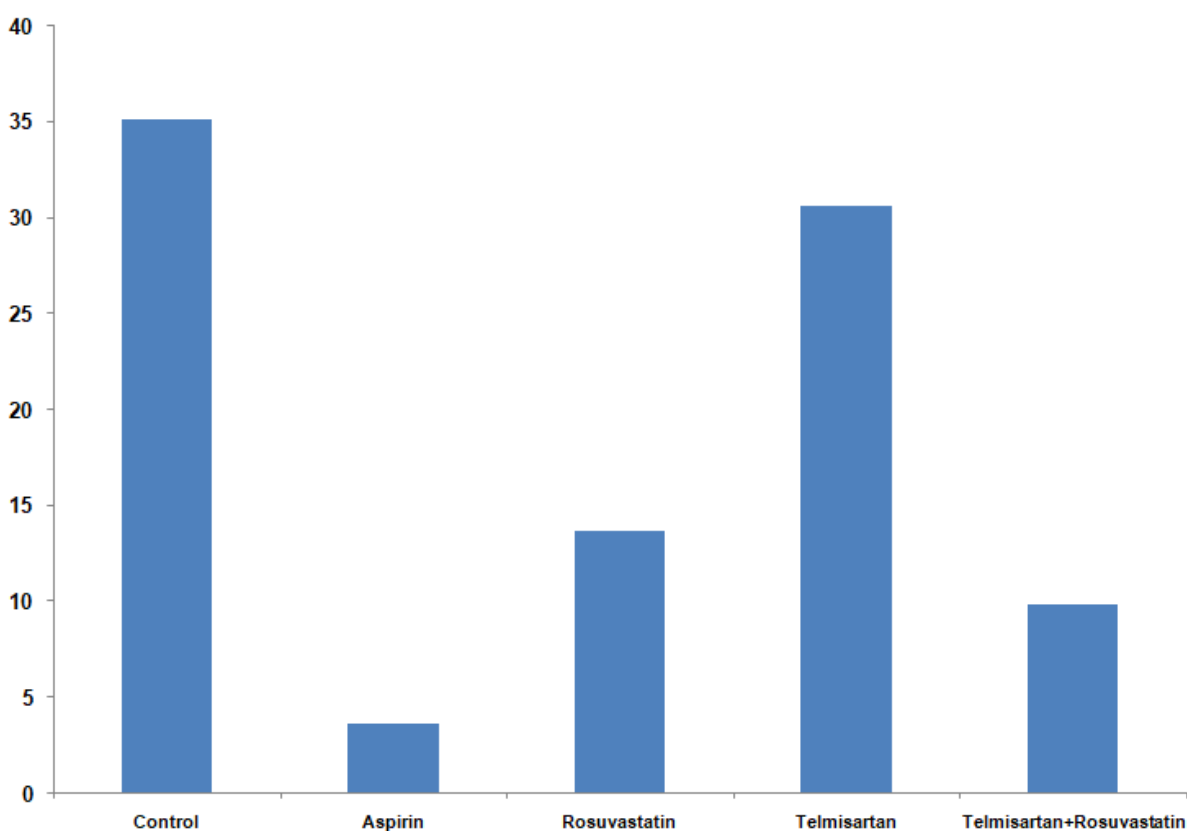
Groups	Basal	I 30Min	60Min	120Min
Control (I)	4.9 ±0.33	4.76 ±0.44	4.86 ±0.313	4.48 ±0.51
Aspirin (II)	5.12 ±0.41	8.5 ±0.563 *	11.167 ±0.477 *	14.167 ±0.307*
Rosuvastatin (III)				
Telmisartan (VI)	4.833 ±0.543	5.29 ±0.242	7.76 ±0.512 *	9.45 ±0.245 *
Rosuvastatin+Telmisartan (V)	4.777 ±0.363	4.99 ±0.291	5.421 ±0.494	5.91 ±0.49

(*p<0.001)

Table 4. Showing the mean and standard error of mean (SEM) of the start of writhing and the number of writhing in 10 minutes for all comparison groups. The percentage of analgesia developed in the control group is also displayed.

Groups	Onset in seconds	No of Writhes in 10min	% of analgesics from control
Control	2.872 ±0.271	36.412 ±1.82"	Not Applicable
Aspirin (standard)	7.124 ±0.121 *	3.712 ±0.51 *	90.12
Rosuvastatin	5.362 ±0.211 *	13.667 ±0.791 *"	61.14
Telmisartan	3.124 ±0.272	31.124 ±0.31 "	14.14
Rosuvastatin+ Telmisartan	6.666 ±0.081 *	9.912 ±0.661 *	73.31

*p<0.001 and "p<0.05 with control and, when compared with aspirin

**Figure 1.** Depicting onset of writhing in Right Y-axis and Number of writhes in 10 minutes in Left Y- axis in acetic acid induced writhing method.

7. Acetic Acid Writhing Method

Both the control and Telmisartan groups started writhing early, with Telmisartan showing no statistical difference from the control group. Writhing began after 5 minutes, within the experimental groups, the Aspirin showed the most delayed onset and had p value as 0.001 with the control. When compared to control, the Aspirin, Rosuvastatin, and Combination groups had considerably fewer writhes in ten minutes (P value 0.001), but Telmisartan and control had no statistically significant difference. In addition, when compared to aspirin, rosuvastatin and telmisartan showed a significant difference with a P value of 0.05, showing that these drugs do not induce as much analgesia on their own. There was

no significant difference between the means of the combination group and aspirin. Aspirin has the largest proportion of analgesia at 89.57 percent, while telmisartan has the lowest at 12.80 percent.

Analgesia of more than 70% is considered to have at least modest analgesia. Aspirin and Combination groups, with analgesia percentages of 89.57 percent and 72.04 percent, respectively, have analgesia percentages greater than 70% [18]. Because this technique concentrates on peripherally acting analgesics, the highest analgesic effect of aspirin was found in this model. On its own, rosuvastatin has a considerable analgesic impact, although it is not as powerful as aspirin. In regularly used experimental models of analgesia, there are no comparative data on the specific analgesic effect of statins or angiotensin receptor blockers.

Analgesics including angiotensin-converting enzyme inhibitors (ACEIs) are uncommon. Based on our data, we can infer that telmisartan has no analgesic effect, but rosuvastatin has little analgesic efficacy, with a percentage inhibition closer to 70%. Furthermore, the combo group had a stronger analgesic effect than the drugs given alone. This difference is also statistically significant only with telmisartan, not with rosuvastatin. When compared to aspirin, these medications have a poor analgesic effect, although rosuvastatin and the combination group have a considerable analgesic effect. It is also obvious that these medicines have no synergistic effect in terms of pain relief [19]. Prostaglandin E2 (PGE2)-induced hypernociception has also been observed to be reduced by rosuvastatin [20].

8. Conclusion

Rosuvastatin has a considerable analgesic effect, according to the findings of this study, but not to the point that it can be classed as an analgesic drug. The analgesic effects of telmisartan, on the other hand, were essentially non-existent. In terms of analgesic activity, the combination group surpasses rosuvastatin. Although the dosages are not similar, both rosuvastatin and telmisartan have greater anti-inflammatory effects than aspirin. However, like aspirin, the combo group has significant anti-inflammatory characteristics. More study into the pleiotropic effects of all statin and angiotensin receptor blocker drugs is needed in order to find new indications for these therapies.

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Ethical Approval

The study was approved by the Institutional Ethics Committee.

Conflict of Interest

The authors declare no conflict of interest.

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