INTRODUCTION

Many drugs like non-steroidal anti-inflammatory drugs and corticosteroids are being used in modern medical practice to suppress pain and inflammation. The drawback of these drugs is they provide symptomatic relief and long-term use of these drugs is associated with serious adverse effects. Hence, the search for a new, safe analgesic and anti-inflammatory drug is on-going.

Vascular wall inflammation plays a key role in the pathogenesis and progression of atherosclerosis, cardiovascular disease and hypertension. Usually hypertension accentuates the progression of atherosclerosis that has an inflammatory component which also plays an integral role in its pathogenesis[1], and which is also present in other conditions associated with cardiovascular events, such as metabolic syndrome[2] and diabetes mellitus[3]. Indeed, inflammation is now recognized as a central mechanism contributing to progression of cardiovascular disease in general, and may be involved in the triggering of myocardial ischemia and infarction[4]. Isolated systolic hypertension results from age associated vascular stiffening and reduced compliance[5]. Arterial stiffness increases with advancing age and in the presence of other cardiovascular risk factors, including hypertension, the metabolic syndrome, diabetes, obesity, hypercholesterolemia, and elevated levels of C-reactive protein.

It is also suggested that many chronic inflammatory pathologies is usually found to be coexisting in people who are obese. Obesity is found to be associated with modest risk of developing rheumatoid arthritis. Given the rapidly increasing prevalence of obesity, this has had a significant impact on rheumatoid arthritis incidence and may account for much of the recent increase in the incidence of rheumatoid arthritis[6]. Also there are many recent studies that allow us to better understand the relationships between osteoarthritis and obesity. Although it is evident that mechanical components contribute to joint destruction in overweight people, osteoarthritis is considered not only a disease of articular cartilage but also a systemic disorder in which circulating factors linked to altered lipid and glucose metabolism may explain the diversity of pathophysiological changes found in generalised osteoarthritis[7].

Treatment of arthritis in modern medicine is currently limited to drugs that provide only symptomatic relief, and these drugs are associated with serious adverse effects. Hence, research for finding a better and safe drug for osteoarthritis has been a continuous process.

The elderly people almost have one or more other major disease conditions, even life-threatening conditions which may be of inflammatory in origin. Also they have senescent changes in all organ systems, whether the heart is normal or diseased. If at all understanding the pathogenesis of the symptoms and signs to establish a diagnosis and prognosis is difficult, it becomes even more challenging for managing them with drugs with their geriatric changes like age related reduction in hepatic blood flow and hepatocyte mass and primary aging changes in hepatic sinusoidal endothelium. This has an effect on drug transfer and oxygen delivery and causes reduction of hepatic drug clearance. Age related changes in renal clearance is evident, although renal clearance reduction in older people is predominantly disease-related and is poorly estimated by standard methods. The geriatric dosing axiom, “start low and go slow” is based on pharmacokinetic considerations and concern for adverse drug reactions since there is lack of clinical trial data[8].

If a single drug can be given to a patient for more than one indication with such coexisting comorbid conditions, it can potentially reduce their drug load and minimize the drug toxicity. This may also prove to be a cost effective method of treatment.

Statins have been shown to decrease the secretion of pro-inflammatory cytokines IL-6 (interleukin-6) and IL-8 (interleukin-8) from macrophages, and inhibit the release of the chemokine CCL2/MCP-1 (macrophage chemotactic protein-1) from these cells. The molecular mechanisms sub serving such anti-inflammatory and/or immunomodulatory activities are unclear[9][10]. Angiotensin II increases adhesion molecules, cytokines and chemokines and exerts a proinflammatory effect on leucocytes, endothelial cells and vascular smooth muscle cells. Telmisartan is a highly selective AT1-receptor antagonist act as a partial agonist on the nuclear peroxisome proliferator-activated receptor-γ (PPAR-γ)
that has been reported to exert anti-oxidative and anti-inflammatory effects\[11\]. Peroxisome proliferator-activated receptor γ (PPAR-γ) partial agonist activity regulates metabolic and inflammatory pathways, and improves left ventricular function\[11\][12]. Rosuvastatin a lipid lowering drug and Telmisartan an anti-hypertensive drug if found to be having anti-inflammatory property, then it would be a great boon to geriatric patients who are suffering with number of comorbidities. Hence, this study was planned to evaluate and compare the anti-inflammatory actions of rosuvastatin and telmisartan in different animal models of inflammation.

MATERIALS AND METHODS

Experimental Animals

Adult Wistar albino rats (Rattus norvegicus) weighing between 200 to 240 gram and Swiss Mice (Mus musculus) of either sex weighing 25 – 30 gram were purchased from King Institute of Preventive Medicine, Guindy, Chennai and maintained in the Central Animal House, Sree Balaji Medical College and Hospital, Chennai, India for acclimatization. All experiment was performed with Institutional Animal Ethics Committee approval numbered 001/01/IAEC/2013 and under CPCSEA guidelines.

Experimental Drugs

Rosuvastatin (from Micro Labs Ltd), Telmisartan (from Micro Labs Ltd) and Aspirin (from Zydus Cadila Healthcare Ltd) were obtained by pure powdered form and given in dosage of Rosuvastatin 5 mg/kg\[13\][14][15], Telmisartan 2 mg/kg\[16\][17][18][19] and aspirin dose of 100 mg/kg\[20\][21][22] orally by gavage feeding tube. For all the oral drugs carboxymethyl cellulose is used as a solvent and 1% Carrageenan via intra-dermal route and 2% Formalin via subcutaneous route as inflammatory agents. In this study, dosages used for evaluation of both analgesic and anti-inflammatory activities were in accordance with their respective studies\[23\][24][25][26][27].

Acute anti-inflammatory action

Carrageenane induced paw oedema.

To assess acute inflammatory action, carrageenana induced paw oedema is used\[28\]. The experimental drugs were given by oral gavage one hour before the start of experiment. With the help of 27 gauge ½-inch needle 0.1 ml of 1% carrageenan is intra-dermally administered into the plantar surface of the right hind paw of rats. The acute phase of inflammatory reaction, i.e., oedema volume of right hind paw was determined using a plethysmometer modified by Harayal Singh and Ghosh\[29\] at time points prior to (basal) and 30 min, 60 min and 120 min after carrageenana injection.

\[P\% = \frac{P_t - P_c}{P_c} \times 100\]

Where,

\[P_t\%\] Percentage inhibition at given time interval

\[P_c\] Paw volume in control group

\[P_t\] Paw volume in test group

Table 1: Table showing mean volume of paw oedema in mL in carrageenana induced paw oedema.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Basal</th>
<th>30 Min</th>
<th>60 Min</th>
<th>120 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I: Control</td>
<td>0.417</td>
<td>0.750</td>
<td>0.950</td>
<td>0.900</td>
</tr>
<tr>
<td>Group II: Aspirin (standard)</td>
<td>±0.031</td>
<td>±0.034</td>
<td>±0.067</td>
<td>±0.037 *^</td>
</tr>
<tr>
<td>Group III: Rosuvastatin</td>
<td>0.400</td>
<td>0.517</td>
<td>0.467</td>
<td>0.383</td>
</tr>
<tr>
<td>Group IV: Telmisartan</td>
<td>0.417</td>
<td>0.700</td>
<td>0.567</td>
<td>0.517</td>
</tr>
<tr>
<td>Group V: Rosuvastatin + Telmisartan</td>
<td>±0.031</td>
<td>±0.026</td>
<td>±0.021 *</td>
<td>±0.031 **</td>
</tr>
<tr>
<td>Group VI: Telmisartan</td>
<td>0.417</td>
<td>0.733</td>
<td>0.600</td>
<td>0.550</td>
</tr>
<tr>
<td>Group VII: Aspirin + Telmisartan</td>
<td>±0.031</td>
<td>±0.033</td>
<td>±0.026 *</td>
<td>±0.022 **</td>
</tr>
</tbody>
</table>

\[^*P < 0.001 when compared to control at same time point, ^*P < 0.05 when compared to aspirin at same time point.\]

Table 2 shows the percentage of inhibition of paw oedema for all study drugs. Percentage inhibition of acute inflammation was greater in aspirin group when compared to rosuvastatin, telmisartan and combination group at all-time intervals. Similarly, the percentage inhibition at 120 minutes of combination group (50.00%) is greater than that of Rosuvastatin (42.59%) and Telmisartan (38.89%). It can also be seen at the same time point that the percentage inhibition of combination group (50.00%) is closer to aspirin (57.41%).


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The mean differences in linear cross section of all the drug treated groups were statistically significantly when compared to control (P < 0.001). There is a significant difference in linear cross section of Rosuvastatin and Telmisartan to that of aspirin group (P<0.001). But there is no significant difference between combination group and aspirin which shows that combined action of rosuvastatin and telmisartan is as effective as aspirin. The least difference in mean linear cross section was found in the aspirin group followed by combination group. Also the percentage of anti-inflammatory effect of aspirin was greater with 90.37% followed by combination group with 83.05% which is followed by rosuvastatin and telmisartan with 70.71% and 65.89% respectively.

### Table 3: Table showing mean Linear Cross Section (LCS) in mm. Also showing percentage of anti-inflammatory effect in formalin induced arthritis.

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial LCS</th>
<th>Day 10 LCS</th>
<th>Difference in LCS</th>
<th>% anti-inflammatory effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.960 ± 0.066</td>
<td>7.283 ± 0.157</td>
<td>3.323 ± 0.168</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Aspirin (standard)</td>
<td>3.883 ± 0.076</td>
<td>4.203 ± 0.017</td>
<td>0.320 ± 0.069 *</td>
<td>90.37%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>3.877 ± 0.060</td>
<td>4.850 ± 0.29</td>
<td>0.973 ± 0.075 ^</td>
<td>70.71%</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>3.897 ± 0.056</td>
<td>5.030 ± 0.021</td>
<td>1.133 ± 0.041 **</td>
<td>65.89%</td>
</tr>
<tr>
<td>Rosuvastatin + Telmisartan</td>
<td>3.890 ± 0.064</td>
<td>4.453 ± 0.056</td>
<td>0.563 ± 0.074 *</td>
<td>83.05%</td>
</tr>
</tbody>
</table>

*p < 0.001 when compared to control, ^ p<0.001 when compared to aspirin

### DISCUSSION

Many inflammatory conditions are associated with disorders of cardiovascular system. Cardiovascular disorders like dyslipidemia, hypertension etc. is usually known to occur together due to sedentary modern life style. These conditions with other chronic inflammatory conditions like arthritis and also the inevitable aging can cause function restricting pain. Statins have been widely used in the treatment of dyslipidemia since long. More recently there has been an interest in the analgesic and anti-inflammatory activities of statins following reports about their ability to relieve pain and inflammation[30][31]. Also angiotensin receptor blocker is used in hypertension which is a usual comorbid condition and it is also suggested to have anti-inflammatory actions.

Carrageenan is a mucopolysaccharide extract, discovered by the British pharmacist Stanford in 1862[32]. Carrageenan is the phlogistic agent of choice for testing anti-inflammatory drugs as it is not known to be antigenic and is devoid of apparent systemic effects. Hence the inflammatory response induced by carrageenan is acute and nonimmune. Carrageenan-induced hind paw oedema has become standard experimental model of acute inflammation. This model exhibits a high degree of reproducibility and has significant predictive value for clinically useful anti-inflammatory drugs[33]. Carrageenan-induced oedema is a biphasic response. The first phase for the first 2 hours is mediated through the release of histamine, serotonin and kines, whereas the second phase is due to the release of prostaglandin and slow reacting substances which starts only after 3 to 4 hours. Inhibition of carrageenan induced oedema by rosuvastatin and telmisartan can therefore be attributed to their ability to inhibit release of histamine, serotonin and kines. This inflammation is usually quantified by increase in paw size using a plethysmometer[29]. It is clearly evident that rosuvastatin, telmisartan and their combinations have a good anti-inflammatory activity when compared to the control. Also the percentage of inhibition of inflammation was very low at 30 minutes but it has increased many folds with in next 30 minutes and the increase was gradual for the next hour. However, at 120 minutes the combination group fared better in respect to inhibiting acute inflammation just below aspirin. The synergistic action of the two drugs is also obvious from the observations.

Formalin a potent inflammatory agent is used by Brownlee in 1950 to induce arthritis in animals. When the formalin is reinforced subsequently it would produce inflammation which would resemble chronic inflammation mimicking arthritis[35]. The nociceptive effect of formalin is biphasic, an early neurogenic component followed by a later tissue mediated response[36]. Thus formalin induced arthritis is a model used for the evaluation of an agent with probable anti-proliferative activity. This experiment is associated with the proliferative phase of inflammation[37]. All group of drugs showed a significant inhibition of chronic inflammation with maximum effect obviously for aspirin and comparable to that of combination group.

There is a significant inhibition of chronic inflammatory action for the combination group, working synergistically when compared to rosuvastatin and telmisartan given alone. Also percentage inhibition of inflammation is more than 80% for aspirin and combination group. Inflammation protective action is present in both drugs and it is also seen to be working synergistically. Chronic inflammation protective effect is more compared to the inhibition of acute inflammation. The important finding will be that with the combined action of drugs there is no significant difference in protection of chronic inflammation from aspirin. In other words these both drugs together can be compared with an anti-inflammatory drug.

Many investigations are on-going to explore the mechanisms underlying the anti-inflammatory activity of statins and angiotensin receptor blockers. Rosuvastatin therapy significantly decreased high-sensitivity C-reactive protein (a bio-marker of inflammation) levels in patients of systemic sclerosis[38].

It is also demonstrated for the first time, in a clinical trial, the anti-inflammatory and antioxidant properties of telmisartan, previously observed only in pre-clinical models[39]. Moreover, the beneficial
effect shown by telmisartan may be explained by its multiple therapeutic characteristics. Indeed, telmisartan is a unique ARB with selective PPAR-y-modulating activity which affects nitric oxide bioavailability thus leading to its anti-inflammatory, antioxidant and anti-proliferative effects on vascular wall cells [40]. Telmisartan was also shown to be potent to increase the number of regenerative endothelial progenitor cells and improve endothelial function independently of its blood pressure lowering action [41]. Additionally, it has also been shown to play a role in lipid and glucose metabolism [42]. Hence, it appears that rosuvastatin and telmisartan can effectively suppress both acute as well as chronic inflammation by inhibiting the release of various mediators of inflammation.

Further investigations for all drugs in both statin group and angiotensin receptor blocker group for their pleiotropic effect must be undertaken so that new indications of these drugs can come to light.

CONFLICT OF INTEREST: None

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