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Rosuvastatin and Simvastatin potentiate antihypertensive effect of amlodipine through vasorelaxation phenomenon

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Abstract: This study is carried out to assess the effects of rosuvastatin and simvastatin on blood vessels for possible vasorelaxant effect. The study is also translating the possible vasorelaxant effect in Wistar rats for a subsequent fall in systolic blood pressure. It is evident from the EC_{50}, that rosuvastatin is more effective on relaxing N.E induced contractions, while simvastatin is more effective on relaxing KCL induced contractions. Simvastatin is equipotent when compared to effects of amlodipine on KCl induced contractions in denuded aortae. Simvastatin produced significant right shift in test concentration 1.1×10^{-6}M with its respective EC_{50} -1.85logCa^{++}M as compared to its respective control EC_{50} -3logCa^{++}M. Rosuvastatin also produced significant right shift in the $EC_{50.}$ In conclusion, it is stated that rosuvastatin and simvastatin relax the aortic strips preparations through inhibition of voltage gated calcium channels and inhibition of N.E induced contractions. Rosuvastatin and simvastatin have additive effects when used in the presence of a standard vaso-relaxant drug like amlodipine, which further confirms its additive effect on decreasing the systolic blood pressure of hypertensive rats ($P<0.05$).

Keywords: Statins, rosuvastatin, simvastatin, amlodipine, verapamil, calcium channel blocking activity.

INTRODUCTION

Statins inhibit HMG-CoA enzyme and reduce the lipid levels (Sirtori, 2014). In most cases, hypercholesteremia and cardiovascular diseases (CVDs) go side by side. It is a general perspective that cardiovascular diseases are more associated with morbidity and mortality (Organization, 2014). CVDs are one of the common causes of deaths. In 2017, 17.8 million deaths occurred due to CVDs. CVDs most commonly include hypertension, dyslipidemia, angina, myocardial infarction and stroke (Mensah *et al*., 2019). For management of these diseases, the practice of polypharmacy is very common. Polypharmacy carries risks of drug interactions as well. The US Food and Drug Administration (FDA) has defined “intolerance” to statin as "the inability to tolerate at least two statins at the lowest approved doses due to musculoskeletal symptoms”. About 9% intolerance to statins has been reported. In addition to several other risks factors, concomitant use of calcium channel blockers is contributing up to 35.5% (Bytyçi *et al*., 2022). Which is why we are designing this study to answer whether rosuvastatin and simvastatin have an additive effect when used in combination with calcium channel blockers. Though, there are reports that combination of antihypertensives and lipid lowering agents provide cardiovascular benefits as well (Margolis *et al*., 2013, Neutel *et al*., 2009). WHO recommended drugs for treatment of CVDs include Beta blockers, Calcium Channel Blockers, Angiotensin Receptor blockers, Statins and Antiplatelet Drugs (Smith and Ashiya, 2007). Some effects of statins are independent or other than of its lipid lowering action. These effects are called pleiotropic effects of statins. The pleiotropic effects include improving endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress, decreasing inflammation and inhibiting the thrombogenic response (Gotto Jr and Farmer, 2001, Liao and Laufs, 2005). Another study has suggested the beneficial effects of statins for decreasing the portal pressure in patients with liver cirrhosis (Bosch *et al*., 2020). The use of statins with antihypertensives has beneficial effect for decreasing risks of dementia (Barthold *et al*., 2020). All these effects are regarded beneficial for the recipient. We have recently reported that current statins have voltage gated calcium channels inhibiting effects in gut tissues (Ali *et al*., 2016). Studies have shown that statins also up-regulate the calcium channels in vascular cell lines (Clunn *et al*., 2010, Lefer *et al*., 2001). Thus, an upregulation of calcium channels will enhance the response to calcium channel blockers. But these effects are associated with long term effects. We have tried to test the statins for a single dose effect to answer the question that whether statins have additive effects to calcium channel blockers or otherwise. As our recent study have shown that statins have inhibitory effects on voltage gated calcium channels (Ali *et al*., 2016) in gut preparations. Therefore, current study will answer possible additive effects in aortic strips preparations, which is being translated in hypertensive rats for possible blood pressure lowering effect. This is

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because, as stated earlier, co-morbid conditions are commonly treated with drug combinations like calcium channel blockers and statins (Johnson *et al*., 2004, Trialists'Collaboration, 2000). In the light of statins pleiotropic effects, and our recent reports about statins for inhibition of voltage gated calcium channels in gut tissues, the current study is carried out to study the possible additive effects of Rosuvastatin and Simvastatin on blood vessel. The study also translates possible additive effects on blood pressure of hypertensive Wistar rats.

MATERIALS AND METHODS

Study settings

This study was conducted at Department of Pharmacology, Institute of Basic Medical Sciences, Khyber Medical University, Peshawar, KP, Pakistan, and in the College of Medicine, Shaqra University, Shaqra, Saudi Arabia.

Raw materials, drugs and solutions, and Standards

All chemicals used were of analytical grade. Rosuvastatin, Simvastatin and Amlodipine were obtained from Feroz-sons laboratories Pvt Ltd Nowshera. Acetylcholine and norepinephrine were purchased from Poole, England. Rosuvastatin, water for injection was obtained from general pharmacy. All solutions were prepared in water for injection. Carboxy methyl cellulose (0.01%) was used to suspend the water insoluble materials. A negative control for 0.01% CMC and water for injection was used to rule out any possible effect of solvent on isolated tissue preparations. All solutions were freshly prepared on the same day of experiments.

Animals

Either sex rabbits weighing 1.5-2.5kg were used in the experiments. The animals were housed at the animal House of Khyber Medical University, Peshawar, KP, Pakistan. Blood pressure lowering effects were determined in Wistar rats. The animals had free access to water. Overnight fasted rabbits were used for aortic strips preparations. The study protocols were approved by the Advanced Study & Research Board and Ethics Board of the Khyber Medical University (Approval No. KMU/IBMS/IRBE/meeting/2022/9303-6.

Data recording

Force Transducer (Model No: MLT 0225 Pan Lab S.1) coupled with bridge amplifier successively connected with 4 channels Power lab (Model No: 4/25T ADInstruments, Australia), was used to measure the isometric tension. Lab chart 7 was used to record the data both for aortic strips and noninvasive blood pressure measuring system. Tail cuff transducer MLT125R was used to record the systolic blood pressure coupled with the Power lab.

Physiological solutions

Three types of Kreb's solutions were used: 1- Kreb's normal 2- Potassium normal (Ca^{++} free) Kreb's solution and 3- Potassium rich (Ca^{++} free) Kreb's solutions. All solutions were freshly prepared in deionized water on the same day of experiments. Solutions were constantly aerated with carbogen gas.

Statins and amlodipine effects on 1uM Norepinephrine (NE) induced contractions

Rabbits were fasted overnight. Following a cervical dislocation, their abdomens were opened. Their aortae were removed and placed in Kreb's solution contained in petri dishes constantly aerated with carbogen gas. Connective tissues were removed from the aortae. Tissues preparations of 2-3 mm diameter were prepared. The preparations were denuded through a gentle rubbing of cotton swab passing through its lumen. Status of denuded aortae were confirmed by applying a quiescent dose of ACh which did not relax the N.E induced contractions. These strips were mounted in Kreb's Solution constantly aerated and maintained with Carbogen gas [95% O_2, 5% CO_2] on 37±1 $^{\circ}$C. The chemical composition of Kreb's solution (mM) was: NaCl 118.2, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.3, Glucose 11.7, $NaHCO_3$ 25.0, $CaCl_2$ 2.5 with pH 7.4 (Ghayur and Gilani, 2005). A baseline 2g tension was applied to the tissues. An incubation period of 45-60minutes was given to the tissues. The rosuvastatin and simvastatin were applied in test concentrations (10^{-8} to 10^{-2}) M on NE (1μM) induced contractions and 80mM KCl-induced contractions. The inhibition of NE (1μM) induced contractions in aortae will signify the blockade of calcium influx through receptors operated calcium channels (Karaki *et al*., 1997, Musha *et al*., 2005). In calcium free Kreb's solution, the NE (1μM) induced contractions follow the stimulation of α_1 adrenergic receptors stimulations with subsequent conversion of phosphoinositides to inositol 1,4 and 5 triphosphate that facilitate calcium release from internal stores (Cauvin *et al*., 1984, Musha *et al*., 2005). Similar studies were done in endothelial intact aortae to explain the possible role of other mechanisms through endothelium. Simvastatin and Rosuvastatin were applied in cumulative manner with a 1-minute gap. Responses were recorded (Rosolowsky *et al*., 1991; Hassan Gilani *et al*., 2005; Sahin and Bariskaner, 2007). The experiments were run four times. Mean Effective Concentrations (EC_{50}) for statins and amlodipine were calculated.

Statins and amlodipine effects on KCl (80mM) induced contractions

It is pertinent to mention that relaxing effects on 80 mM KCl- induced contractions will testify the inhibition of voltage gated calcium channels (Karaki *et al*., 1997). But usually, it is also considered that every relaxation on 80 mM KCl-induced contractions do not necessarily follow relaxation via inhibition of voltage gated calcium

channels, which is why it requires further confirmation through constructions of calcium concentrations response curves (CCRCs) in the absence and presence of test substance (Pietrobon and Hess, 1990, Godfraind *et al*., 1992, Ghayur and Gilani, 2005). Therefore, we produced sustained contractions in nuded and denuded aortic strips via KCl (80mM). A period of 40-60 min stabilization was given. Rosuvastatin, Simvastatin and Amlodipine in similar test concentrations were applied in cumulative manner with a minute gap. Mean Effective Concentrations (EC_{50}) were noted for test statins and Amlodipine (Ali *et al*., 2016, Gilani *et al*., 2005). The experiments were run four times.

Statins effects on calcium concentration response curves (ccrcs)

As Rosuvastatin and Simvastatin relaxed the aortic strips contractions induced by NE (1µM) and 80 mM KCL induced contractions, therefore, it is suggested that rosuvastatin and simvastatin may act via inhibition of voltage gated calcium channels. It is also considered that every relaxation on 80mMKCl- induced contractions does not necessarily follows relaxation via inhibition of voltage gated calcium channels, which is why it further needs confirmation through constructions of calcium concentrations response curves (CCRCs) in the absence and presence of test substances as well as in presence of a standard calcium channel blocker. Therefore, to find out the underlying mechanisms, CCRCs in test concentrations of calcium range: 1×10^{-4} - 256×10^{-4} Log Calcium Molar were constructed in the absence and presence of different concentrations of statins (with a visible relaxing effect on 80 mM KCl-induced contractions). A standard calcium channel blocker such as Verapamil was used for comparison. Briefly describing the procedure, Kreb's solution was used for aortic strips maintenance. For decalcification, the aortic strips were exposed to a series of wash with K-rich (Ca^{++} free) Kreb's solution followed by exposure to K-rich Normal solution, after a brief period of stabilization. Test concentrations of rosuvastatin and simvastatin were applied with an incubation period of 45-60 minutes. Then CCRCs were constructed. Similarly, in the absence of rosuvastatin and simvastatin, control CCRCs were also constructed. Similarly, the curves for verapamil were also drawn. Any possible right shift will indicate the inhibition of voltage gated calcium channels (Ali, 2013; Ali *et al*., 2014; Hassan Gilani *et al*., 2005; Khan and Gilani, 2009; Ghayur and Gilani, 2005).

Effects of statins on systolic blood pressure in hypertensive rats

As Rosuvastatin and Simvastatin relaxed the aortic strips preparations, therefore, we translated these effects for possible decrease in systolic blood pressure. Hence, we used Wistar rats. Briefly describing, Wistar rats were housed in the animal house for 2 weeks before start of the experimentations. They were subjected to a shame test for the whole procedure. Hypertension was induced in the rats using Depomedrol S/C injection (Kohlmann Jr *et al*., 1981).

Their blood pressure was checked regularly on alternate days. Rats with systolic blood pressure greater than 140 mmHg (on separate 3 different intervals) were declared hypertensive rats. The hypertensive rats were divided into 4 groups containing 5 rats in each group. One group served as negative control that received only vehicle. Other group was treated with amlodipine 0.0714mg/kg po that served as positive control treatment. Statins in their respective EC_{50} concentrations were administered to Rosuvastatin and Simvastatin treated groups per oral route. Their blood pressure was noted on respective Tmax. The experiments were run in triplicate (Aziz *et al*., 2013). Responses were recorded.

STATISTICAL ANALYSIS

Responses to test and standard drugs were plotted on y-axis versus respective concentrations on X-axis using Graph Pad Prism Version 8. Their EC_{50} were determined. For CCRCs control curves, log calcium molar concentration was plotted on X-axis as independent variable. Responses were plotted on Y axis as dependent variable. Similarly, systolic blood pressure values were plotted in the Graph Pad Prism which were compared with amlodipine. The student t test was used to compare the effects of systolic blood pressure for statins treated groups and amlodipine treated group. p-value< 0.05 was considered statistically significant.

RESULTS

The effects of Rosuvastatin on N.E and KCl induced contractions in aortic preparations are shown in fig 1. Similarly, the effects of Simvastatin and Amlodipine on N.E and 80 mM KCl induced contractions are respectively shown in fig. 2 and fig. 3. Relaxing effects of Rosuvastatin and Simvastatin, and Amlodipine with their respective EC_{50} are also shown in table 1. It is noteworthy that Rosuvastatin and Simvastatin relaxed both nuded and denuded tissues suggestive of involving mixed pathways. It is clear from the EC_{50}that Rosuvastatin is more effective to relax N.E induced contractions, while simvastatin is more effective to relax the KCL induced contractions. Moreover, Simvastatin is equipotent when compared to effects of Amlodipine on KCl induced contraction in denuded aortae. The effects of Amlodipine, a standard calcium channel blocker in the presence of respective Rosuvastatin and Simvastatin are shown in table 2. Reading table 1 and table 2 simultaneously for respective EC_{50} values, it is evident that there is a left shift in the EC_{50} on KCL induced contractions as well as on N.E (1uM) induced contractions. CCRCs in the absence and presence of statins are shown in fig. 4. While

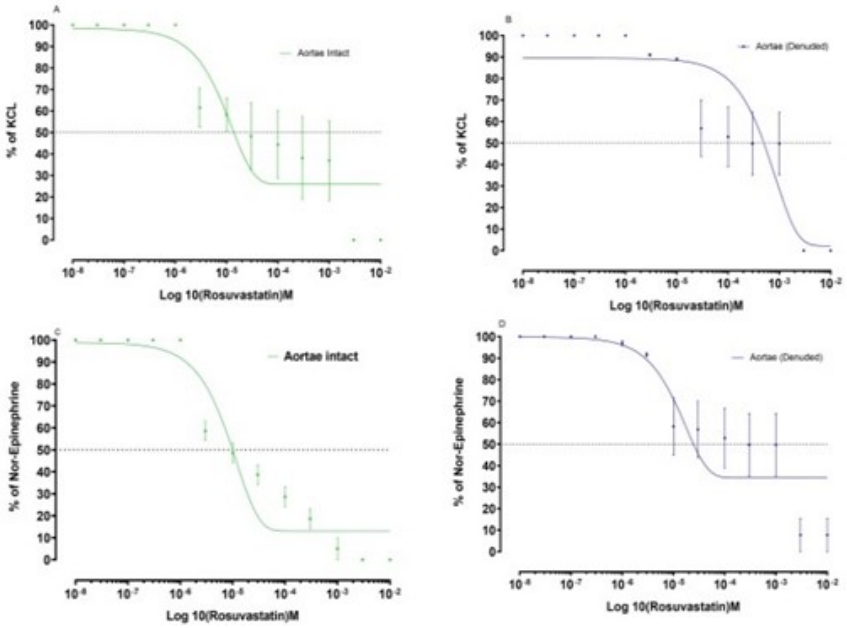

Fig. 1: (a) Effects of Rosuvastatin on KCL-induced contractions in isolated aortic strip preparations to show relaxant effects in intact tissues (all values are mean ± SD, *n* = 4). (b) Effects of Rosuvastatin on KCL-induced contractions in isolated aortic strip preparations to show relaxant effects in denuded tissues (all values are mean ± SD, *n* = 4). (c) Effects of Rosuvastatin on Nor-Epinephrine induced contractions in isolated aortic strip preparations to show relaxant effects in intact tissues (all values are mean ± SD, *n* = 4). (d) Effects of Rosuvastatin on Nor-Epinephrine induced in isolated aortic strip preparations to show relaxant effects in denuded tissues (all values are mean ± SD, *n* = 4).

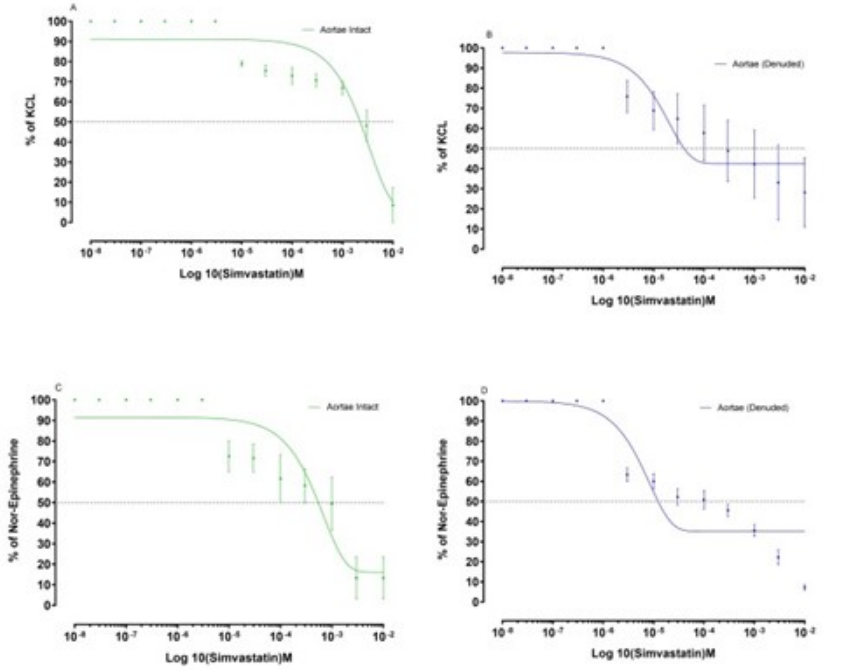

Fig. 2: (a) Effects of Simvastatin on KCL-induced contractions in isolated aortic strip preparations to show relaxant effects in intact tissues (all values are mean ± SD, *n* = 4). (b) Effects of Simvastatin on KCL-induced contractions in isolated aortic strip preparations to show relaxant effects in denuded tissues (all values are mean ± SD, *n* = 4). (c) Effects of Simvastatin on Nor-Epinephrine induced contractions in isolated aortic strip preparations to show relaxant effects in intact tissues (all values are mean ± SD, *n* = 4). (d) Effects of Simvastatin on Nor-Epinephrine induced in isolated aortic strip preparations to show relaxant effects in denuded tissues (all values are mean ± SD, *n* = 4).

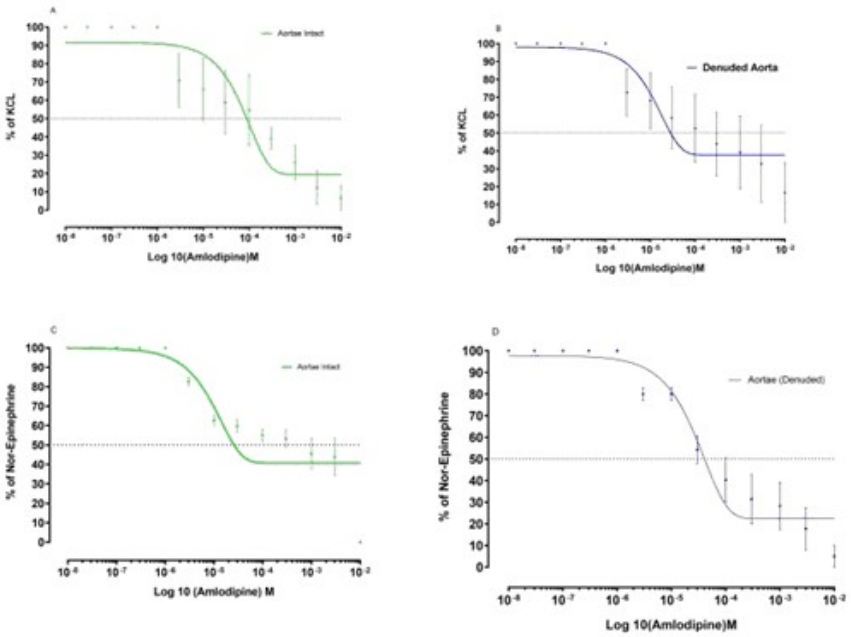

Fig. 3: (a) Effects of Amlodipine on KCL-induced contractions in isolated aortic strip preparations to show relaxant effects in intact tissues (all values are mean ± SD, *n* = 4). (b) Effects of Amlodipine on KCL-induced contractions in isolated aortic strip preparations to show relaxant effects in denuded tissues (all values are mean ± SD, *n* = 4). (c) Effects of Amlodipine on Nor-Epinephrine induced contractions in isolated aortic strip preparations to show relaxant effects in intact tissues (all values are mean ± SD, *n* = 4). (d) Effects of Amlodipine on Nor-Epinephrine induced in isolated aortic strip preparations to show relaxant effects in denuded tissues (all values are mean ± SD, *n* = 4).

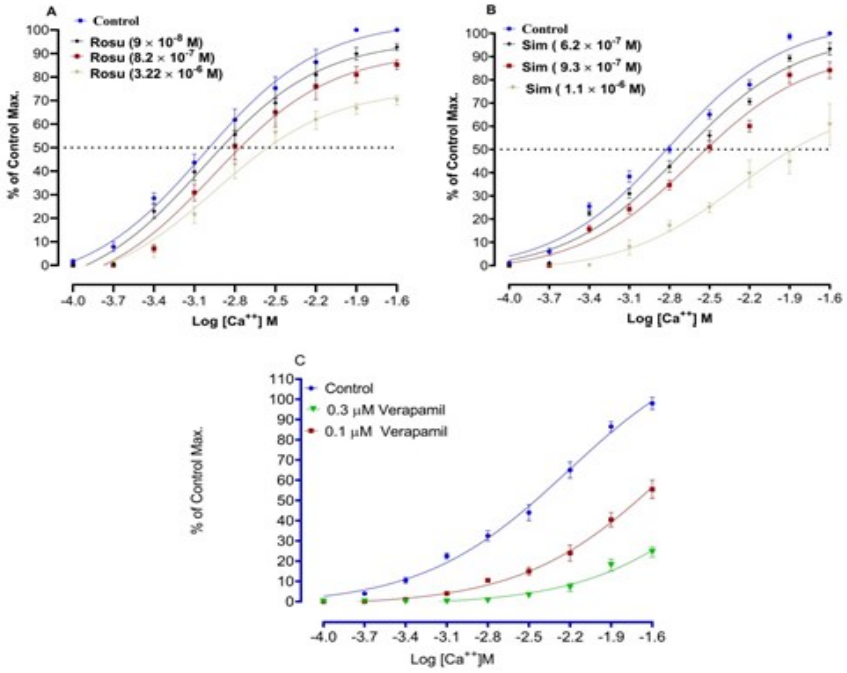

Fig. 4: (a) To show construction of CCRCs in absence and presence of different concentrations of Rosuvastatin in isolated aortic strips preparations (all values are mean ± SD, n=4). (b) To show construction of CCRCs in absence and presence of different concentrations of simvastatin in isolated aortic strips preparations (all values are mean ± SD, n=4). (c) To show construction of CCRCs in absence and presence of different concentrations of verapamil in isolated aortic strips preparations (all values are mean ± SD, n=4).

derived EC_{50} for CCRCs are shown in table 3. There is a right shift in EC_{50} indicating the involvement of statins for inhibition of voltage gated calcium channels.

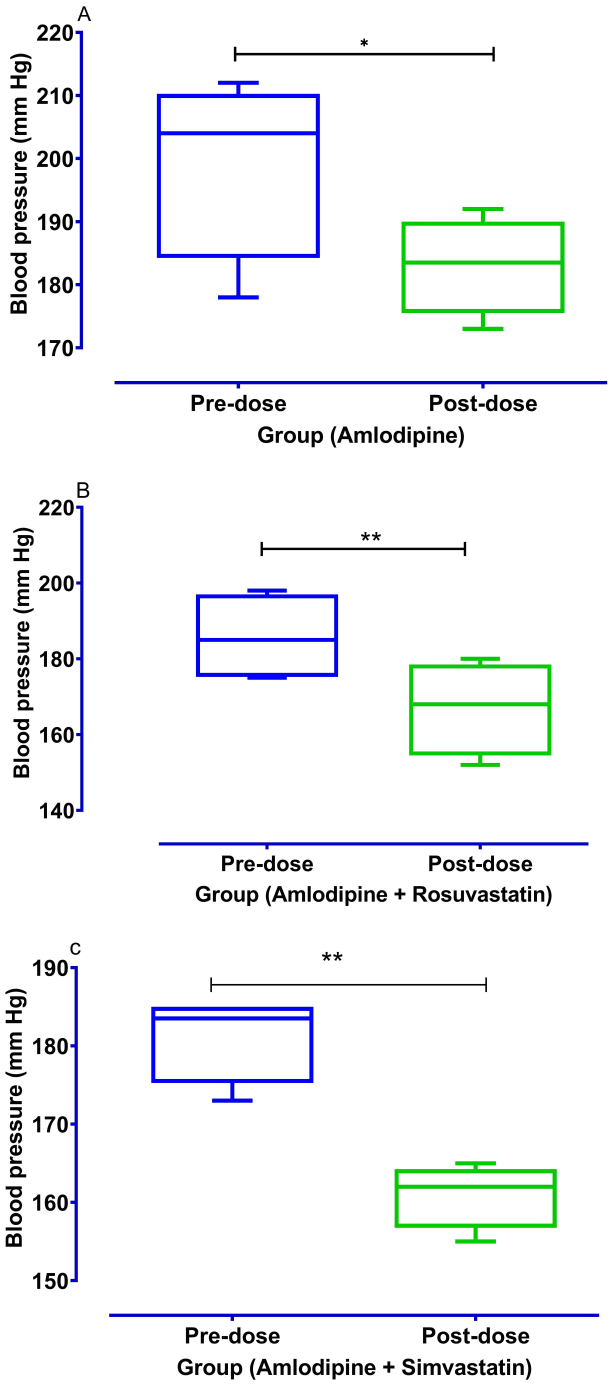

Fig. 5: (a) Effects of Amlodipine on systolic blood pressure. (b) Additive effects of Rosuvastatin with Amlodipine on systolic blood pressure. (c) Additive effect of Simvastatin with Amlodipine on systolic blood pressure of Wistar rats (all values are mean ± SD, n=4).

It is very pertinent to mention that Simvastatin produced significant right shift in test concentration 1.1×10^{-6}M with its respective EC_{50} -1.85logCa^{++}M as compared to its respective control EC_{50} -3logCa^{++}M. Results for studying effects of Rosuvastatin and Simvastatin on systolic blood pressure of rats are shown in fig. 5. Simvastatin showed significant blood pressure lowering additive effect as compared to Rosuvastatin ($p<0.05$) using amlodipine as standard.

DISCUSSION

There are different types of ailments that require practice of polypharmacy. For example, practice of ploy pharmacy is common while treating cardiovascular diseases and related complications. Statins are advised to patients who are hypercholesterolemic and hypertensive. Sometimes statins are combined with calcium channel blockers that may adversely affect the therapeutic goals. Intolerance to satins is very common. Researchers have found that in cell lines, the statins up-regulate the L-type calcium channels with an additive effect on voltage gated calcium channels (Clunn *et al*., 2010). But this upregulation requires time to develop. The novelty of our study is that it translates the direct first dose effects of statins alone or, if used, in combination with a calcium channel blocker. We have recently reported that current statins have inhibitory effects on voltage gated calcium channels in intestinal preparations (Ali *et al*., 2016). In the light of our recent research, possibilities for drug drug interactions cannot be ruled out. This study is answering possible effects of Rosuvastatin and Simvastatin which are very common in practice. This study also answers a possible additive or synergistic effect on blood vessels. The results imply that Simvastatin is more effective than Rosuvastatin in denuded aortae so far, its effects on KCL induced contractions are concerned. Relaxing effects on high 80 mM KCl-induced contractions are suggestive of involving inhibition of voltage gated calcium channels (Musha *et al*., 2005). The relaxation produced by Simvastatin is equipotent to Amlodipine. But the in denuded aortae, the effect of Rosuvastatin is as potent as Amlodipine tested on1µM NE induced contractions. This implies that both the statins follow mixed pathways for relaxing of aortae through receptors operated calcium channels as well as through inhibition of voltage gated calcium channels (Musha *et al*., 2005). But inhibition of voltage gated calcium channels is relatively more as we have already reported that current statins have calcium channels blocking activity. These effects in aortae were confirmed through constructions of CCRCs. It is evident that in rosuvastatin treated denuded aortae, the amplitude of maximum tension dropped to 34% of controlled maximum of N.E (1µM) induced contractions. Similarly, amplitudes for KCl (80mM) induced contractions were relaxed up to 31.1% in case or Rosuvastatin. These effects are significant in intact and denuded tissues, which implies that Rosuvastatin and Simvastatin relax the aortic strips by more than one pathway. Relaxing effects on

Table 1: To show relaxing effects of Rosuvastatin, Simvastatin and Amlodipine along with their respective EC_{50} values (All values are mean ± SD, n=4).

Drugs		Aortae Status	% of KCL (Control max)	% of NE (Control max)	EC_{50} ± SD KCL Induced (Molar)	EC_{50} ± SD NE Induced (Molar)
1	Rosuvastatin	Denuded	31.1%	34%	6.9 × 10-5± 1.63	2.52 × 10-5± 0.03
		Intact	26%	13.8%	1.39 × 10-5± 1.57	1.01 × 10-5± 1.84
2	Simvastatin	Denuded	42.7%	35.8%	3.83 × 10-5± 1.22	1.20 × 10-5± 0.07
		Intact	9.91%	14.4%	2.38 × 10-3± 3.89	5.6 × 10-4± 3.43
3	Amlodipine	Denuded	39.1%	22..7%	3.29 × 10-5± 1.69	3.83 × 10-5± 1.52
		Intact	40%	40.6%	2.3 × 10-5± 1.11	2.52 × 10-5± 1.81

Table 2: To show relaxing effects of Rosuvastatin, Simvastatin and Amlodipine and their respective EC_{50} values (All values are mean ± SD, n=4)

Drugs		Aorta Status	% of KCL (Control max)	% of NE (Control max)	EC_{50} ± SD KCL Induced (Molar)	EC_{50} ± SD NE Induced (Molar)
1	Amlodipine+ Rosuvastatin	Denuded	3.6%	4.73%	4.4 × 10-6± 1.63	5.7 × 10-6± 0.03
		Intact	12.2%	24.5%	1.39 × 10-5± 1.57	3.4 × 10-6± 1.84
2	Amlodipine+ Simvastatin	Denuded	6.6%	4.4%	2.1 × 10-6± 1.22	5.0 × 10-6± 0.07
		Intact	2.8%	4.7%	2.3 × 10-6± 0.89	3.1 × 10-6± 3.43

Table 3: To show right shift EC_{50} of Rosuvastatin, Simvastatin and Verapamil on calcium concentration response curves P<0.05, paired t test, versus respective control curves.

Statins	CCRCs Specifications	Mean EC_{50} Log $[Ca^{++}]M$
Rosuvastatin	Control	-2.97
	Test Concentration (9× 10^{-8}M)	-2.89**
	Test concentration (8.2× 10^{-7}M)	-2.73**
	Test Concentration (3.22× 10^{-7}M)	-2.5**
Simvastatin	Control	-3.00
	Test Concentration (6.2× 10^{-7}M)	-2.88**
	Test concentration (9.3× 10^{-7}M)	-2.70**
	Test concentration (1.1× 10^{-6}M)	-1.85***
Verapamil	Control	-2.42
	Test Concentration (0.03 µM)	-1.41**
	Test concentration (0.1 µM)	-0.69**

KCL induced contractions are usually, but not necessarily, considered to follow the inhibition of voltage gated calcium channels (Godfraind *et al*., 1992).

Therefore, we constructed CCRCs in the absence (control curve) and presence of the tested statins (Rosuvastatin and Simvastatin). Right shift in the EC_{50} (Log Ca^{++} M) of CCRCs of both the statins implies that these statins have calcium channel blocking activity. It is very pertinent to mention that simvastatin in test concentration 1.1× 10^{-6}M, with its respective EC_{50} -1.85logCa^{++}M, produced potent right as compared to its respective control EC_{50}-3logCa^{++}M. This right shift confirms that Rosuvastatin and Simvastatin have significant vasorelaxant effect through inhibition of voltage gated calcium channels. This also confirms our previous report about statins that have calcium channel blocking effect in the isolated jejunal preparations. It is noteworthy that Rosuvastatin and Simvastatin relaxed the NE induced contractions and KCl induced contractions. This implies that these statins have dual mode of actions through inhibition on receptor operated calcium channels and inhibition of voltage gated calcium channels in aortae. However, the possibility of endothelium derived relaxing factors cannot be ruled out as the test statins also relaxed the intact aortae. Nevertheless, our concern was mainly for inhibition of voltage gated calcium channels, which we have confirmed in our experiments that both Rosuvastatin and Simvastatin inhibit the voltage gated calcium channels in isolated aortic strips preparations. These additive effects of test statins and standard calcium channel blocker Amlodipine were translated in an *in vivo* study for studying its effects on systolic blood pressure. It is evident from Fig.5 that systolic blood pressure is significantly reduced (p<0.05) when statins were added in their respective EC_{50} concentrations to amlodipine in hypertensive Wistar rats. This states that the additive effect of statins on lowering blood pressure is dose dependent.

This vasorelaxation effect can be of prime interest in stress related hypertension which is associated with increase in catecholamines surge. Thus, statins can be helpful for this additive effect that relaxes the NE induced contractions as well. Thus, dual action of statins makes it more interesting for translating its vasorelaxation phenomenon in a prospective randomized clinical trial. Similar effects were observed in rat pulmonary artery relaxation by simvastatin through inhibiting the calcium entry (Absi *et al*., 2019). The only concern is that accurate right dose of the test statins shall be translated for possible additive vasorelaxation effect. As till now, there are different meta-analysis which portrays very less effect on decreasing blood pressure so far, the statins daily current recommended hypocholesterolemic doses are concerned (Briasoulis *et al*., 2013, Bytyçi *et al*., 2022). One way froward is to study these statins on test concentrations which are simulated to their in-vitro EC_{50} values deduced in this study. And the second test dose will be to test these statins on test concentrations which is proportional to its Emax on their respective dose response curves.

CONCLUSIONS

Rosuvastatin and Simvastatin relax the aortic strips preparations predominantly through inhibition of voltage gated calcium channels in high molar KCL induced contractions. These statins also inhibit the effects of N.E induced contractions. Rosuvastatin and Simvastatin additive effect on vasorelaxation is the main factor for decreasing systolic blood pressure.

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