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The effect of sertraline-selenium combination on cardiac contractile strength

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ABSTRACT

Objectives: Individuals with myocardial infarction (MI) frequently exhibit a heightened prevalence of depression, which elevates the likelihood of negative cardiovascular outcomes. This study aimed to assess the potential synergistic effects of sertraline, an antidepressant utilised for the prevention and treatment of depression commonly associated with cardiac disorders, and selenium, an antioxidant trace element, on atrial contraction force.

Methods: Thirty-two adult male Wistar albino rats were randomly allocated into four groups. Atrial strips were positioned in the organ bath, and the tension was calibrated to 2 g. In the control group, isometric contractions were elicited using 10-3 M adrenaline, and the contractions were documented. Sertraline (S) was incrementally administered to the S group in dosages of 0.01 mM, 0.1 mM, 1 mM, and 2 mM. In the Selenium (Se) Group, selenium was incrementally administered at concentrations of 0.1, 1, 2, and 4 mmol/L. S+Se group, S cumulative (0.01 mM, 0.1 mM, 1 mM, 2 mM) and Se cumulative (0.1, 1, 2, 4) mmol/L were administered at fifteen-minute intervals.

Results: The S group had a statistically significant reduction in contraction compared to the control group. Statistically substantial inhibition was noted in the Se group relative to the control group. Statistically significant contraction inhibition was noted in the S+Se group relative to the S group and Se group (P=0.035 and P=0.02, respectively).

Conclusions: According to the results of our study, sertraline-selenium combination showed an effect by inhibition of cardiac Ca2+ channels in rat atrium. Additional research is needed to elucidate the mechanism of action of sertraline, which is used in the treatment of depression that often accompanies cardiac disorders, and selenium, an effective trace element with antioxidant properties.

Keywords: Sertraline, selenium, rat atrium, contraction, relaxation

The onset of early depression is a prevalent issue among individuals undergoing heart surgery [1]. Approximately 50% of individuals with coronary heart disease exhibit concomitant depression [2, 3]. About two-thirds of patients hospitalised following myocardial infarction (MI) exhibit mild depression symptoms, whereas 15% of individuals with cardiovascular illness manifest more severe depressed symptoms. Depression correlates with heightened vulnerability to cardiovascular illness,

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along with an elevated occurrence of eventual mortality and other cardiovascular events [4-6]. The incidence of depression fluctuates according on the classification and severity of cardiovascular disease. The incidence of depression is thrice greater in myocardial infarction patients compared to the general population [7].

Sertraline (S) is the predominant selective serotonin reuptake inhibitor (SSRI) employed in the management of depression, anxiety, and obsessive-compulsive disorder. S inhibits the reuptake of 5-HT from the synaptic cleft in the central nervous system, facilitating the accumulation of 5-HT in the synaptic cleft. Consequently, sertraline exerts its impact via elevating the 5-HT levels in the central nervous system [8]. Despite the fact that selective serotonin reuptake inhibitors (SSRIs) exhibit safer cardiotoxicity profiles compared to tricyclic antidepressants, literature indicates that SSRIs may induce mild bradycardia, negligible QT interval prolongation, dysrhythmic syncope, and orthostatic hypotension [9]. Certain clinical investigations indicate that SSRIs may diminish the occurrence of cardiac events in individuals with myocardial infarction by inhibiting platelet aggregation [10].

Social stress can induce oxidative damage. Distressed personality (Type D), characterised by a propensity for negative feelings and the suppression of emotional expression in social settings, has been demonstrated to forecast a bad prognosis for coronary artery disease, independent of other biological and psychosocial risk factors [11]. MI is marked by damage to myocardial cells and, in serious cases, permanent necrosis. Rapid haemoperfusion (reperfusion) is a critical salvage therapy for myocardial infarction patients, essential for preserving cardiac tissue from irreversible necrosis. Reperfusion of ischaemic myocardium may exacerbate myocardial ischaemic injury, known as myocardial ischaemia-reperfusion injury (MIRI), resulting in cardiomyocyte death [12]. Oxidative stress denotes the disparity between reactive oxygen species (ROS) activity and antioxidant defences, and is associated with the development of chronic heart failure (CHF). Xanthine oxidase (XO) generates reactive oxygen species (ROS), which contribute to the pathophysiology of both experimental and clinical heart failure by influencing several characteristics of the failing heart, including contractile performance, interstitial fibrosis, endothelial dysfunction, and myocyte hypertrophy. Xanthine oxidase expression is elevated in ischemia-induced heart failure, and its inhibition enhances cardiac contractility in patients with congestive heart failure. Antioxidant defence systems involve the activation of heat shock proteins. Inducible heat shock protein (Hsp) 70 synthesis escalates when cardiomyocytes encounter acute hypoxia or ischaemia. Inducible Hsp70 plays a protective effect following ischaemia and diminishes the risk of coronary artery disease progression. Reduced Hsp70 levels and elevated XO levels result in heightened oxidative damage, augmented myocardial oxidative stress, and raised tumour necrosis factor (TNF) levels, hence negatively impacting cardiac prognosis [11].

Cardiac surgery is linked to oxidative stress generated by ischaemia-reperfusion. Oxidative stress induces an inflammatory response marked by endothelial dysfunction and damage to vital organ systems. Strategies to mitigate oxidative stress-induced inflammation have garnered significant interest in recent years. Selenium, a vital trace element, facilitates host-specific anti-inflammatory and antioxidant mechanisms [13]. Heart cells in mice were safeguarded against damage from cancer treatments that can induce cardiac injury by minimising cellular harm and inhibiting necrosis. Se safeguards cells from apoptosis by diminishing oxidative stress, modulating inflammation, inhibiting endothelial dysfunction, and providing cellular protection against apoptosis [14].

Major surgical procedures elevate the risk of depression in postoperative patients. Numerous scheduled surgeries have been linked to depression, with cardiovascular procedures being the most extensively studied in relation to postoperative depression. This study aimed to assess the potential synergistic effects of sertraline, an antidepressant utilised for the prevention and treatment of depression commonly associated with heart disorders, and selenium, an antioxidant trace element, on atrial contraction strength.

METHODS

All experimental protocols conducted in this study received approval from the Necmettin Erbakan University Animal Experiments Local Ethics Committee (HADYEK, protocol number 047/2021). Adult Wistar

Albino rats, weighing between 230 and 260 grammes, were utilised for this study.

Atrium excision from all subjects in the experimental groups was conducted between 08:00 and 09:00 hours in the morning. Cervical dislocation was performed on the animals under ketamine/xylazine anaesthesia (75 mg/kg - 10 mg/kg), and the atria were then immersed in Krebs solution. Following the excision of tissue and blood remnants, 3-4 millimetre strips obtained from the atria were affixed to hooks in the transverse orientation within an isolated organ bath containing Krebs solution, which was continuously aerated with 95% O_2 and 5% CO_2 at 37˚C, with a tension set to 2 g. The tissues were cleaned for one hour at 15-minute intervals post-hanging to mitigate the influence of anaesthetic drugs. Adrenaline (0.001 M) was administered to the tissue chambers to elicit isometric contractions.

Control Group (n=8): Contractions were recorded in the recording system. Contraction amplitude values were determined as contraction parameter.

Sertraline Group (S) (n=8): After the plateau of contractions was observed (approximately 30 minutes), S (0.01 mM, 0.1 mM, 1 mM, 2 mM) dissolved in crepe was added cumulatively at fifteen minutes intervals. Contraction amplitude values were determined as contraction parameter [15].

Selenium Group (Se) (n=8): After the observation of the plateau where contractions occurred (approximately 30 minutes), (0.1, 1, 2, 4) mmol/L selenium was added cumulatively at ten minutes intervals, respectively. Contraction amplitude values were determined as contraction parameters.

Sertraline+Selenium (S+Se) (n=8): After the observation of the plateau where contractions occurred (approximately 30 minutes), S (0.01 mM, 0.1 mM, 1 mM, 2 mM) and Se cumulatively (0.1, 1, 2, 4) mmol/L were added at fifteen minutes intervals and sequentially.

Statistical Analysis

All tests were two-tailed, and findings were deemed statistically significant at $P<0.05$. The variation in tension values over time and within groups was examined using a mixed-effects two-way repeated measures ANOVA model incorporating interaction variables (group × time). The tension values of the groups at different time intervals were analysed using the Tukey-Kramer post-hoc test.The outcomes of the post-hoc analysis are represented by Mean Difference and Standard Error (SE).The analyses were conducted using JASP Team (2019). JASP (version 0.11.1).

RESULTS

In groups 2 and 3, adrenaline 10-3 was applied in isolated organ bath and cumulative sertraline and selenium were administered every 15 minutes. There was a statistically significant decrease in group 2 compared

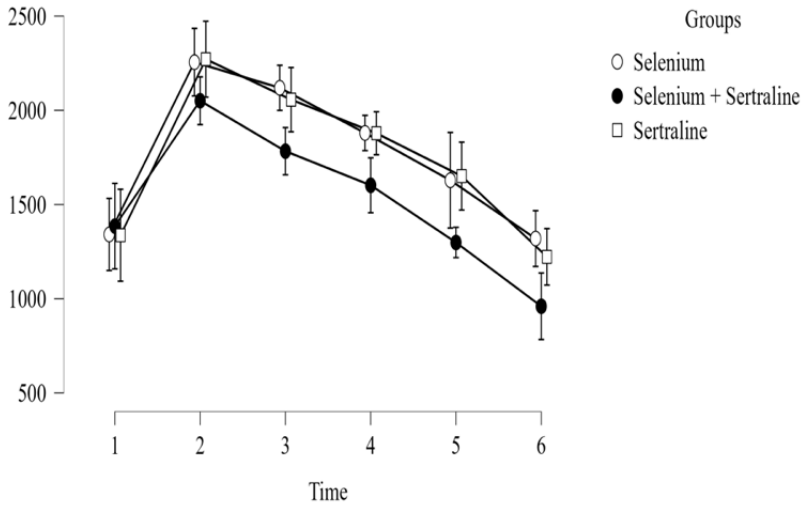

Fig. 1. No significant difference was observed between groups 2 and 3. Group 4 Isometric tension relationship between groups 2 and 3 Significant inhibition was observed after administration of sertraline 0.01 mM dose (n=8 for each group).

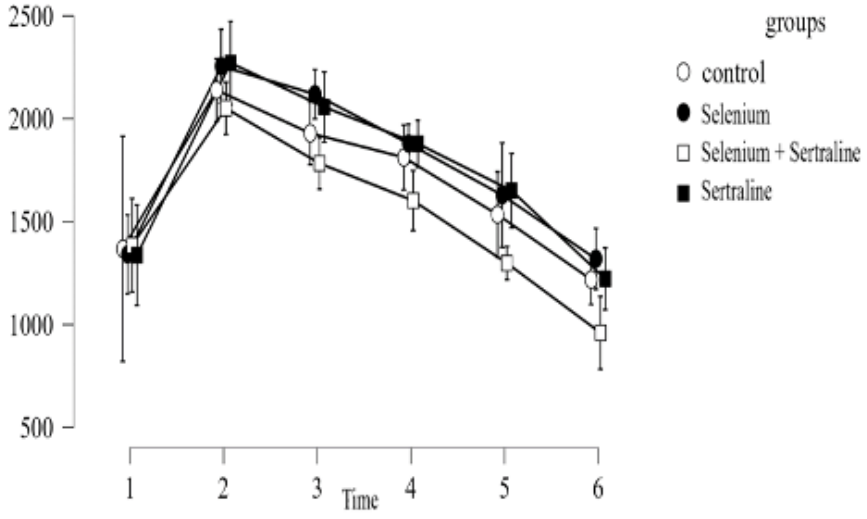

Fig. 1. The time intervals in groups 2, 3, and 4 show 15 minute intervals after adrenaline administration. Group 1 shows the 30-minute period after adrenaline administration. Contraction inhibition was observed in rats in the control group after 60 minutes (n=8 for each group).

to the control group (P<0.05). There was a statistically significant decrease in group 3 compared to the control group (P<0.05), (Fig. 1).

Group 4 showed a statistically significant contraction inhibition in muscle tension compared to groups 2 and 3 (P<0.05). There was no significant difference in group 2 and group 3 (P>0.05). The time intervals in groups 2, 3, 4 show intervals of 15 minutes after adrenaline administration. Group 1 shows the 30-minute period after adrenaline administration. In the control group, contraction inhibition was observed after 60 minutes (Fig. 2), (Table 1).

DISCUSSION

To the best of our knowledge, this is the first study investigating the possible synergistic effects of sertraline and selenium on the contractile force of the heart. According to our study findings, sertraline decreased the contraction power of the heart depending on the cumulative dose. In combination with selenium, it increased the negative inotropic effect depending on the cumulative dose.

A prospective cohort research was done to examine the correlation between depression and the occurrence of significant adverse cardiac events in individuals with acute myocardial infarction (AMI). The trial included 3,568 participants and featured a 2-year follow-up period to assess the incidence of significant adverse cardiac events. The study indicated an elevated occurrence of the major adverse cardiac event (MACE) rate (cardiac death, recurrent non-fatal myocardial infarction, revascularization, and stroke) in persons experiencing both anxiety and depression [16]. A meta-analysis published in 2011 examined the correlation between depression and mortality rates in individuals with MI. This thorough study encom-

Table 1. Results of sertraline-selenium administration in rat atrium

Comparison	Mean Difference	SE	t	P value
Selenium vs. (Selenium + Sertraline)	243.977	82.940	2.942	**0.020**
Selenium vs. Sertraline	21.197	82.940	0.256	0.965
(Selenium + Sertraline) vs. Sertraline	-222.781	82.940	-2.686	**0.035**

Post Hoc Comparisons (Tukey)

passed 29 trials with a cumulative total of 16,889 subjects. Research indicated that patients exhibiting depressive symptoms faced a 2.25-fold heightened risk of all-cause mortality and a 2.71-fold elevated risk of cardiovascular mortality. Additionally, the likelihood of negative cardiac events escalated by 59% in these patients [17]. Consequently, SSRIs have been employed in the management of depression associated with cardiovascular illnesses since the 2000s [18].

Research indicates that SSRIs possess effects beyond the inhibition of neuronal 5-HT reuptake; for instance, fluoxetine has been documented to obstruct sodium, calcium, and potassium channels in cardiac and vascular tissues [19]. Short-term administration of sertraline in healthy individuals results in the attenuation of sympathetic nervous system activity, evidenced by a reduction in heart rate. Sertraline acutely diminishes sympathetic nervous system activity by agonist action at 5-HT 1 A receptors [20]. It should also be noted that sertraline may influence QT variability independently of treatment effects. When we look at the studies with fluoxetine, another antidepressant of the SSRI group. Fluoxetine suppresses the activities of 5-HT2C, 5-HT3, and nicotinic receptors, which are primarily implicated in the control of vasomotor tone, as well as voltage-dependent Na, Cl, and K channels. Consequently, fluoxetine may directly influence cardiac contractility and heart rate due to its negative inotropic action. It has been suggested that similar processes prolong the QT interval and may cause tachycardia [21]. Research by Akıncı *et al*. [22] on human saphenous vein grafts demonstrated that the arterial relaxation effects of fluoxetine are not reliant on endothelium-derived dilator factors or potassium channel activation. Fluoxetine is believed to induce endothelium-independent relaxation by disrupting calcium signalling pathways responsible for contraction in vascular smooth muscle [22]. A separate study has demonstrated that acutely given selenium influences ventricular cardiac contractility in two distinct periods. A preliminary transient rise in developed force was succeeded by a decline in contractility, which coincided with an elevation in the resting tension of this force. This phenomenon was linked to a disturbance in Ca2+ homeostasis and an alteration in contractility. The findings from isolated myocytes suggest that the transient positive inotropy is partially attributable to selenium's direct influence on myofilaments, while the reduction in developing force and the elevation in resting tension stem from diminished Ca2+ transients [23]. In a separate study, Ayaz *et al*. [24] showed that chronic administration of sodium selenite at micromolar concentrations for 4 weeks led to significant changes in the kinetics of both Ca2+ and K+ currents, although there were no significant changes in the mechanical and electrical activities of the heart, although there were marked prolongation trends in the repolarisation phase of action potentials. The authors showed that the small prolongation in the repolarisation phase of action potentials was mostly attributable to changes in the kinetics of these currents [24]. Another study shown that selenium deficiency or excess does not directly influence the contraction mechanism; rather, it impacts the signalling pathway of β-adrenoreceptors, which includes adrenoreceptors, G-proteins, adenylate cyclase (AC), protein kinase A (PKA), and calcium channels in cardiac tissue. Their study detailed an alteration in the signalling pathway of β-adrenoceptors in rats low in selenium. The total quantity of β-adrenoceptors in the cardiac membranes of these animals was found to be roughly 30% lower than that in control rats [25]. Similar to other SSRIs, instances of significant bradycardia have been documented with sertraline [26, 27].

A study by Pousti *et al*. [28] involving guinea pig atrium demonstrated that sertraline (2-16 µg/mL) treatment resulted in a dose-dependent reduction in contraction rate (17-46%) and contraction force (26-48%). According to these findings, it was elucidated that sertraline has direct cardiac effects likely due to the blockage of cardiac Na+ and Ca2+ channels [28]. A separate investigation demonstrated that the cumulative injection of sertraline at concentrations ranging from 10-9 to 10-4 M in rat atrial resulted in a dose-dependent reduction in cardiac contractile force [29]. The effects of sertraline may result from the suppression of Ca2+ currents [30]. In our investigation, cumulative treatment of sertraline led to a dose-dependent reduction in cardiac contraction rate and force. These findings elucidate our data indicating that sertraline exerts a direct cardiac effect, maybe attributable to the blockage of cardiac Ca2+ channels in rat atria.

Selenium is a crucial trace element that exhibits significant antioxidant properties by inhibiting the generation of reactive metabolites induced by several toxicants in humans and animals [31]. Selenium is es-

sential for numerous biological activities, encompassing thyroid hormone metabolism, the body's antioxidant defence mechanisms, the adaptive and acquired immune systems, and the prevention of specific malignancies [32]. Research indicates that low serum or plasma selenium concentrations may correlate with several illnesses, including acute myocardial infarction, chronic ischaemic heart disease, congestive heart failure, cardiomyopathy, and hypertension [33, 34]. Gunes *et al*. [32] demonstrated a significant reduction in elevated heart damage biomarker enzymes induced by cyclophosphamide due to selenium application during cyclophosphamide treatment.

A further study demonstrated that selenium shortage in rat cardiac tissue resulted in elevated reactive oxygen species levels and reduced total antioxidant levels, leading to oxidative damage in cardiomyocytes. At the conclusion of the trial, an elevation in antioxidant enzyme levels was seen following selenium supplementation [35]. This outcome can be ascribed to the inhibitory influence of Se on lipid peroxidation, a factor in the pathogenesis of cardiovascular disease [36]. A further study demonstrated that pretreatment with Se reduced the expression of inflammatory genes, including TNF-α and NF-κB, in an animal model of myocardial infarction. Consequently, Se may be seen as safeguarding cellular activities through the modulation of the inflammatory response [37]. In our investigation, the cumulative administration of selenium to atrial tissue adversely affected the heart's inotropic response following a 2 mM selenium dose. Se may adversely impact the inotropic action of the heart by blocking Ca^{2+} ion channels, contingent upon the dosage.

Limitations

The first limitation of the study is that it is an invitro study. Optimum conditions were tried to be provided in the isolated organ bath. However, the next stage of the study is also planned as invivo. Secondly, the prophylactic effect of selenium was not investigated. The prophylactic effect will also be analysed in the in vivo study.

CONCLUSION

In conclusion, both the independent and combined treatment of sertraline and selenium adversely affected cardiac contractile strength. Observational studies indicate an inverse correlation between selenium levels and the occurrence of coronary heart disease; however, the reliability of this information remains questionable. Further investigation is necessary to elucidate the specific mechanism by which selenium influences cell survival, particularly its cardioprotective properties.

Ethical statement

The study was approved by Necmettin Erbakan University Animal Experiments Local Ethics Committee (HADYEK, protocol number: 047/2021).

Consent to Participate

Not applicable.

Data Availability

Datasets that support the conclusions of this article are included in the article. However, data are available from the authors upon reasonable request and with the permission of (Third party name).

Authors' Contribution

Study Conception: ZISG, HS, RÖK; Study Design: ZISG, HS, RÖK; Supervision: ZISG, NG; Funding: NG, ZISG, HS, RÖK, MA; Materials: : ZISG, HS, RÖK; Data Collection and/or Processing: HS, RÖK, MA; Statistical Analysis and/or Data Interpretation: HS, MA; Literature Review: HS; Manuscript Preparation: HS and Critical Review: ZISG, NG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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