Does SSRI have a neuroprotective effect in patent after ischemic stroke?

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SUMMARY

Introduction and purpose:

Ischemic stroke accounts for the majority of all stroke cases, with recurrence rates of around 12% within the first year, rising to around 30% within five years.

Thrombolytic therapy based on the intravenous administration of rtPA (recombinant plasminogen activator) is the only treatment that has been proven to improve treatment outcomes after ischemic stroke. New methods that would increase the number of motor function returns are still being sought.

A brief description of the state of knowledge:

SSRIs, selective serotonin reuptake inhibitors are used primarily in the treatment of depression and emotional lability after stroke. Many clinical and preclinical studies have suggested that SSRIs have a beneficial effect on the outcomes of stroke patients.

Our work is a brief overview of the current knowledge and clinical trials conducted. Review of the available literature using the PubMed database. Search criteria for scientific articles published from 2010 to 2020, search term: "SSRI ischaemic stroke". Ultimately, 12 randomized clinical trials were analyzed (3 articles apply for one study). One of the studies does not have unequivocal results.

Conclusions: The safety of SSRIs in stroke patients has been confirmed. Further multi-center studies are required to investigate the neuroprotective role of SSRIs.

Key words: SSRI, stroke, neuroprotective effect

Introduction and purpose:

1. **Definition of a stroke. Ischemic stroke.**

It is estimated that in the United States a stroke occurs every 40 seconds, and every 4 minutes someone dies because of stroke. About 87% of all strokes are ischemic strokes, in which blood cannot flow to the brain. Factors such as high blood pressure, high cholesterol, smoking, obesity and diabetes are the main causes of stroke. The risk of stroke increases with age, but it can affect people of any age.

The word stroke is used to denote focal neurological defects and CNS injuries of vascular origin. Stroke can be divided into two main categories, ischemic and hemorrhagic. Acute ischemic stroke (AIS) accounts for 87% of strokes[2]. Ischemic stroke (IS) is one of the leading causes of death and disability in the adult population worldwide[3]. In 2013, there were 6.5 million stroke-related deaths (11.75% of all deaths) and 10.3 million new strokes worldwide, for a total disability-adjusted life-year cost (DALY) of 113 million[4].

Acute brain damage and progressive neurodegenerative disease represent one of the most difficult medical challenges. Only in the United States, treatment costs are nearly $ 800 billion a year[5].

Symptoms of a stroke include: sudden numbness or weakness of the face, arm or leg, especially on one side of the body, sudden confusion, trouble speaking or understanding speech, sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or lack of coordination, sudden severe headache[6].

2. **Pathomechanism of trauma in stroke brain injury.**

In contrast to tissue atrophy, acute brain injuries, such as stroke and penetrating traumatic brain injuries, cause volumetric tissue loss characterized by cavitation and loss of cells and matrix. The tissues surrounding this cavitation are also damaged and typically undergo acute and subacute neuronal loss associated with reactive gliosis and angiogenesis. Atrophy of damaged periodontal tissue may also occur. Pharmacological therapies such as neuroprotective agents focus primarily on saving acutely dying neurons, while anti-inflammatory agents target the immune system's response to damage caused, seeking to reduce secondary tissue damage[7].

3. **Therapeutic procedure**

Thrombolytic therapy based on the intravenous administration of rtPA (recombinant plasminogen activator) is the only treatment that has been proven to improve treatment outcomes after ischemic stroke. Intravenous thrombolysis is the primary treatment of acute ischemic stroke management in any patient with neurological deficits who report to the hospital within 4.5 hours of onset of symptoms[8].

New methods that would increase the number of motor function returns are still being sought.

Methods:

Review of the available literature using the PubMed database. Search criteria for scientific articles published from 2010 to 2020, search term: "SSRI ischaemic stroke". Among of the 110 publications available, 16 were randomized trials, 4 articles were inconsistent with the subject matter and they were rejected. Ultimately, 12 randomized clinical trials were analyzed (3 articles apply for one study). One of the studies does not have unequivocal results.

Description of the state of knowledge:

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is primarily used to treat depression and emotional lability after stroke. Many clinical and preclinical studies have suggested that SSRIs have a beneficial effect on the outcomes of stroke patients. It has been suggested that the positive effect of SSRIs is due to neuroplasticity and the promotion of neurogenesis[9].

In the last few years, a certain SSRIs ability to improve the functioning of people without depression has been reported, and also knowledge about depression after stroke has increased. Thanks to this, many studies have been created, including clinical trials, meta-analyzes of post-stroke patients, which suggest benefits in restoring neurological function after stroke, while using SSRIs. There is some worldwide coherency in the results of studies showing that the use of SSRIs for 3 months in post-stroke patients without depression improves recovery, taking into account the benefit-risk ratio[10].

The neuroprotective effect, and thus the restoration of neurological functions after a stroke by SSRIs, may depend on the dose of the drug and the location of the damaged neurons. One study investigated the neuroprotection of fluoxetine in a C57BL/6 mouse model. At a dose of 10 mg/kg fluoxetine, mice developed a protective effect on caudate neurons after complete cerebral ischemia. At the administered dose, no such effect was noted for hippocampal neurons. At the dose of 5 mg/kg, fluoxetine was not found to be neuroprotective[11].

Earlier this year, Zhou S et al. published a meta-analysis evaluating the effects of SSRIs on patients in the early stage of stroke. Researchers found no difference in improved functional independence in the SSRI group versus the placebo group (p=0.10)[12].

Ischemic stroke accounts for nearly 80% of all stroke cases, with a recurrence rate of around 12% within the first year, rising to around 30% over five years. The safety of

antidepressant drugs in stroke patients depends on the type of antidepressant group being used. Antidepressants such as tricyclic antidepressants carry a 1.41 times risk of recurrence, according to a study by Wang C.L. et al. However, the use of SSRIs does not affect the risk of repeated stroke events, which confirms their safety[13].

SERT (serotonin transporter) encoded by the SERT gene regulates serotonin levels by influencing serotonin reuptake. SERT gene expression may affect the regulation of cognitive functions, it is noted that SSRIs may improve cognitive functions after stroke. In another study by Damsbo AG. et al. also the effectiveness of the SSRI was not confirmed. The polymorphism of the SERT gene was taken into account in 270 patients who had not been treated for depression, who had had an acute ischemic stroke for the first time in their lives. Patients were then randomly assigned to receive citalopram and placebo. There was no difference in cognitive function between patients treated with citalopram and placebo by genotype. However, it was noticed that low SERT gene expression may contribute to the reduction of cognitive functions after a stroke[14].

A multicentre, randomized, double-blind study conducted by the Danish group TALOS (The Efficacy of Citalopram Treatment in Acute Stroke) did not confirm the efficacy in improving vascular revascularization after stroke using early citalopram treatments. The study included 642 patients, treatment duration was 6 months, in the acute phase of stroke (day 0-7), an oral SSRI (citalopram) 20mg (10mg) was administered (10mg, age $\geq$ 65 years and/or hepatic impairment). Treatment with citalopram was generally well-tolerated, with a low risk of mortality and side effects. It can be hypothesized that SSRI is well-tolerated in post-stroke patients. It does not contribute to the improvement of motor functions[15,16]. Platelet aggregation was not altered during treatment with citalopram[17].

A study was conducted in which the effects of fluoxetine and rTMS- repetitive transcranial magnetic stimulation were compared as a method to improve the motor movement of the upper limb in patients after ischemic stroke. 27 patients with hemiparesis 2 years after the stroke incident were divided into three groups. The first group received active rTMS and fluoxetine, the second group received fluoxetine and inactive rTMS, the last group received placebo. The study consisted of 18 1-Hz rTMS sessions in an intact primary motor cortex. Fluoxetine was used for 90 days at a dose of 20mg/day. The Jebsen-Taylor Hand Function (JTHF) and Fugl-Meyer Assessment (FMA) scores were used to assess the motor function of the muscles. The corticospinal excitability was checked by TMS. It has been shown that the combination of fluoxetine and rTMS leads to better motor function in stroke compared to fluoxetine or placebo alone. Interestingly, the authors observed that the use of fluoxetine alone led to the smallest improvement in motor functions, even compared to the placebo group. The fluoxetine group had less improvement than placebo on both scales (JTHF: P=0.038; and FMA: P=0.039). The authors suggest that fluoxetine may have a detrimental effect on the improvement of motor functions[18].

A large multicentre, randomized, double-blind study called FOCUS evaluated the effect of fluoxetine on the functional outcomes of patients after acute stroke. 1,564 patients were assigned to fluoxetine (20mg) treatment and 1,563 received placebo. After 6 months, the functional status of the patients was assessed using the modified Rankin scale (mRS). In both the fluoxetine and placebo groups, patients achieved similar results on mRS. This suggests that fluoxetine does not contribute to functional improvement 6 months after

stroke[19].

In the literature, there are more and more reports regarding the beneficial effect of selective serotonin reuptake inhibitors in patients after ischemic stroke on neuroregeneration and vascular condition.

Nevertheless, in a randomized study conducted by Asadollahi M et al., in which the effectiveness of fluoxetine and citalopram was compared, no significant differences were found between the drugs, however, a significant improvement in motor functions and faster recovery in patients after ischemic stroke were noted[20].

The efficacy of citalopram was evaluated in a randomized study of 144 patients with acute IS who had not been diagnosed with depression. One group received citalopram 20mg, the other group received placebo. After 3 months of taking citalopram, the reference of the study was a reduction in NIHSS score for at least 50%. This improvement was more common in the citalopram group than in the placebo group (p <0.001). The study results suggest that citalopram may improve the prognosis in patients with acute IS. Moreover, the research showed that citalopram is a safe and well-tolerated drug[21].

Chollet F et al. tested the effect of fluoxetine on recovery after ischemic stroke. 118 patients who achieved 55 points or less on the Fugl-Meyer Motor Scale (FMMS) were enrolled in the double-blind study. Patients were randomly assigned to receive oral fluoxetine (20mg) or placebo. 113 patients were included in the analysis. After 90 days, FMMS evaluation was performed. The results showed that patients taking fluoxetine achieved a statistically higher improvement on the FMMS scale (p=0.003). This may be considered as a beneficial effect of fluoxetine in patients with ischemic stroke and moderate or severe motor deficits. The results are promising[22].

He Y. et al observed a reduction in the frequency of recurrences after the use of fluoxetine. 90-day treatment with fluoxetine (20mg) in patients after acute ischemic stroke significantly reduces the frequency of recurrences of ischemic stroke within three years. The study was performed on a group of 404 (control group: 202, study group: 202) patients after acute ischemic stroke. Importantly, at the beginning of the study and after 90 days, additional factors such as aspartate aminotransferase, creatinine, fasting glucose, glycosylated hemoglobin, lipid profile, and blood homocysteine   concentration were additionally evaluated. The evaluation was based on the NIHSS National Institute of Health Stroke Scale. In addition, blood pressure was measured between 8:00 and 9:00 within 24 hours of recording. MRI was performed in patients with symptoms of ischemic stroke. The ischemic stroke relapse-free survival rate was significantly lower in the treated group than in the control group. Evaluations were made using the Kaplan-Meier test (p=0.016) as well as relapse-free survival after day 90 in a three-year follow-up (p=0.043). Selective Serotonin Reuptake Inhibitors (SSRIs) have initially been confirmed to improve the long-term regeneration of neuronal function in ischemic stroke with or without post-stroke depression, as well as blood glucose, blood pressure, and blood lipids [23].

In a prospective, randomized, single-blind study in China, patients were divided into two groups: control and treated. All patients received basic post-stroke therapy and patients in the treated group received additional oral fluoxetine for 90 days. The observation period was

180 days. It was found that in the treated group, the NIHSS result was significantly lower than in the control group (P=0.009). The average BI scores on days 90 and 180 were significantly higher in the treated group (P = 0.026) than in the control group (P = 0.011). The improvement in NIHSS and BI scores on days 90 and 180 compared to baseline in the treatment group was significantly greater than in the control group (P=0.033, P=0.013, P=0.013, P=0.019 respectively). Fluoxetine treatment was an independent factor influencing the NIHSS and BI scores at day 180 post-treatment. It can be concluded that treatment with fluoxetine for 90 days after ischemic stroke may improve long-term functional outcomes of the nervous system[24].

Another study in China tested the effect of fluoxetine at various time intervals after an ischemic stroke on neurological functional prognosis. The patients were randomly assigned to three groups. In group A, patients immediately received fluoxetine in the dose of 20 mg per day; group B received fluoxetine 7 days after stroke in the same dose as group A, and group C did not take the drug. The duration of treatment was 90 days, and observation was 180 days. The average NIHSS score on day 90 was significantly lower in group A than in group C (P=0.005), while on day 180 the average score in group A was significantly lower than in groups B and C (P=0.035, P=0.000). The average BI score on day 90 was significantly higher in group A than in group C (P=0.001), while on day 180, the average score in group A was significantly higher than in groups B and C (p=0.036, p=0.000) respectively. Regression analysis showed that the lower NIHSS score and higher BI score at day 180 were attributed to the early administration of fluoxetine. Early administration of fluoxetine may improve prognosis of patients with ischemic stroke[25].

Conclusions:

Among 12 randomized trials, the benefits of using SSRIs in the treatment of stroke lesions were reported in 7 publications. In 4 studies there were no positive effects found. It should be noted that one of the studies, in which the sufficient effect of SSRIs on the neuroprotective effect was not noticed, was one of the largest studies conducted so far. All studies conducted, so far, confirm the safety of SSRIs in patients after stroke. Different results indicate the need for further studies to finally confirm or exclude the positive effect of SSRIs on recovery in patients after ischemic stroke.

References
1. https://www.cdc.gov/stroke/facts.htm (Accesed: 25.07.2020).
2. Writing Group Members, Mozaffarian D, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association [published correction appears in Circulation. 2016 Apr 12;133(15):e599]. Circulation. 2016;133(4):e38-e360. doi:10.1161/CIR.0000000000000350.
3. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in Stroke.

2019 Aug;50(8):e239]. Stroke. 2013;44(7):2064-2089. doi:10.1161/STR.0b013e318296aeca.

4. Feigin VL , Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990–2013: the GBD 2013 study. Neuroepidemiology2015; 45: 161–76.

5. Gooch CL, Pracht E, Borenstein AR. The burden of neurological disease in the United States: A summary report and call to action. Ann Neurol. 2017;81(4):479-484. doi:10.1002/ana.24897.

6. https://www.cdc.gov/stroke/signs_symptoms.htm (Accesed: 18.07.2020).

7. Neuhaus AA, Couch Y, Hadley G, Buchan AM. Neuroprotection in stroke: the importance of collaboration and reproducibility. Brain. 017;140(8):2079-2092. doi:10.1093/brain/awx126.

8. Prabhakaran S, Ruff I, Bernstein RA. Acute stroke intervention: a systematic review. JAMA. 2015;313(14):1451-1462. doi:10.1001/jama.2015.3058.

9. Chollet F, Tardy J, Albucher JF. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10:123–130.

10. Chollet F, Rigal J, Marque P, et al. Serotonin Selective Reuptake Inhibitors (SSRIs) and Stroke. Curr Neurol Neurosci Rep. 2018;18(12):100. Published 2018 Oct 23. doi:10.1007/s11910-018-0904-9.

11. Taguchi N, Nakayama S, Tanaka M. Fluoxetine has neuroprotective effects after cardiac arrest and cardiopulmonary resuscitation in mouse. Resuscitation. 2012;83(5):652-656. doi:10.1016/j.resuscitation.2011.11.004.

12. Zhou S, Liu S, Liu X, Zhuang W. Selective serotonin reuptake inhibitors for functional independence and depression prevention in early stage of post-stroke: A meta-analysis. Medicine (Baltimore). 2020;99(6):e19062. doi:10.1097/MD.0000000000019062.

13. M.T. Wang, C.L. Chu, C.B. Yeh, et al. Antidepressant use and risk of recurrent stroke: a population-based nested case-control study. J. Clin. Psychiatry, 76 (2015), pp. e877-e885.

14. Damsbo AG, Kraglund KL, Buttenschøn HN, Johnsen SP, Andersen G, Mortensen JK. Serotonergic Regulation and Cognition after Stroke: The Role of Antidepressant Treatment and Genetic Variation. Cerebrovasc Dis. 2019;47(1-2):72-79. doi:10.1159/000498911.

15. Kraglund KL, Mortensen JK, Damsbo AG, et al. Neuroregeneration and Vascular Protection by Citalopram in Acute Ischemic Stroke (TALOS). Stroke. 2018;49(11):2568-2576. doi:10.1161/STROKEAHA.117.020067.

16. Kraglund KL, Mortensen JK, Grove EL, Johnsen SP, Andersen G. TALOS: a multicenter, randomized, double-blind, placebo-controlled trial to test the effects of citalopram in patients with acute stroke. Int J Stroke. 2015;10(6):985-987. doi:10.1111/ijs.12485.

17. Kraglund KL, Mortensen JK, Johnsen SP, Andersen G, Grove EL. Antiplatelet effects of citalopram in patients with ischaemic stroke: A randomized, placebo-controlled,

double-blind study. Sci Rep. 2019;9(1):20048. Published 2019 Dec 27. doi:10.1038/s41598-019-56487-8.

18. Bonin Pinto C, Morales-Quezada L, de Toledo Piza PV, et al. Combining Fluoxetine and rTMS in Poststroke Motor Recovery: A Placebo-Controlled Double-Blind Randomized Phase 2 Clinical Trial. Neurorehabil Neural Repair. 2019;33(8):643-655. doi:10.1177/1545968319860483.

19. FOCUS Trial Collaboration. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. Lancet. 2019;393(10168):265-274. doi:10.1016/S0140-6736(18)32823-X.

20. Asadollahi M, Ramezani M, Khanmoradi Z, Karimialavijeh E. The efficacy comparison of citalopram, fluoxetine, and placebo on motor recovery after ischemic stroke: a double-blind placebo-controlled randomized controlled trial. Clin Rehabil. 2018;32(8):1069-1075. doi:10.1177/0269215518777791.

21. Savadi Oskouie D, Sharifipour E, Sadeghi Bazargani H, et al. Efficacy of Citalopram on Acute Ischemic Stroke Outcome: A Randomized Clinical Trial. Neurorehabil Neural Repair. 2017;31(7):638-647. doi:10.1177/1545968317704902.

22. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial [published correction appears in Lancet Neurol. 2011 Mar;10(3):205]. Lancet Neurol. 2011;10(2):123-130. doi:10.1016/S1474-4422(10)70314-8.

23. He Y, Cai Z, Zeng S, et al. Effect of fluoxetine on three-year recurrence in acute ischemic stroke: A randomized controlled clinical study. Clin Neurol Neurosurg. 2018;168:1-6. doi:10.1016/j.clineuro.2018.02.029.

24. He YT, Tang BS, Cai ZL, Zeng SL, Jiang X, Guo Y. Effects of Fluoxetine on Neural Functional Prognosis after Ischemic Stroke: A Randomized Controlled Study in China. J Stroke Cerebrovasc Dis. 2016;25(4):761-770. doi:10.1016/j.jstrokecerebrovasdis.2015.11.035.

25. Guo Y, He Y, Tang B, et al. Effect of using fluoxetine at different time windows on neurological functional prognosis after ischemic stroke. Restor Neurol Neurosci. 2016;34(2):177-187. doi:10.3233/RNN-150535.