JCHR (2021) 11(1), 91-98

Journal of Chemical Health Risks

www.jchr.org

ORIGINAL ARTICLE

Serum Estrogen Level in Postmenopausal Women with Ischemic Stroke: An Analytic Cross-Sectional Study

Nooshin Masoudian[1], Hamed Veshkouiee[2], Seyyed Afshin Samaie[1], Majid Foroutan[3], Maryam Ghooshchian[4], Abbas Ziari[5], Maryam Naderi Eram[*6]

[1]*Neurologist, Neurology ward, Department of Internal Medicine, Kowsar Hospital, Medical school, Semnan University of Medical Sciences, Semnan, Iran*

[2]*Student Research Committee, Semnan University of Medical Sciences, Semnan, Iran*

[3]*Endocrinologist, Department of Internal Medicine, Kowsar Hospital, Medical school, Semnan University of Medical Sciences, Semnan, Iran*

[4]*Kowsar Hospital, Medical school, Semnan University of Medical Sciences, Semnan, Iran*

[5]*Social Determinants of Health Research Center, Semnan University of Medical Sciences, Semnan, Iran*

[6]*Department of pediatrics, Semnan University of Medical Sciences, Semnan, Iran*

(Received: 7 January 2020 Accepted: 3 January 2021)

KEYWORDS

Stroke;
Ischemic;
Estrogen;
Menopause;
Women

ABSTRACT: Stroke is the third cause of death worldwide. The present study aimed at determining serum estrogen levels in postmenopausal women with ischemic stroke and compare with a control group admitted to Department of Neurology in Kowsar Hospital of Semnan, Iran in 2017.In this analytic cross-sectional study, serum estrogen levels in 33 women with ischemic stroke (who were eligible to be included in the study) were compared with a control group through the convenience sampling method. The demographic data were collected, and serum estrogen levels were measured through the quantitative luminescence Immunoassay technique in both groups and, the degree of disability was determined using the Modified Rankin Scale (MRS) in case group. In case and control group, the age of patients was 74.48±13.44 (mean ± SD) and 73.35±12.89 years respectively, and estrogen levels were 16.65±2.83 and 22.94±3.11 pg/dl respectively, with a significant difference (p=0.03). Hypertension was the most common risk factor in case and control group (84.8% and 78.7%). In case group there was a significant relationship between the degree of disability at discharge from the neurology ward and the degree of disability before undergoing stroke treatment (p<0.001) and, there was no statistically significant relationship between serum estrogen levels and age, number of risk factors, and disability at admission and at discharge. The results showed that serum estrogen levels in postmenopausal women with ischemic stroke were significantly lower than control group and normal estrogen range in healthy postmenopausal women.

INTRODACTION

Stroke refers to an acute nerve injury caused by impaired blood supply to a part of brain tissue due to blockage or rupture of one of its feeding vessels [1]. Stroke is the most significant and prevalent chronic neurological disease in

*Corresponding author: Dr.m.n.e1361@gmail.com (M. Naderi Eram)
DOI: 10.22034/jchr.2021.1890283.1085

adults [2]. It is also the most common cause of physical disability and the third cause of death worldwide, with over 795,000 cases of stroke reported annually in the United States alone [3, 4]. In addition to high mortality, stroke causes significant disabilities, in a way that 31% of these patients need assistance for self-care and 20% for motor problems. An annual 327 per 100,000 individuals suffer from stroke in Iran, constituting the most common cause of disability among Iranian adults[5, 6]. Ischemic stroke, which occurs due to inadequate blood supply to the brain, is the most common type of cerebrovascular accident [7-11]. According to previous studies in Iran, the prevalence of ischemic stroke varies from 23 to 103 per 100,000 people in different age ranges. This type of stroke occurs mainly in the 7th decade of life [9]. In a study on 3,243 people over 15 years from 1995 to 2010, researchers found that stroke was more prevalent in women with an average 75 years of age (menopause age) and that, contrary to men, the incidence of stroke in women did not decrease during this period [12]. Other evidence suggests that the risk of cerebrovascular accidents increases in postmenopausal women[13]; whereas, the incidence of cerebral stroke in premenopausal women is lower than men in the same age range [14]. A limited number of studies show that the prevalence of cerebral stroke in women increases rapidly after menopause following decrease in steroid hormone levels in the bloodstream. To account for this, a theory has been proposed to the effect that ovarian hormones seem to protect women against the onset of ischemic stroke before menopause [14]. The effects of estrogen on stroke have been discussed for over a decade, but there is still no clear evidence in this regard. A number of studies show that not only the oral administration of exogenous estrogen (either alone or in combination with progesterone) does not have a preventative effect on this condition, but is a risk factor for ischemic stroke in women over 50 years of age [15-17]. Meanwhile, a number of other studies have shown that estrogen has a significant protective effect on various regions of the brain, including cortex, hippocampus, and striatum [18] preventing a range of degenerative neurological diseases, including ischemic stroke, Alzheimer and Parkinson diseases; however, such conclusions remain debatable [19-23]. Other studies have suggested that steroid hormones have a significant correlation with the risk of ischemic stroke, with little or no relevance to hemorrhagic stroke[24]. Based on animal studies and tissue models, diminished steroid hormones increase the risk of brain damage [25-27]. Considering the significance of stroke-induced complications and disabilities, the lack of adequate studies on sex hormone levels in stroke, and the contradictory results in previous studies, the present research aimed to evaluate serum estrogen levels in postmenopausal women with ischemic stroke and compare with a control group.

MATERIALS AND METHODS

This analytic cross-sectional study was conducted to determine serum estrogen levels in postmenopausal women with ischemic stroke, and compare with other women admitted to Kowsar Hospital of Semnan's Department of Neurology in 2017. The study was registered in the Ethics Committee of the Semnan University of Medical Sciences with the code IRSEMUS.REC.1395.114 on 09/13/2016 and research project number is A-10-316-3 in the Semnan University of Medical Sciences. Prior to initiating the study and after coordination with the relevant authorities, patients were informed about the objectives and methods of the study, the confidentiality of their information, the right to participate in or leave the study, and the non-imposition of any costs or harms to them. Informed written consents were subsequently obtained. The patients were selected through the convenience sampling method.

Inclusion criteria

Women with ischemic stroke (based on history, examination, neuroimaging findings, and the opinion of a neurologist) as a case group, and women without ischemic stroke as a control group hospitalized in Kowsar Hospital of Semnan's Department of Neurology in 2017, and exhibiting symptoms of menopause (i.e., 50-54 year-old women with no menstruation for at least 12 months, or women over 54 years of age with no menstruation in the last 6 months).

Exclusion criteria

1) Liver problem and cirrhosis; 2) renal failure; 3) hormone therapy; 4) treatment with antiepileptic and estrogen-interfering drugs such as rifampin, cimetidine, and clarithromycin; 5) history of ischemic or hemorrhagic stroke or any other neurological disease; 6) smoking; 7) traumatic brain injury; and 8) body temperature of above 37.5 °C.

From a total of 58 women with ischemic stroke admitted to the hospital within one year from the study baseline, 25 were excluded and 33 were included in this research as a case group according to history, physical examination, neuroimaging findings, and the neurologist opinion and 33 other patients as a control group without ischemic or hemorrhagic stroke in the same ward after matching demographic characteristics. A researcher recorded patients' information in a checklist containing questions about the characteristics of patients including age, history, clinical examination, and related risk factors (heart disease, diabetes, hypertension, atrial fibrillation, congestive heart failure, and hyperlipidemia) by asking them and using their files. The degree of ischemic stroke-induced disability of each patient was determined using the MRS (modified Rankin Scale), once on the first day of admission and then at the time of discharge, by the same researcher. MRS is a well-known measure for determining the degree of disability or dependence of people due to stroke or other neurological lesions; MRS is scored according to Table 1 [28].

Table 1. Modified Rankin Scale (MRS) Score

Patiant disability	MRS Score
No symptoms at all	0
No significant disability despite symptoms; able to carry out all usual duties and activities	1
Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	2
Moderate disability; requiring some help, but able to walk without assistance	3
Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	4
Severe disability; bedridden, incontinent and requiring constant nursing care and attention	5
Dead	6

After confirming the diagnosis of ischemic stroke by a neurologist (in case group), and in order to measure estrogen levels, 5 mL of blood was collected from the cubital vein of patients in both groups in an EDTA (Ethylene diamine tetra acetic acid)-containing tube by an experienced nurse using a 20-G syringe during a maximum of 72 hours after admission [29]. Blood samples were labeled and immediately sent to the hospital's central laboratory, where they were centrifuged and their serum was isolated by an experienced technician. The sera were stored at -20 °C until sending to a specialized laboratory for measuring the serum estrogen levels. The measurement was performed by a pathologist using a quantitative luminescence- Immulite2000 based device with a German made Siemens kit. After consulting with two endocrinologists and valid references [20], the normal range of estrogen (estradiol) in healthy postmenopausal women was assumed between 0 and 40 pg/dl; this range was used in statistical analysis of the data. To remove any interfering effect, the patients who had received estrogen-interfering drugs in the last 48 hours were excluded. Blood collection did not require certain conditions, such as fasting. Patients whose blood could not have been taken within the first 72 hours were excluded from the study. The obtained data were analyzed through independent T-test and Spearman correlation coefficient and Wilcoxon Signed Ranks Test at the significance level of 0.05 using SPSS-16.

RESULTS

in case group a total of 33 women of 74.48±13.44 years (mean ± SD) with an age range of 50-98 years, and in control group a total of 33 women of 73.35±12.89 years with an age range of 51-95 years, were evaluated in this study and there was no significant difference between two groups in age ($p > 0.05$). The frequency distributions of the type and number of risk factors are depicted in Tables 2. The disability rate of patients in case group (MRS) at admission to the department of neurology and at discharge is shown in Table 3. Serum estrogen levels and the difference between two groups is shown in Table 4.

Table 2. Type and number of risk factors in patients.

Types of risk factors	Case No. (%)	Control No. (%)	Number of risk factors	Case No. (%)	Control No. (%)
Cardiac Disease	8 (24.2)	7 (21.2)	0	3 (9.1)	5 (15.1)
Diabetes Mellitus	11 (33.3)	12 (36.3)	1	10 (30.3)	13 (39.3)
Hypertension	28 (84.8)	26 (78.7)	2	14 (42.4)	12 (36.3)
Atrial Fibrillation	4 (12.1)	2 (6.1)	3	3 (9.1)	2 (6.0)
Congestive Heart Failure	1 (3.0)	3 (9.0)	4	3 (9.1)	1 (3.0)
Hyperlipidemia	7 (21.2)	10 (30.3)	Total	33 (100)	33 (100)

Table 3. Frequency of disability (MRS) at admission and discharge of case group

MRS Score	At admission		At discharge	
	No.	%	No.	%
1	1	3	2	6.1
2	1	3	5	15.2
3	7	21.2	8	24.2
4	11	33.3	9	27.3
5	13	39.4	9	27.3
6	0	0	0	0
Total	33	100	33	100

Table 4. Serum estrogen levels in case and control group

Group	Serum estrogen level (pg/dl)			p-value
	Min	Max	Mean ± SD	
Case	16	29	16.65 ± 2.83	0.03
Control	18	33	22.94 ± 3.11	

As it is seen, serum estrogen level in case group is significantly lower than control group (p=0.03). There was also a significant difference between patients' serum estrogen levels and normal level (p=0.04) in case group. In addition, no statistically significant relationship was found between serum estrogen levels and age (p=0.38, p=0.21), number of risk factors (p=0.88, p= 0.34), disability at admission (p=0.77, p= 0.12), and disability at discharge from the department of neurology (p=0.99, p= 0.45) in case and control group respectively.

The results of this study showed a significant relationship between patients age and disability at admission (R=0.501 and p=0.003) and disability at discharge from the neurology ward (R=0.554 and p=0.001) in case group, meaning that the degree of disability at admission and discharge increased with age. The results of Wilcoxon Signed Ranks Test also showed a significant relationship between the degree of disability at admission and that at discharge (p<0.001) in case group, meaning that patients with greater disability at admission had greater disability at discharge. However, there was no significant relationship between the number of risk factors and the degree of disability (MRS) at admission (p=0.500) and the degree of disability (MRS) at discharge (p=0.747) in case group.

DISCUSSION

The present research is one of the few studies that descriptively investigated serum estrogen levels in postmenopausal women with ischemic stroke and its related factors. The results of this study showed that the mean estrogen level (estradiol) in patients participated in the study was 16.65 pg/dl, which was significantly different from the normal estrogen range in healthy postmenopausal women mentioned in valid sources. The results of this study also showed that there was no significant relationship between serum estrogen levels in postmenopausal women with the degree of stroke-induced disability. In the studies of, the mean serum estrogen levels in non-menopause women with ischemic stroke was 35.72 and 51.9, respectively; both greater than our results and the standard mean range [30, 31]. This contradiction can be attributed to the kit used or the population and the menopause situation in our study. However, the results of a limited number of studies showed that after menopause and following a reduction in steroid hormones in the bloodstream, the incidence of stroke was significantly higher than normal population [30-33]. Several other studies showed the protective effect of estrogen against stroke through protecting cerebrovascular endothelial cells and reducing the production of free radicals; it also plays a protective role in the cortex, hippocampus, and striatum [18, 19, 23, 34 and 35]; however, such conclusions remain debatable [33]. In a study of year 2012, examined the serum estrogen metabolite and its association with ischemic vascular disease in postmenopausal women and found that high levels of estrogen metabolites can be used to predict ischemic vascular events [31].

In a study, long-term treatment with exogenous estrogen increased the risk and complications of stroke [36]. These inconsistencies can substantiate the destructive effect of long-term estrogen therapy in a number of studies, as a systematic review in 2006 revealed that mere administration of estrogen before or up to 4 hours after stroke can significantly decrease the extent of the lesion, with no study demonstrating the effect of estrogen administration in a longer period after the stroke [14]. The results of a number of animal studies have also shown that only endogenous estrogen levels can have a positive effect on stroke and that injection of exogenous estrogen has no effect on this complication after menopause [37, 38].

There are a limited number of studies that have directly and descriptively evaluated endogenous estrogen levels and the degree of stroke-induced disability, pointing to the necessity of conducting the present study. The results of this research, i.e. the lack of a significant relationship between serum estrogen levels and the degree of stroke-induced disability, did not correspond to those of a number of studies, including Lee et al.'s; while they were consistent with those of Saberi study. [30, 39]. This difference may be attributable to differences in sample size, long-term follow-

ups and aging of the patients during long follow-ups, as age is one of the most irreversible risk factors for stroke [12, 40 and 41].

The results of this study showed that 90.9% of stroke patients had a risk factor for this condition, the most common ones were hypertension (84.85%), diabetes (33.3%), heart disease (24.2%), and dyslipidemia (21.2%). These results are consistent with the findings of previous researchers [30].

CONCLUSIONS

The results showed that serum estrogen levels in postmenopausal women with ischemic stroke were significantly lower than other women admitted in Department of Neurology and normal estrogen range in healthy postmenopausal women.

Limitations

In addition to its strengths, this study had some limitations, for example, the serum estrogen levels were measured only at baseline, and serial measurement was not performed, due to limited financial resources and timespan. For a more generalizable evaluation, it is necessary to do a multi-centered study with a larger sample size.

ACKNOWLEDGEMENTS

Research reported in this publication was supported by a grant [number: A-10-316-3] from the Semnan University of Medical Sciences, Semnan, Iran.

Furthermore, the authors would like to thank Kowsar Hospital Research Deputy and Clinical Research Development Unit of Semnan University of Medical Sciences for cooperation and providing facilities to this work.

Conflicts of interest

There are no conflicts of Interests in this study.

REFERENCES

1. Brown M.M., 1992. Balloon angioplasty for cerebrovascular disease. Neurological Research. 14(2), 159-162.

2. Robinson R.G., Jorge R.E., 2016. Post-stroke depression: A review. Am J Psychiatry. 173(3);221-231

3. Black J., Hawks J., 2009. Medical Surgical Nursing: Clinical Management for Positive Outcomes, 8e (2 Vol Set) without CD, 1st Edition. 15th September. 1-2368.

4. Lin L.Y., Lee C.H., Yu C.C., Tsai C.T., Lai L.P., Hwang J.J., Chen P.C., Lin J.L., 2011. Risk factors and incidence of ischemic stroke in Taiwanese with nonvalvular atrial fibrillation—a nation wide database analysis. Atherosclerosis. 217(1), 292-295.

5. Outpatient ST. Therapy-based rehabilitation services for stroke patients at home. 2003.

6. Hawkey B., Williams J., 2009. Role of rehabilitation Nurse. Royal College Nurs. 3(178), 4-28.

7. Menken M., Munsat T.L., Toole J.F., 2000. The global burden of disease study: implications for neurology. Archives of Neurology. 57(3), 418-420.

8. Azarpazhooh M.R., Etemadi M.M., Donnan G.A., Mokhber N., Majdi M.R., Ghayour-Mobarhan M., Ghandehary K., Farzadfard M.T., Kiani R., Panahandeh M., 2010. Excessive incidence of stroke in Iran: evidence from the Mashhad Stroke Incidence Study (MSIS), a population-based study of stroke in the Middle East. Stroke. 41(1), e3-e10.

9. Hosseini A.A., Sobhani-Rad D., Ghandehari K., Benamer H.T., 2010. Frequency and clinical patterns of stroke in Iran-Systematic and critical review. BMC Neurology. 10(72), 1-10.

10. Roger V., Go A., Lloyd-Jones D., Benjamin E., Berry J., 2012. Borden W., Heart disease and stroke statistics-2012 update: a report from the American Heart Association. 125(1), e2-20.

11. Dirnagl U., Iadecola C., Moskowitz M.A., 1999. Pathobiology of ischaemic stroke: an integrated view. Trends in Neurosciences. 22(9), 391-397.

12. Kolominsky-Rabas P.L., Wiedmann S., Weingärtner M., Liman T.G., Endres M., Schwab S., Buchfelder M.,

Heuschmann P. U., 2015. Time trends in incidence of pathological and etiological stroke subtypes during 16 years: the Erlangen Stroke Project. Neuroepidemiology. 44(1), 24-29.

13. Wenger N.K., Speroff L., Packard B., 1993. Cardiovascular health and disease in women. New England Journal of Medicine, 329(4), 247-256.

14. Gibson C.L., Gray L.J., Murphy S.P., Bath P.M., 2006. Estrogens and experimental ischemic stroke: a systematic review. Journal of Cerebral Blood Flow & Metabolism. 26(9), 1103-1113.

15. Hendrix S.L., Wassertheil-Smoller S., Johnson K.C., Howard B.V., Kooperberg C., Rossouw J.E., Trevisan M., Aragaki A., Baird A.E., Bray P.F., 2006. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. Circulation. 113(20), 2425-2434.

16. Wassertheil-Smoller S., Hendrix S., Limacher M., Heiss G., Kooperberg C., Baird A., Kotchen T., Curb J.D., Black H., Rossouw J.E., 2003. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. Jama. 289(20), 2673-2684.

17. Grodstein F., Manson J.E., Stampfer M.J., Rexrode K., 2008. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. Archives of internal medicine. 168(8), 861-866.

18. Jayedi A., Soltani S., Abdolshahi A., Shab-Bidar S., 2020. Healthy and unhealthy dietary patterns and the risk of chronic disease: an umbrella review of meta-analyses of prospective cohort studies. British Journal of Nutrition. 124(11), 1133-1144.

19. Brann D.W., Dhandapani K., Wakade C., Mahesh V.B., Khan M.M., 2007. Neurotrophic and neuroprotective actions of estrogen: basic mechanisms and clinical implications. Steroids. 72(5), 381-405.

20. medscape, Reference range of estradiol. URL: available www.emedicine.medscape.com.

21. Simpkins J.W., Singh M., Brock C., Etgen A.M., 2012. Neuroprotection and estrogen receptors. Neuroendocrinology. 96(2), 119-130.

22. Yao J., Brinton R.D. 2012. Estrogen regulation of mitochondrial bioenergetics: implications for prevention of Alzheimer's disease Advances in pharmacology. pp. 327-371: Elsevier.

23. de Leciñana M.A., Egido J.A., 2006. Estrogens as neuroprotectants against ischemic stroke. Cerebrovascular Diseases, 21 (Suppl. 2), 48-53.

24. Lobo R., 2009. The risk of stroke in postmenopausal women receiving hormonal therapy. Climacteric, 12 (sup1), 81-85.

25. Simpkins J., Yang S., Wen Y., Singh M., 2005. Estrogens, progestins, menopause and neurodegeneration: basic and clinical studies. Cellular and molecular life sciences: CMLS. 62(3), 271-280.

26. Hasanzadeh H., Rezaie-Tavirani M., Seyyedi S., Emadi A., 2015. Proteomics Study of extremely low frequency electromagnetic field (50 Hz) on human neuroblastoma cells. Koomesh. 17(1), 233-238.

27. Nasr R., Hasanzadeh H., Khaleghian A., Moshtaghian A., Emadi A., Moshfegh S., 2018. Induction of apoptosis and inhibition of invasion in gastric cancer cells by titanium dioxide nanoparticles. Oman Medical Journal. 33(2), 111-117.

28. Van Swieten J., Koudstaal P., Visser M., Schouten H., Van Gijn J., 1988. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 19(5), 604-607.

29. Daroff R.B., Jankovic J., Mazziotta J.C., Pomeroy S.L., 2015. Bradley's neurology in clinical practice e-book. Elsevier Health Sciences; Oct 25.

30. Saberi A., javadpoor M., farahmand N., kazemnezhad E., 2015. The serum level of estrogen and progesterone and their ratio in patients with ischemic stroke: a comparative study. Caspian Journal of Neurological Sciences. 10,1(1), 35-42.

31. Scarabin-Carré V., Canonico M., Brailly-Tabard S., Trabado S., Ducimetière P., Giroud M., Ryan J., Helmer C., Plu-Bureau G., Guiochon-Mantel A., 2012. High level of plasma estradiol as a new predictor of ischemic arterial disease in older postmenopausal women: The three-city cohort study. Journal of the American Heart Association. 1(3), e001388.

32. Raz L., 2014. Estrogen and cerebrovascular regulation in menopause. Molecular and Cellular Endocrinology. 389 (1-2), 22-30.

33. Sheikh N., Tavilani H., Rezaie A., 2010. Decreased endogenous progesterone and ratio of progesterone to estrogen in stroke ischemia. African Journal of Biotechnology. 9(5), 732-734.

34. Alkayed N.J., Harukuni I., Kimes A.S., London E.D., Traystman R.J., Hurn P.D., 1998. Gender-linked brain injury in experimental stroke. Stroke. 29(1), 159-166.

35. Krause D.N., Duckles S.P., Pelligrino D.A., 2006. Influence of sex steroid hormones on cerebrovascular function. Journal of Applied Physiology. 101(4), 1252-1261.

36. Viscoli C.M., Brass L.M., Kernan W.N., Sarrel P.M., Suissa S., Horwitz R.I., 2001. A clinical trial of estrogen-replacement therapy after ischemic stroke. New England Journal of Medicine.345(17), 1243-1249.

37. Dubal D.B, Kashon M.L., Pettigrew L.C., Ren J.M., Finklestein S.P., Rau S.W., Wise P.M., 1998. Estradiol protects against ischemic injury. J Cereb Blood Flow Metab. 18(11), 1253-1258.

38. Lee J.S., Yaffe K., Lui L.Y., Cauley J., Taylor B., Browner W., Cummings S., 2010. Prospective study of endogenous circulating estradiol and risk of stroke in older women. Archives of Neurology. 67(2), 195-201.

39. Farajzadeh M., Darand M., 2009. Analyzing the influence of air temperature on the cardiovascular, respiratory and stroke mortality in Tehran. Iranian Journal of Environmental Health, Science and Engineering. 6(4), 261-270.

40. Plesnila N., Zhu C., Culmsee C., Gröger M., Moskowitz M.A., Blomgren K., 2004. Nuclear translocation of apoptosis-inducing factor after focal cerebral ischemia. Journal of Cerebral Blood Flow & Metabolism. 24(4), 458-466.

41. Yu S.W., Wang H., Dawson T.M., Dawson V.L., 2003. Poly (ADP-ribose) polymerase-1 and apoptosis inducing factor in neurotoxicity. Neurobiology of Disease. 14(3), 303-317.