MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 2521-2527
DOI: 10.12659/MSM.894662

Received: 2015.05.14
Accepted: 2015.06.21
Published: 2015.08.25

Association Between Changes in Serum 5-Hydroxy-Tryptamine Concentrations and Improvement in Clinical Symptoms in Primary Premature Ejaculation with Paroxetine Treatment

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AE 1 Yu Guo
C 1 You Wang
C 1 Xi Wang
C 2 Gang Ye
C 1 Yuanbin Jiang
ABFG 1 Wei Xiong

1 Department of Urology, Traditional Chinese Medicine Hospital, Chongqing, P.R. China
2 Department of Urology, Second Affiliated Hospital, Third Military Medical University, Chongqing, P.R. China

Corresponding Author: Wei Xiong, e-mail: xiongwei197143@163.com
Source of support: Departmental sources

Background: This study aimed to investigate the association between changes in serum 5-hydroxy tryptamine (5-HT) concentrations and improvement in clinical symptoms in primary premature ejaculation with paroxetine treatment.

Material/Methods: A total of 142 men aged 18–65 years with a history of lifelong premature ejaculation and an intravaginal ejaculation latency time (IELT) <120 s were included in this study. Patients were divided into 3 groups according to IELT: IELT ≤30 s (group A), (IELT >30 s and ≤60 s (group B), and IELT >60 s and <120 s (group C). Patients in the 3 groups were administered paroxetine hydrochloride 20 mg/d for 8 weeks. Blood samples were obtained from the candidates in the screening period and after 8 weeks of treatment. Plasma 5-hydroxy-tryptamine (5-HT) concentrations were measured by enzyme-linked immunosorbent assay.

Results: Reliable data from 125 patients were obtained. There were 41 patients in group A, 40 in group B, and 44 in Group C. IELT and serum 5-HT concentrations were significantly improved in the 3 groups after treatment (all P<0.001). The mean change and fold increase in IELT and the mean change in serum 5-HT concentrations in group A were significantly higher than those in groups B and C (all P<0.001). The mean change and fold increase in IELT and the mean change in serum 5-HT concentrations in group B were significantly higher than those in group C (all P<0.001). Significantly more patients in group A achieved clinical benefits than those in groups B and C (P<0.001).

Conclusions: Improvement in serum 5-HT concentrations has obvious association with primary premature ejaculation symptom improvement with paroxetine use.

MeSH Keywords: Paroxetine • Premature Ejaculation • Receptor, Serotonin, 5-HT1A

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Background

Primary premature ejaculation (PE) is a widely observed male sexual dysfunction and has become one of the most common diseases in urology. Recently, selective serotonin reuptake inhibitors (SSRIs), such as dapoxetine and paroxetine, have been used as the first-line treatment of PE, and dapoxetine is specifically used for the treatment of PE in many countries [1,2]. The mechanism of SSRIs for the treatment of PE is still not clear.

The neurotransmitter 5-hydroxy tryptamine (5-HT) has been widely studied for playing an important role in the process of control of ejaculation. Previous studies have shown that 5-HT has the strongest relationship with PE [3–5]. There are at least three 5-HT receptor subtypes that play an important role in the process of ejaculation: 5-HT1A receptor, 5-HT1B receptor, and 5-HT2C receptor. These three 5-HT receptor subtypes have high levels in the lumbosacral and thoracic segments of the spinal cord, vas deferens, and seminal vesicle. Additionally, 5-HT levels are high in many ejaculation-related nerve nuclei, including the MPOA (medial preoptic area), PAG (periaqueductal gray), and nPGi (nucleus paragigantocellularis) . All of the processes of ejaculation are mediated by 5-HT [6,7]. Moreover, stimulation of 5-HT1A receptors promotes ejaculation. Increased intrasynaptic 5-HT after inhibition of transporter-mediated uptake leads to increased activation of postsynaptic 5-HT receptors and inhibition of ejaculation [8]. Therefore, because 5-HT plays an important role in control of ejaculation, it is closely implicated in the pathogenesis of PE and in the mechanism of treatment with PE. There is little research on the association between changes in plasma 5-HT levels during treatment and treatment efficacy with SSRIs [9].

In this study, we investigated changes in 5-HT levels before and after treatment with paroxetine. We examined the association between plasma 5-HT levels and the severity of primary PE, and the association between plasma 5-HT levels and the treatment efficacy of primary PE.

Material and Methods

Patients

Healthy men aged 18–65 years, who met the definition of lifelong PE of the International Society for Sexual Medicine (ISSM), and had a stable, monogamous, heterosexual relationship with a duration >6 months were eligible for the study. The ISSM definition of PE was the only accepted definition in this study, where lifelong PE was defined as "ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, the inability to delay ejaculation on all or nearly all vaginal penetrations, and the presence of negative personal consequences, such as distress, annoyance, frustration, and/or the avoidance of sexual intimacy" [10]. The exclusion criteria of the study were a history of psychiatric disorders requiring therapy/medication, risk of suicide, other sexual dysfunction (including erectile dysfunction as defined by the ISSM), congenital malformations of the genitourinary system, PE attributable to situational issues, sexual intercourse usually less than once per week, sexual dysfunction in the partner, and current use of medication with potential to cause sexual dysfunction [11]. Patients who met the definition of ISSM had a screening period in which the patient's sex partner documented intravaginal ejaculation latency time (IELT) by stopwatch results of at least 3 events of sexual intercourse. The patients' mean IELT <120 s was finally included. Patients were divided into 3 groups according to the mean IELT as follows: group A (IELT ≤30 s), group B (IELT >30 s and ≤60 s), and group C (IELT >60 s and <120 s). According to this method, 142 outpatients with primary PE who were admitted to the Traditional Chinese Medicine Hospital of Chongqing and Second Affiliated Hospital of the Third Military Medical University Hospital during May 2013 to February 2014 were included. There were 41 patients in group A, 40 patients in group B, and 44 patients in Group C.

Method

A fasting blood specimen was collected in the upper limb vein from all patients in the 3 groups before treatment. A total of 3 ml of blood was collected and immediately centrifuged at 1006.2 (×g) . The plasma was saved and placed in a 1-ml Eppendorf pipe and then cryopreserved at -80°C. Before treatment, we recorded the latest IELT 3 times, which was measured in the screening period, and completed the premature ejaculation profile (PEP) questionnaire according to personal feelings in the screening period. The premature ejaculation profile (PEP) questionnaire included measures of perceived control over ejaculation, satisfaction with sexual intercourse, ejaculation-related personal distress, and ejaculation-related interpersonal difficulty. Each measure regarding ejaculation is scored on a 5-point scale (0 to 4 point). The mean IELT and PEP scores were used as the baseline of this study. Patients in the 3 groups took paroxetine 20 mg/d for 8 weeks. After 8 weeks of treatment, patients recorded the IELT of the latest 3 times of sexual intercourse and completed the PEP questionnaire. Plasma was extracted again and cryopreserved in all of the patients. The IELT, PEP scores, and plasma were all well recorded for every patient. Plasma 5-HT concentrations were measured with a 5-HT ELISA Kit (Clound-clone Corporation, Houston, TX,USA) (Figure 1).

Statistical analysis

Statistical analyses were performed using SPSS 17.0 software. The mean change in IELT was calculated as the absolute change

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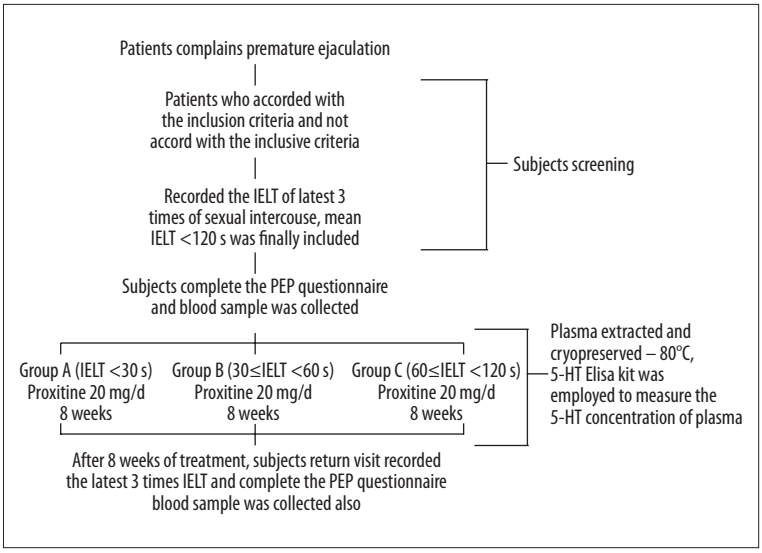

Figure 1. Technology route of research.

Table 1. Mean IELT at baseline and the endpoint in the three groups.

Variables	Group A (n=41)	Group B (n=40)	Group C (n=44)
Geometric mean IELT (SE)			
Baseline (minutes)	0.32 (0.11)	0.77 (0.58)	1.48 (0.73)
Endpoint (minutes)	12.13 (6.18)*	6.78 (4.15)*	4.52 (2.36)*
Increase in mean IELT	11.81	6.01**	3.04**,#
Fold increase in mean IELT	37.90	8.81**	3.05**,#

* P<0.001 compared with baseline; ** P<0.001 compared with group A; # P<0.001compared with group B. SE – stand error; IELT – intravaginal ejaculation latency time.

(endpoint geometric mean IELT minus baseline geometric mean IELT). The fold increase in IELT was endpoint geometric mean IELT divided by baseline geometric mean IELT. The endpoint geometric mean IELT was the geometric mean IELT of the latest 3 sexual intercourse events at the end of the treatment period. The baseline geometric mean IELT was the geometric mean IELT of 3 sequential sexual intercourse events from the beginning of the screening period. The mean change in 4 measures of PEP was calculated as the end line geometric mean score minus the baseline geometric mean score. Criteria for clinical benefit were defined as achieving a 2-category or greater increase in the mean change in control and a 1-category or greater increase in the mean change in distress. Differences between the endpoint and baseline in each group were determined by analysis of variance. Differences across treatment groups were analyzed using the Wilcoxon rank-sum test. P<0.05 was considered statistically significant.

Results

IELT

We obtained reliable data from 125 patients. The geometric mean IELT was significantly improved at the endpoint in the 3 groups compared with baseline (P<0.001). Compared with baseline, the mean change and fold increase in geometric mean IELT in group A were significantly higher than those in groups B and C (all P<0.001). Additionally, these variables in group B were significantly higher than those in group C (P<0.001, Table 1).

PEP scores and clinical benefits

The mean PEP score was significantly improved in all groups after treatment compared with before treatment (Table 2). The mean PEP score in group A was significantly higher than that in groups Band C. The mean PEP score in group B was significantly higher than that in group C (P<0.001, Table 2). A significantly higher percentage of patients achieved one category or greater improvement in group A compared with groups

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Table 2. Change in PEP score and percentage improvement from baseline by PEP question.

Items	Group A (n=41)	Group B (n=40)	Group C (n=44)
Mean change in satisfaction with sexual intercourse (treatment period: baseline) (SE)	1.87 (1.48)	1.53 (0.42)	1.02 (0.33)
ANOVA P value*	P<0.001	P<0.001	P<0.001
Achieved 1 category or greater improvement, n (%)	33 (80.5)	28 (70.0)	25 (56.8)
P value across the groups	Groups A *vs.* B P<0.001	Groups B *vs.* C P<0.001	Groups A *vs.* C P<0.001
Mean change in control over ejaculation (treatment period: baseline) (SE)	1.75 (1.49)	1.43 (1.12)	1.27 (0.61)
ANOVA P value*	P<0.001	P<0.001	P<0.001
Achieved 1 category or greater improvement, n (%)	34 (82.9)	29 (72.5)	26 (59.1)
P value (group A *vs.* groups B and C, group B *vs.* group C)**	P<0.001	P<0.001	P<0.001
Mean change in ejaculation-related distress (treatment period: baseline) (SE)	1.64 (1.38)	1.33 (1.03)	1.09 (0.82)
ANOVA P value*	P<0.001	P<0.001	P<0.001
Achieved 1 category or greater improvement, n (%)	36 (87.8)	33 (82.5)	31 (70.5)
P value (group A *vs.* groups B and C, group B *vs.* group C)**	P<0.001	P<0.001	P<0.001
Mean change in ejaculation-related interpersonal difficulty (treatment period: baseline) (SE)	1.28 (0.92)	1.04 (0.79)	0.83 (0.61)
ANOVA P value*	P<0.001	P<0.001	P<0.001
Achieved 1 category or greater improvement, n (%)	31 (75.6)	28 (70.0)	28 (63.6)
P value (group A *vs.* groups B and C, group B *vs.* group C)**	P<0.001	P<0.001	P<0.001

** Bonferroni corrected, with significance set at P<0.025. * All tests were 2-sided and conducted with a 5% significance level.

Table 3. Plasma 5-HT concentrations before and after treatment.

Items	Group A (n=41)	Group B (n=40)	Group C (n=44)
Baseline 5-HT concentrations (ng/ml) (SE)	74.5 (32.44)	81.2 (36.72)	96.3 (42.64)
Endpoint 5-HT concentrations (ng/ml) (SE)	134.5 (75.41)	125.2 (58.54)	119.2 (59.47)
Mean change (SE) ANOVA P value	14.4 (9.35) P<0.001	11.2 (6.54) P<0.001	3.67 (2.45) P<0.001
P value across the groups	Group A *vs.* group B P<0.001	Group B *vs.* group C P<0.001	Group A *vs.* group C P<0.001

B and C after treatment (P<0.001), and this improvement in group B was significantly higher than that in group C (P<0.001).

Plasma 5-HT concentrations

At baseline, the mean 5-HT concentration in group A was significantly lower than that in groups B and C, and that in group B was significantly lower than that in group C (P<0.001, Table 3). After treatment, the mean 5-HT concentration was significantly increased at the endpoint compared with before treatment in the 3 groups (all P<0.001). The mean change in 5-HT concentration in group A was significantly higher than that in groups B and C, and that in group B was significantly higher than that in group C (all P<0.001, Table 3).

Association between plasma 5-HT concentrations and IELT at baseline and the endpoint

At baseline, the mean IELT of the 3 groups was: group A< group B< group C. Mean plasma 5-HT concentrations were: group A<

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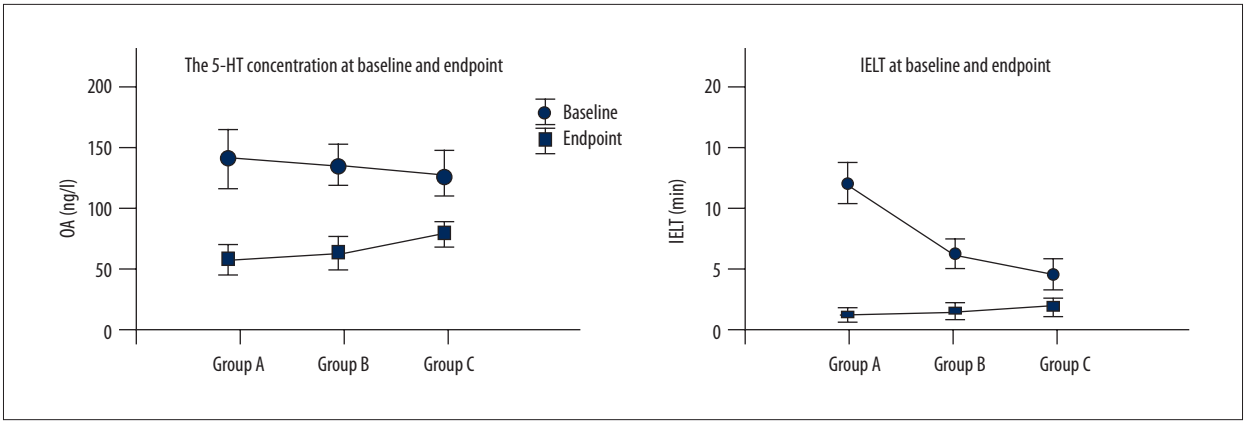

Figure 2. Plasma 5-HT concentrations and IELT at baseline and the endpoint in the 3 groups.

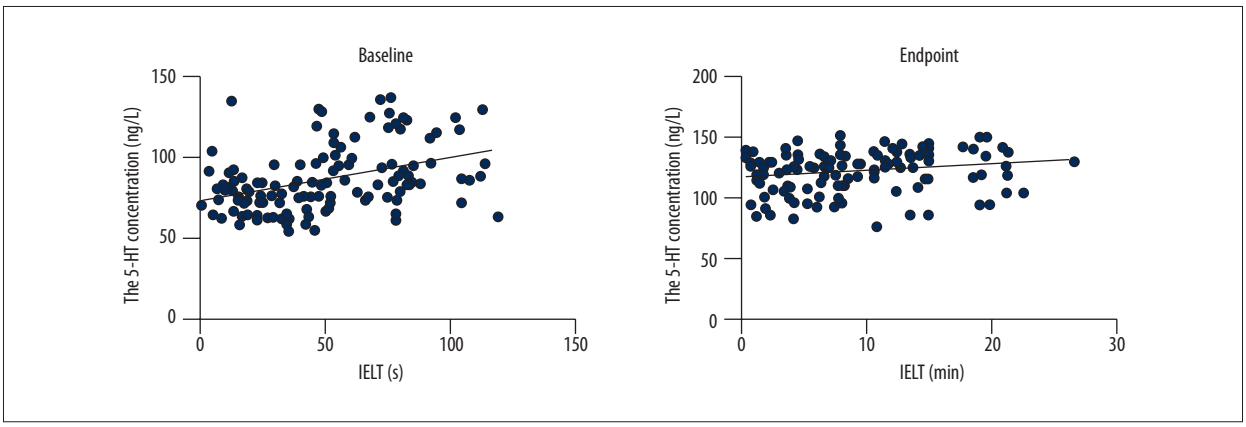

Figure 3. Linear regression analysis between IELT and 5-HT concentrations at baseline and the endpoint.

group B< group C. The mean changes in plasma 5-HT concentrations in the 3 groups were: group A> group B> group C. The mean changes in IELT and PEP scores in the 3 groups were: group A> group B> group C. These findings suggest that PE patients who have more serious clinical symptoms of PE (ie, those who have lower IELT and PEP scores), have lower plasma 5-HT concentrations and show the greatest improvement after treatment (Figure 2). An increase in serum 5-HT concentrations is clearly associated with improvement of symptoms in primary PE patients. The mean plasma 5-HT concentration in all of the patients was 82.94±32.12 ng/ml at baseline, and it improved to 126.69±48.64 ng/ml at the endpoint. Plasma 5-HT concentrations and the mean IELT were positively correlated before treatment (correlation index: 0.163. After treatment, 5-HT concentrations and the mean IELT were also positively correlated (correlation index: 0.–352 Figure 3).

Discussion

Recently, 5-HT has gradually become the focus of etiological studies on PE, and is probably the most widely studied neurotransmitter implicated in mediating ejaculation and the most important with regard to PE [12,13]. At least 3 subtypes of the 5-HT receptor play a role in ejaculation: 5-HT1A, 5-HT1B, and 5-HT2C. These three 5-HT receptor subtypes are concentrated in the ejaculation control nuclei in the vas deferens, and seminal vesicles [14]. Additionally, 5-HT is present at a high concentration in many of the crucial nuclei mediating ejaculatory control (e.g., MPOA, PAG, and nPGi) [15,16]. Stimulation of 5-HT1A receptors promotes ejaculation. Increased intrasynaptic 5-HT after inhibition of transporter-mediated uptake leads to increased activation of postsynaptic 5-HT receptors and inhibition of ejaculation [17–19]. Levels of 5-HT are closely implicated in mediating ejaculation and in the mechanism of treatment for PE [20].

Paroxetine, a selective serotonin re-uptake inhibitor, was first used for treatment of PE by Waldinger et al. in a placebo-controlled study in 1994 [21]. They used paroxetine for treatment of psychiatric disorders, and found that it can delay ejaculation in humans. Currently, paroxetine is widely used "off-label" for treatment of PE. Paroxetine needs 1–2 weeks of dosing to be effective for treatment of PE, because the mechanism of paroxetine in the treatment of PE is to desensitize 5-HT1A and 5-HT1B receptors, similar to its use for treatment of depression [22,23]. Chronic use of SSRIs could lead to high 5-HT

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concentrations compared with short-term SSRIs (e.g., dapoxetine) [24]. Therefore, long-term dosing of paroxetine could increase the risk of adverse events. In our study, 8% of patients had adverse effects, such as dry mouth, drowsiness, nausea, and reduced libido, as well as erectile dysfunction. These adverse effects mostly disappeared after 2 weeks of treatment.

A previous study reported that high 5-HT concentrations could reduce glans penis sensitivity and improve IELT, leading to improvement in symptoms of PE patients [25]. Kara et al. showed that plasma 5-HT concentrations in PE patients are much lower than those in healthy people. The researchers administered SSRI treatment for 8 weeks and found that plasma 5-HT concentrations improved, as well as symptoms of patients [26]. They also confirmed a correlation between plasma 5-HT levels and IELT. In our study, the 5-HT concentrations in the 3 groups were all significantly improved at endpoint. McMahon CG's study [27] showed that the baseline and endpoint 5-HT concentration were 62.74 ng/ml and 106.69 ng/ml, respectively. It significantly improved in McMahon's study but the baseline concentration and the change in concentration were different from our results. This difference between studies may have been caused by subjects, sample processing, and testing and treatment of different drugs.

Our study showed that the mean 5-HT concentration was different in each group at baseline. Group A, which had a lower mean IELT, showed a lower mean 5-HT concentration. After treatment, the IELT improved in the three groups. These results suggested that paroxetine improved PE patients' symptoms and improved their sexual satisfaction. Serum 5-HT concentrations significantly improved with treatment of paroxetine, and this finding was more obvious in patients with lower serum 5-HT concentrations at baseline. However, patients with lower serum 5-HT concentrations show better clinical results. Plasma 5-HT concentrations were positively correlated with IELT. This finding shows that 5-HT concentrations could be an indicator in predicting therapeutic effects in PE patients. This could be important for clinicians in the diagnosis of PE, determining the prognosis of PE patients, and individualizing treatment of PE [29].

In the current study, plasma 5-HT concentrations greatly improved in 9 patients, but there was no corresponding improvement in the IELT. This finding suggests that 5-HT is not a unique factor that participates in regulation of ejaculation. Therefore, there may be other mechanisms that are involved in the regulation of ejaculation. Future research needs to investigate changes in plasma 5-HT concentrations and the reaction of patients to treatment with different methods to classify patients with PE, thus providing a clinical basis for individualized treatment plans.

In this study, baseline IELT between 0–120 s was enrolled, which was not rigorous according to the definition of ISSM, which is "ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration"[10]. The definition of PE has been debated for many years. The most widely accepted definitions currently are that in the DSM (Diagnostic and Statistical Manual of Mental Disorders) and the ISSM definition; however, it keeps changing. As the aim of our study was to investigate the association between 5-HT and clinical symptoms, the enrolled subjects should not be limited by IELT of about 1 minute. Many people have an IELT of 60–120 s, but they still complain of fast ejaculation and low PEP scores, which deserves further study; therefore, we choose 0–120 s baseline IELT for the present study.

Conclusions

The IELT and plasma 5-HT concentrations of patients with primary PE were correlated before treatment. Lower 5-HT concentrations were associated with a shorter IELT. After treatment, plasma 5-HT concentrations and IELT were both increased. Patients with a shorter baseline IELT show a better improvement of IELT and plasma 5-HT concentration. Improvement in serum 5-HT concentrations was clearly associated with improved symptoms in primary PE patients. Concentrations of 5-HT could be an indicator for predicting therapeutic effects in PE patients, which could be important for diagnosing and determining the prognosis of PE patients, and individualized treatment of PE.

Competing interests

There are no conflicts of interests to disclose.

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