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Randomized Control Trial (RCT) Hatha Yoga Online Efficacy for D5 Dopamine Receptor mRNA Expression and mRNA Nuclear Factor Activated Kappa B cell (NF- κ B) mRNA Expression in Peripheral Lymphocyte Cell in Adolescence Whose Suffering Internet Addiction during Pandemic COVID-19

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Abstract---Internet addiction become higher problem during pandemic COVID-19 because of a lot of use internet activity. Adolescence is the highest population whose suffer for Internet Addiction. Hatha Yoga had been studied could reduce of internet addiction in adolescents, however have not understand how does its work in biology molecular perspectives. We developed yoga capsule program for Adolescence whose suffering internet addiction, to evaluate effect D5 Dopamine Receptor mRNA expression and Nuclear Factor Activated Kappa B Cell (NF- κ B) mRNA expression in peripheral lymphocyte cell. Adolescent whose suffer Internet addiction are recruited from senior high school. After internet addiction assessment using Internet Addiction Test Indonesian version (IAT-Ina), 34 adolescents divided into 2 group with random allocation became Hatha Yoga Group and Control Group. Sample advised 60 minutes and three times per week on 8 weeks program, led by Yoga instructor certified. Before and post intervention all participant had check D5 Dopamine receptor mRNA Expression and NF- κ B mRNA expression in peripheral lymphocyte cell and also IAT-Ina score. Hatha Yoga Online allows treatment for internet addiction in adolescent during pandemic COVID-19 and future. Forthcoming result may contribute about Hatha Yoga could affect the biology molecular to reduce symptoms and sign in Internet addiction.

Keywords---Hatha Yoga online, internet addiction, adolescent, pandemic COVID-19, study protocol.

Introduction

Internet user around the world was 66.2% of the population or 5.2 billion people [1]. Since March 2020, WHO declared that COVID-19 become pandemic disease[2] and this pandemic effect restriction a lot of activity such as social distancing, physical activity and recommendation to stay at home and online activity to prevent the spread of COVID-19 [3]. This condition particularly increases of internet use and internet addiction especially among adolescent.

Internet addiction is non substance or behavior addiction which is marked by uncontrol internet use that bring negative impact to their live such as distress and serious problem in social life and daily activity [4], [5]. Criteria of internet addiction still under debated, but psychiatrist and clinical psychologist agree that internet addiction consist of four essentials sign to diagnosis : Excessive and Uncontrol internet use (characterized by loss of time or neglecting primary function), withdrawal symptoms (like as mood swing, anger, depression and anxiety when its unavailable of internet), tolerance effects (like as need more amount of time on using the internet in order to relieve negative emotional feeling) and negative consequences in daily life like as psychosocial disturbance, loss of works, hobbies, education and lies with regards to using the internet [5].

Adolescent is the most population whose suffer from internet addiction [6]–[9]. In Asia about 40% of adolescent suffer from internet addiction, whereas Philippines had the highest (51%), follow by Japan (48%) and Hong Kong (32%) [10]. After COVID-19 amount of Internet addiction in adolescence is predicting will be increase. One in five (20.7%) adolescent whose suffer the internet addiction had psychosocial problem [11]. Others negative impact of internet addiction were cyber-bullying, increase suicide thought, and lack of social interaction [7], [9], [12], [13].

Internet addiction leads neuroanatomical and neurochemical alterations in cortex of the brain and also dopaminergic circuit reward system. Integrative therapy like yoga has proven to be affective in internet addiction [13] but lack of study about biology molecular of yoga on internet addiction. Biomolecular study on game online addiction as a part of internet addiction found that hyperstimulation dopamine pathway in mesolimbic area and significantly decrease of D5 dopamine receptor expression compare with control group design [14]. Functions of D5 Dopamine receptor is to decrease the motivation to addictive behavior[14], so lack of D5 dopamine receptor condition in adolescent due to increase the motivation of using the internet that lead the internet addiction.

NFkB is the transcription factor that influence effect after alcohol addiction and other substance abuse[15]. NFkB as a heredity immune factor of Mammalia cell. Activation of NFkB can active the mediator inflammation such as opioid receptor, neurokinin-1 receptor and opioid peptide. In alcohol study and other substance abuse found that there was NFkB increasing expression that effect to the gene

inflammation and neurotoxicity in brain cell and impulsive behavior to reuse of alcohol or other substance use[15]. This NFkB factor can be used for accurate biomarker to assess and prevention a substance addiction in psychiatry [16] which may be same as internet addiction process.

Yoga exercise could decrease significantly in the prevalence of internet addiction in addict case among the school and collage students in India [17] but there is no explanation about biology molecular alteration that change the condition. Hatha yoga was significantly decrease craving sign in cigarette addiction during 5 weeks exercise [18], and internet addiction symptoms can be alleviated through exercise but the effects of neurology pathway is unclear[19]. According this condition, it has become great deal for research attention to know about neurobiology effect especially D5 dopamine receptor mRNA expression and NFkB mRNA expression in the peripheral lymphocyte cell after Hatha Yoga intervention in internet addiction case.

Methods

Design of the study is randomized community trial control-group pre-test-posttest to evaluate the efficacy of Hatha Yoga online intervention in Internet addiction. Replication, randomization and random allocation did and totally group divided into 2 group Hatha yoga intervention and control. Internet addiction assessment using Internet addiction test Bahasa Indonesia version (IAT-Ind) share to senior high school randomizable and recruited 34 sample to inclusion in this research before intervention and immediately samples are allocated in a 1:1 ratio to the intervention group and control group. Control group gave cognitive behavior therapy (CBT) as a standard treatment from clinical psychologist every week, and after 8 weeks all the samples would be checked D5 receptor mRNA expression and NFkB mRNA expression in peripheral lymphocyte cell and internet addiction score for staging the level of internet addiction.

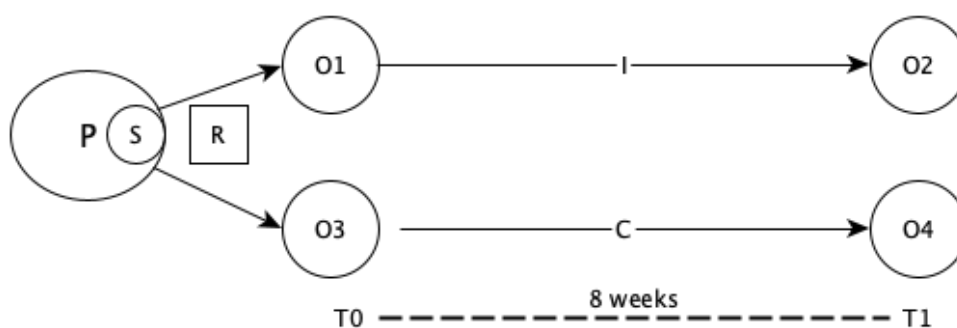


Figure 1 Study design

P = Population, S = Sample, R = Random Allocation, O1, O3 = Pretest Observation Hatha Yoga Group Sample, O2, O4 = Posttest Control Group Sample Observation,

I = Intervention with hatha Yoga Online 3x/week, C = Control with Cognitive behavior Therapy (CBT) 1x/week, T0 = Start Time, T1 = End Time (after 8 weeks).

Participant

Between October and December 2021 participant included all adolescence whose join senior high school in Denpasar area after online IAT-Ina assessment selection. According eligibility criteria (Table 1) we would to collect. We aim include 34 participants according WHO sample size application with significant level $\alpha = 5\%$, power of test = 80% and drop out estimation 10%. All participant divided into 2 group (17 per group). Every effort will be intention to treat analyses. Participant would give intervention according their group Yoga or CBT for each after informed consent. Participant we got around Denpasar senior high school using multi stage random sampling in four particular senior high school into 9 participants public senior high school, 8 participants from public vocational high school, 8 participants from private senior high school and 9 participants from private vocational senior high school. Our eligibility sample consist of inclusion criteria, exclusion criteria and exclusion criteria after inform consent. Inclusion criteria:

- Adolescence 15-17 years old
- Suffering Internet addiction
- Informed consent acceptance

Exclusion criteria:

- Participant who has psychiatry disorder
- Participant who has systemic disorder
- Participant who has Muscle disability or pain
- Participant who has routine exercise more than 150 minutes/week

Exclusion criteria after informed consent:

- Injured during exercise session
- Refuse to continue the exercise because of particular reason

Intervention

Hatha yoga online program is used in this study. After recognized for addiction internet via online survey and informed consent, the first meeting did on school each participant to give hatha yoga module, matrass, took peripheral blood cell by analyst and measure the height, body weight with standard scale. Intervention gave every 3 times per weeks on 60 minutes time every Tuesday and Thursday at 4-5 pm, Sunday 8-9 am via zoom application. Adherence to the program is acceptable $\geq 80\%$ complete. Hatha Yoga sequence consist of Open Prayer, muscle stretching, core of Hatha Yoga, muscle loosening, meditation and closing prayer (Table 2).

Measure

Outcome measures of the study decided into three criteria, D5 dopamine receptor mRNA expression, NfKB mRNA expression peripheral lymphocyte cell and internet addiction score (IAT-Ina). Demographic participant data also need to viewed participant characteristic, body weight, height, oxygen saturation and pulse rate.

D5 dopamine receptor mRNA expression and NfKB mRNA expression peripheral lymphocyte cell check immediately before intervention and after intervention using PCR analysis. Self-report behavior of internet addiction checks by score after fulfill the IAT-Ina online also immediately before and after intervention.

Table 2
Yoga capsule for internet addiction

Capsule	Types of Yoga Techniques		Round	Duration (minutes)
Open prayer	Open the exercise		1	4
Muscle stretching	head to toes (Pavamuktasana)		1	10
Asana (Posture)	Surya Namaskar 1 st -2 nd week		4	30
	Surya Namaskar 3 rd -4 th week		5	
	Surya Namaskar 5 st -6 nd week		6	
	Surya Namaskar 7 st -8 nd week		8	
Asana Addition	Tuesday (4-5 pm)	Standing pose: <ul style="list-style-type: none"> • Tiryaka Tadasana • Wrksasana • Trikonasana 	1	5
	Thursday (4-5 pm)	Sitting pose: <ul style="list-style-type: none"> • Ardha Matsyendrasana • Maricasana • Sasangkasana 	1	
	Sunday (8-9 am)	Laying pose: <ul style="list-style-type: none"> • Salabasana • Ardaha Salabasana • Danurasana 	1	
	Sawasana			5
Pranayama (Breathing Exercise)	Nadhisuddham Pranayama		5	2
Dhyana (Meditation)	Dyana mudra		1	3
Closing prayer	Closing the exercise		1	1
	Total			60

Discussion

Pandemic COVID-19 situation had disrupted normal activities globally, in particular internet use. Internet disorder or internet addiction may become high

prevalence (24,4%) among adolescence [20] because effect of internet use during pandemic. Internet addiction test is one of the most popular assessment for internet addiction and already validation in our country (Indonesia) with high internal reliability[21]. Children and adolescences might show emotional respond with this condition and its need general measures of countering stress like exercising and relaxation technique [22]. As of yet, there is not guideline approach for treating internet addiction [21].

Yoga is one of skill exercise that give more beneficial compare with aerobic exercise like treadmill, bicycling etc., because yoga give more of executive function improvement [23] and already as approval adjunctive treatment to prevent the internet addiction beside CBT and motivational enhance therapy (MET) as usual [24]. This protocol is the first to evaluate the efficacy of biology molecular in D5 dopamine receptor mRNA expression and NfKB mRNA expression after Hatha Yoga intervention including asana (posture), pranayama (breathing exercise) and Dhyana (meditation).

Yoga is a Physical and mental practice that come from the Sanskrit word “*yuj*”, meaning “to join” or union of the body with the consciousness in mind and spirit originate in India over than 2000 years ago [25]. There are eight limbed of yoga path, that’s call ashtanga yoga as Patanjali’s classical description that consist of Yama (ethical behavior), niyama (personal behavior), asana (physical posture), pranayama (breathing regulation exercise), pratyahara (sensory inhibition), dharana (concentration), dhyana (meditation), samadhi (integration) [25], [26]. Yoga is an exercise to control mind wave, to reach true self-awareness and free from different states [26], [27]. Hatha yoga is the most commonly practice in USA and the important component as well as yoga philosophy that is physical posture (asana), breathing exercise (pranayama) and meditation (dhyana) [28]. Since 1960 Hatha yoga has become a practice to promote stress reduction, relaxation and physical fitness and growing number of yoga studio and private home and the American Collage of Sport Medicine (ACSM) / American Hearth Association (AHA) guidelines encourage 30 minutes of moderate intensity aerobic physical activity five days per weeks [29] or 60 minutes three days per weeks [30] like asana Surya Namaskar.

Surya Namaskar on hatha yoga practice could increase blood flow level in cerebrospinal that could increase protein regeneration in the brain [31] through *peroxisome proliferator-activated receptor gamma co-activator 1-alpha* (PGC-1 α) and *orphan nuclear receptor estrogenic-related receptor alpha* (ERR α) that induce Brain Derive Neurotropic Factor (BDNF) and *fibronectin type III domain-containing protein 5* (FNDC5) expression in brain neuroplasticity processes [32], [33] that might increase mRNA D5 dopamine receptor expression and decrease mRNA inflammation factor like NfKB expression. Surya Namaskar also active *hypoxia inducible transcription factor 1 alpha* (HIF-1 *alpha*) when body tissue become lack of oxygen to increase neurogenesis, synaptogenesis and angiogenesis. HIF-1 α also modulate glucose gen transporter expression like Glucose transporter 1 (GLUT-1) and Glucose transporter 3 (GLUT-3) to facilitate neuron connectivity [23]. Lack of D5 dopamine receptor in internet addiction might increase by Surya Namaskar (asanas) posture.

Pranayama increase activity in HIF-1 alpha and HIF-1 beta that will affect gene expression to control angiogenesis process [34]. This mechanism might affect the regeneration a part of brain cell like D5 receptor dopamine. In otherwise, pranayama decrease stress by turn down the sympathetic nerve and turn up the parasympathetic nerve which impact to decreasing cortisol level through HPA-Axis to decrease NfKB signal factor[35] that affect to decrease phase of inflammations process. This effect explain that pranayama exercise might decrease NfKB in internet addiction pathology.

Meditation (dhyana) training in studied randomized controlled trial 8 weeks could decrease mRNA NfKB gene expression that associate with decrease of gene expression *gen Interferon Response Factor 1* (IRF-1) bind with antiinflammation gene patient respond to antibody after virus infection [36]. Pranayama and meditation work at the same path that might decrease inflammation factor which mark by NfKB expression.

A few studies have been conducted on effectiveness of Hatha yoga in biomolecular process to improve symptom and sign internet addiction, for example RCT yoga effect in adolescent whose suffer internet gaming disorder in India evaluate yoga effect just about questionnaire and have not explain about biomolecular effect of yoga[37]. The effects of Hatha Yoga online will be examine in adolescents whose suffer internet addiction during pandemic COVID-19. If this trial proves to be effective, we may be able to improve preventive and supportive treatment care for internet addiction in adolescent just by implementing easily exercise from home.

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