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Modulation of Stress Mediator and Asthma Control Level with Hypnotherapy in Psychogenic Asthma Patient

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Abstract : Hypnosis that uses mind ability to affect symptoms and physical function has been rarely developed as standard therapy in asthma. This study aimed to observe hypnotherapy effectivity as standard asthma therapy indicated by asthma level control and stress mediator (norepinephrine and cortisol). The method used pre and post-test design started from September 2014 to May 2015 in Pulmonology Division, Sebelas Maret University/Dr Moewardi Hospital Surakarta. 30 non-atypic psychogenic asthma patients were chosen randomly that completed full inclusion criterias. Variation of variables (norepinephrine and cortisol) was measured with Wilcoxon test, Marginal Homogeneity test to evaluate asthma control level, and Ordinal Regression and Logistic Regression test to analyze external variables that may influence hypnotherapy effects. The results showed norepinephrine levels significantly increased in both of groups after hypnotherapy [106,40 (4,9–365,30) pg/mL vs 276,70 (80,80–679,60) ng/mL; p =0,001], insignificant decreased cortisol levels in both of groups after hypnotherapy [10,93 (0,31–52,00) μg/mL vs 9,6 (0,26 – 23,58) μg/mL; p =0,382], and also increased asthma control levels in both of groups after hypnotherapy (0% vs 46,7%; p =0,001). There was no external variables that influence hypnotherapy result in norepinephrine levels, but The research found significant external variables that may influence hypnotherapy result in cortisol levels that is allergens trigger history (p=0,048), and also smoking history (p=0,005) and sex (p=0,03) in asthma control levels. It can be concluded that hypnotherapy was effective to repair stress mediators and increase asthma control level in standard asthma therapy of psychogenic asthma patients.
Keywords: psychogenic asthma, hypnotherapy, epinephrine, cortisol, asthma control level.

Introduction

The long of psychological stress can lead to disturbance in neuroendocrine, inflammation, metabolism, and transcription process, resulting in susceptibility to disease[1]. Asthma bronchial is a chronic airway inflammation disease indicated by reversible airway obstructions due to inflammation and airways hyperesponsives[2]. To date, pharmacotherapy fails to achieve controlled asthma state. Long term of

physiological and psychological stress in asthma patient will activate hypothalamic-pituitary-adrenocortical (HPA) axis and also sympathetic-adrenal-medullary (SAM) axis that trigger cortisol secretion, adrenalin (epinephrine), and noradrenalin (norepinephrine), that can reduce immunoprotection functions, as well as increase in Th2 cell[3]. Th1/Th2 balancing paradigm is an important thing to understand in inflammation immunity process. In asthma patient, there is airway inflammation through increase in Th2 cell response. Neuroimmunology of psychological symptoms are dominated by "immunity activation" and "immunity suppression" hypothesis. The balancing of Th cell shift to Th1 cell in depression or anxiety conditions[5]. Many studies show that when stress considered as threatening and uncontrolled, it will activate HPA axis and SAM axis. HPA is activated when paraventricular hypothalamus neurons secreting CRH, then secretes ACTH through hypophysis circulation portal to anterior pituitary glands. ACTH signal is carried through peripheral circulations to adrenal glands that produce cortisol in fasciculata zone. SAM consists of symphatic and parasymphatic branch that have effector molecules including epinephrine, norepinephrine, and acetylcholine[5]. Lymphocyte and monocyte express receptor for many stress hormones, including CRH, ACTH, Cortisol, epinephrine, and norepinephrine. Therefore, neuroendocrine hormones released during stress (epinephrine, and norepinephrine) can change immune functions and then change disease pathway based on immunity[6].

Many efforts has been done to decrease stress conditions such as adjuvant therapy, that involved mind ability to influence physical symptoms and functions, including hypnotherapy that also has been studying in asthma[6]. Hypnosis has been applied in clinical practice to treat many diseases that cannot be treated by medical treatment, including asthma. However, hypnotherapy clinical application in asthma treatment is still rare[7]. There is no study that clearly describes the underlying mechanism of hypnotherapy to treat asthma. Brown studies has found that hypnosis have good efficacy in emotional stress controlling that cause obstructive airways exacerbation and also can stabilize hyperresponsive airway in many asthma patients. Freeman and welton' study found impairment of asthma status after imagery hypnosis therapy, although this study is not formally recommended in asthma therapy[7,8]. Thus, this study aims to evaluate effect of hypnotherapy in improvement of asthma control level and stress mediator in both of controlled and also partial controlled psychogenic asthma patients.

Methods

The study design is pre and post test design. Blind sampling was used to choose sample. This Study started in September 2014 until May 2015 in Pulmonology Division Sebelas Maret University/Dr Moewardi Hospital Surakarta. Subjects were non atypic psychogenic asthma patients that completed full inclusion criterias: (a) Uncontroll asthma patient based on GINA 2012[10]; (b) more than 18 years old; (c) willing to follow studies procedures and agreed to sign informed consent; (d) last formal education is more than Junior High School; (e) well understand Indonesians language; (f) not smoking; (g) not including in *asthma COPD overlap syndrome* (ACOS) criterias. Exclusion criterias are: (a) Severe psychological stress disorders with measurment by clinical interview; (b) Severe physical disorders; (c) severe hearing disorders that disturb verbal communications.

Hypnotherapy is described as unconsciousness induction followed by some suggestions that can change general observations in conscious subjective minds (including the change of sensations, perceptions, emotios, minds, and also behaviours). This studyused short hypnotherapy procedures for 6 sessions with *sensory-imagery* hypnotherapy methods. Psycogenic asthma is described as asthma initiated by psychological stress factors. *Peak Expiratory Flow* (PEV) is measured by *peak expiratory flow meter* (PEF meter) devices.

Descriptions of controlled asthma, partial controlled asthma, and uncontrolled asthma was in accordance with GINA 2012[10], through over 4 weeks Assessment of current clinical control which criterias are :

No	Characteristic	Controlled	Partly Controlled	Uncontrolled
1	Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma
2	Limitations of activities	None	Any	
3	Nocturnal symptoms/awakening	None	Any	
4	Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	
5	Lung function (PEF or FEV1	Normal	<80% predicted or personal best (if known)	

This research used *sensory-imagery* hypnotherapy methods. Hypnotherapy of controlling asthma used 3 important target areas: (1) Anxiety component : patients were led to hypnotic state and asked to their imaginations to initiate full relaxations phase; (2) Conditional response to predispotition factors that lead to asthma exacerbatios : Patients were down to hypnotic state and used pleasant suggestions to create nice response to spesific conditions; (3) Physiological response to predispotition factor to initiate asthma exacerbations: patient were guided to deeper hypnotic state and focused on suggestions that change breathing activity that can initiate asthma exacerbation, it is useful to re-frame all things that can trigger asthma exacerbation to normaly thingsf or patient[8,9].

To analyze hypnotherapy modulation effects to stress mediator variables (*Norepinephrine* and *cortisol)* and also *VEP 1*, this study use *Paired T-test* and also *Wilcoxon test* as alternative. This study use *Marginal Homogeneity test* to analyze asthma control levels as hypnotherapy effects parameters. To analyze external variables that may influence hypnotherapy effects in this study result, this study perform multivariate analysis *Ordinal Regression* and also *Logistic Regression test.* All the result is siginificance if *p-value* <0,05.

Result and Discussion

Research subjects involved 30 uncontroled asthma patients according to *GINA 2012* criterias that all of them are non-atopic psycogenic asthma patients that belongs inclusion criterias. Demographic characteristic of samples were 70 % females, which normoweight for average *BMI* (23,78±4,50 kg/m^2), 87,13±34,94 for *SCL-90* scores, 83,3 % have asthma family history, and 86,7 % have allergens triggers history. There were only few elementary school graduations, in which most of them can follow the instructions in this study (Table 1).

Table 1. Demographic Charateristics

Characteristics	Frequency
Old (Years)	48,2±16,0
BMI (kg/m^2)	23,78±4,50
SCL-90 scores	87,13±34,94
Female	70%
Family history of asthma	83,3%
Smoking history	26,7%
Allergens triggers history	86,7%
Weathers triggers history	30%
Physicals activity triggers history	16,7%
College educations levels	50%

Hypnotherapy Modulations to Stress

This study found that hypnotherapy significantly increased norepinephrines levels. Norepinephrines levels before hypnotherapy were 106,4 (4,9–365,3) ng/mL, and increased to 276,7 (80,8–679,6) ng/mL after hypnotherapy ($p < 0,005$, $p = 0,001$). (Figure 1)

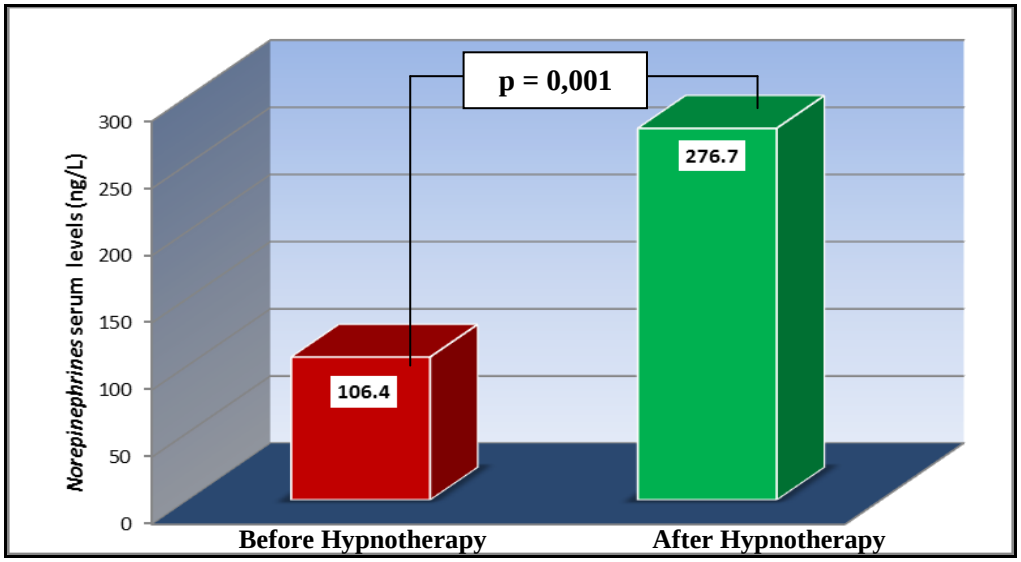

Figure 1. Hypnotherapy effects that increasing *Norepinephrines* serum levels

The result of the other stress mediators showed that hypnotherapy also reduced cortisol serum levels. Cortisol levels before hypnotherapy were 10.93 (0,31–52,00) ng/mL, and decreased to 9.60 (0,26–23,58) ng/mL after hypnotherapy, but statistically less significant, ($p > 0.05$, $p = 0.382$) (Figure 2). These findings might be due to external variable (allergens trigger history) that influence the significant hypnotherapy result ($p<0,05$, $p = 0,048$).

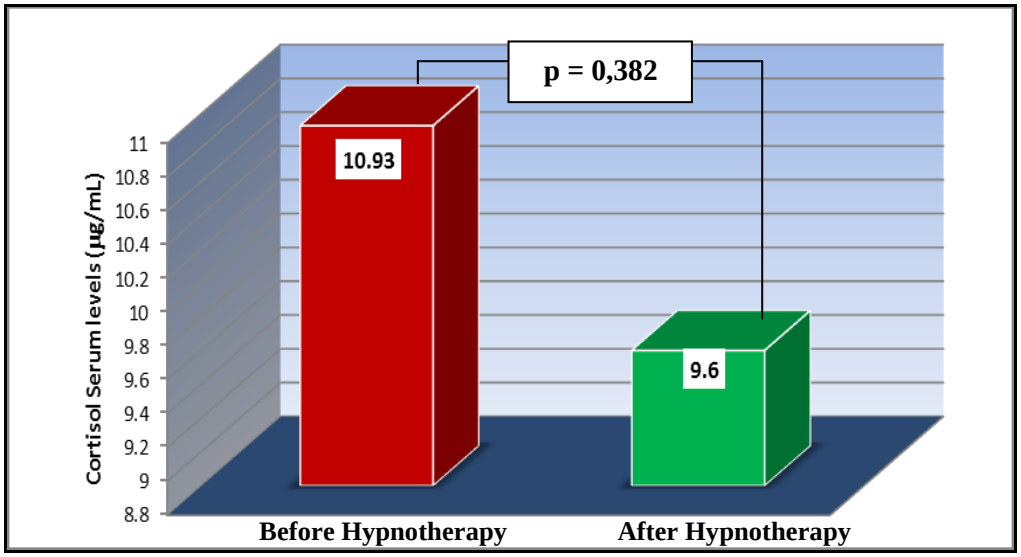

Figure 2. Hypnotherapy effects on *Cortisol* serum levels

Hypnotherapy modulation in Asthma Control Level

In this study, hypnotherapy improved standard therapy response in psycogenic asthma patients related to improvement of daily asthma symptomps more than twice a day ($p < 0,001$), nocturnal symptoms/awakening ($p = 0,001$), requirement of reliever/rescue treatment> 2 times / week ($p < 0,001$), improvement of limitations of activities ($p= 0,008$) and improvement of lung fungctions with VEP 1 ($p = 0,001$) (Table 2).

Table 2. Percentage comparison of *Asthma Control Levels* before and after hypnotherapy.

Asthma Control Levels Variables	Before Hypnotherapy	After Hypnotherapy	P Value
Daytime symptoms> 2 times/day	80,0	16,7	<0,001**
Nocturnal symptoms / awakening	56,7	13,3	0,001**
Need for reliever/rescue treatment> 2 times/week	70,0	20,0	<0,001**
Limitations of activities	26,7	3,3	0,008**
Lung fungctions with *VEP 1*	72,97±15,20	75,95±15,05	0,001*
Note :			
*Paired T-test			
**Wilcoxon test			

Overall, the results of this study indicate that hypnotherapy can improve asthma control level, from uncontrolled asthma and also partial controlled asthma to be full controlled asthma status that statistically significance with p = 0.01 (p < 0,05). Before hypnotherapy full controlled asthma subject was 0 %, but after hypnotherapy, this study found that full controlled asthma subjects were 46.7% (Figure 3).

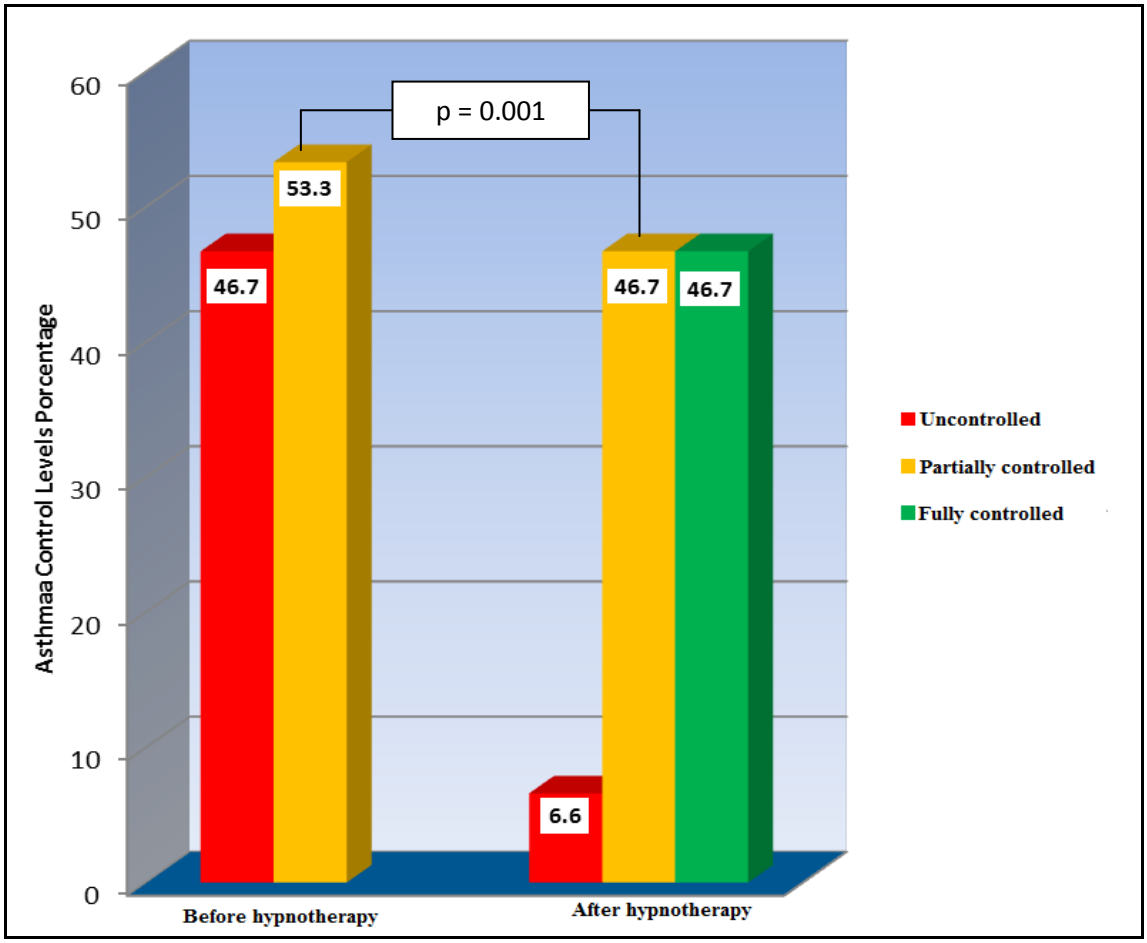

Figure 3. Hypnotherapy effectivity in Asthma Control Levels

After adjusted external variable, and performed Ordinal Regression and also Logistic Regression test, there was no external variables that influence hypnotherapy result in norepinephrine levels, but this studyfound significant external variables that may influence hypnotherapy result in cortisol levels which was allergens

trigger history (p=0.048), and also smoking history (p=0.005) and sex (p=0.03) in asthma control levels (p<0.05).

The corelation between stress and asthma is complex, and partially mediated and modified by environmental exposure (i.e outdoor air pollution, cigarette smoke), medication (treatment) obedience and also coping mechanisms (ie, coping strategies, family support). Among them, the stress likely to affect the onset of asthma, and work directly on airway pathogenic mechanisms. Although this pathway remains unclear, early evidence indicates the role of stress in lung development modulations, autonomic nervous system responses, neuroendocrine and also immune system[10]. Stress will modify the activity of the HPA axis and SAM axis, through effector molecules including epinephrine, norepinephrine, and acetylcholine[4].

Asthma is a heterogeneous disease with many phenotypes, and can affect all of age groups. Age is an important factor in separating the phenotype. Genetic factors, atopy, and early respiratory infections are predisposing factors of asthma onset in children. The asthma's onset in adults is more often associated with obesity, smoking, depression, or other lifestyle or environmental factors, although genetic factors and respiratory infections may also play a role in adults' asthma onset[11]. In this study all subjects were over 18 years old, with an average age between 48.2□16,0 years old. Aging can cause remodeling and decrease of immune system, which ultimately affects health[12]. Aging also increase pro-inflammatory pathogens and decline species that modulate immunity that will facilitate inflammations[13]. In addition, psychogenic stress levels in this study showed an average score of SCL-90 (87.13□34.94), that indicates decreased immune functions and also increased Th2 responses due to psychological stress which is almost equal in all subjects in this study.

Obesity is a risk factor in the development of asthma. The results of this study showed that the average subjects are norm weight. Asthma patient with obesity is frequently defined as severe asthma and uncontrolled, that might be caused by less responsive to corticosteroids and distinct inflammatory phenotype. Obesity is associated with low-grade chronic systemic inflammation that increases the systemic complications. The adipose tissue can regulate systemic inflammation through the production of various adipocytes. Obesity increases the risk of asthma developing and implicated in immunologic mechanisms that are relevant to the mechanical disorders and asthma. Moreover, these pathways may also increase airway inflammation, so asthma becomes more difficult to control[14,15].

Leptin is primarily secreted by adipose tissue and the levels are increased in line with obesity. Leptin and leptin receptor are expressed by lungs cells, including epithelial cells, type II pneumocystis, and macrophages. Leptin has systemic activity as pro-inflammatory that can contribute to bronchial asthma. Some studies indicate that systemic leptin is associated with the severity of asthma symptoms, and lung function impairment induced by activity[15].

This study was largely followed by women (70 %). This is consistent with the literature that mentions the adult prevalence of asthma is greater in women than men. Sex differences in asthma incidence reflect to sex hormones effect on the immune system, and also other lifestyle factors[16]. From the characteristics of the level of asthma control in this study, the subjects were more uncontrolled asthma patients. These results are consistent with previous studies that puberty is the common stage of asthma occurrence in women and the conditions is more severe. The incidence of non - allergic asthma is higher in women than in men (HR 3.51, 95 % CI 2.21 to 5.58), while the incidence of allergic asthma is no difference in the sex type[17].

This study found that clinical hypnotherapy significantly increased norepinephrine levels from psychogenic asthma patients. Norepinephrine is major catecholamine released by the sympathetic nervous system and significantly affects the lymphocytes, including T cells, B cells and natural killer cells (NK), which plays a role in the pathogenesis of asthma. Norepinephrine binds to adrenergic receptors that expressed on the surface of various immune cells. Beta-2 adrenergic receptor is the primary receptor on T-cells and B cells that directly modulate cellular activity through norepinephrine[18], this signal is the nervous system pathway to regulate the body's immune system. Beta-2 adrenergic receptor is expressed by Th1 cells, but it is not expressed by Th2 cells [18, 19].

Receptors norepinephrine activates the cAMP-dependent pathway that affect the synthesis and release of cytokines and cell proliferation. After binding with cortisol, a glucocorticoid receptor cytoplasm/nucleus dimerization and also translocate to nucleus where they act to modulate lymphocyte proliferation and cytokine

gene transcription[18]. Under stress condition, balance of systemic glucocorticoids and catecholamine change, as well as their concentration in primary and secondary lymphoid organs[4,18].

Macrophages and lymphocytes have receptors of these hormones (glucocorticoid receptors for cortisol, receptors alpha and beta adrenergic for catecholamine), and receptor ligation change this repertoire cell gene expression, that generate the implications such as trafficking, signaling, proliferation and differentiation and effector function. Through the influence of modulation, chronic stress is potential in reactivity of asthma, i.e.: allergens, and infections, that worsen inflammation and airway obstruction[4,20]. Thus, hypnotherapy will promote modulation to achieve cortisol and norepinephrine levels balance. Hypnotherapy is also able to lower cortisol levels from psychogenic asthma patients. These results are consistent with previous research, that hypnosis can lower HPA pathway mediators including cortisol. Modulation of neuroendocrine mediators (such as cortisol) by hypnosis will have different effects on Th1 and Th2 cells[21]. This study shows carry over effect of hypnotherapy. Discontinuous hypnosis will arise cortisol levels again. Patients treated with strong dose hypnotic showed extreme decrease in cortisol levels, and then its levels increased again due to an emotional state after hypnosis was stopped. Cortisol was significantly lower at controlled emotional state after hypnotherapy, compared to emotion before hypnotherapy. Few evidences show that hypnosis has the potential effects in modulation of HPA pathway. On the other hand, the significance of hypnosis to decrease cortisol levels were unconvincing[22]. These results were confirmed by Varga and Kekecs research (2014) that showed the changes of cortisol levels after hypnosis is not related to patient susceptibility to hypnosis, but to patient's relational experience[21].

Overall, hypnotherapy can improve the level of asthma control; both uncontrolled asthma and partly controlled asthma state are to be controlled asthma state. Hypnotherapy provides positive emotional induction in asthmatic patients through two pathways: (i) Directly affected Model (a main (direct) effect model); (ii) Buffer Stress Model (a stress-buffering model). The first models are the positive emotions associated with decreased cortisol levels and norepinephrine, decreased sympathetic nervous system activation and also activation of parasympathetic nervous system. This parasympathetic nervous system activation quickly and specifically inhibits macrophage activation in tissue, resulting in decreased pro inflammatory cytokines release (IL-17). The second model is positive emotions that act as a buffer from stress response, thereby it will reduce the negative perspective of stress and facilitate adaptive coping.

Emotional factors such as stress can disrupt physiological pathways, including respiratory tract autonomic control, endocrine system, and also immune function, which all of it can lead to asthma onset. Stress causes Th-2 immune response corresponding to asthma characteristics. Positive emotions induction induced by hypnosis is able to improve HPA activation and also the autonomic nervous system (SAM) that associated with stress. Overall, hypnotherapy improves the level of asthma control, indicated by increased control asthma from 0% prior to treatment, to 46.7% after hypnotherapy. These results also showed that six sessions over four weeks standard medical therapy without hypnotherapy for asthma patients did not improve their asthma control levels.

Psychosocial stress is one of asthma risk factors that cause physiological pathway disorders in respiratory tract autonomic control, endocrine system, and immune function, which can lead to asthma[23]. Hypnotherapy reduces allergic response and bronchial inflammation in asthma patients at hypnosis state. Hypnotherapy affects non-adrenergic nervous system and also non-cholinergic nervous system found in airway smooth muscle that extends time of Broncho dilation[24].

Some studies show that people with asthma have a decreased ability to respond to oxidative stress caused by dysregulation of antioxidant function. Oxidative stresses change the balance of Th1/Th2 cells immune response and activate powerful pro-inflammatory genes, Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF□B) (1.26). The low plasma antioxidants concentration is related to the severity of asthma, otherwise the increase of antioxidants will help reduce the severity of asthma. The effective oxidative stress management in asthma patients is very important to control intracellular immune system mechanisms that play important role in promoting airway inflammation of asthma patients[25,26,27]. Therefore, it is necessary to maintain the free radicals with antioxidants in the treatment of asthma, one of which is hypnotherapy.

Conclusion

Hypnotherapy is effective to repair stress mediator and also asthma level control in standard therapy response of psychogenic asthma patient.

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