Editorial

iMedPub Journals
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Journal of Headache & Pain Management
ISSN 2472-1913

2017
Vol. 2 No. 3:11

DOI: 10.4172/2472-1913.100041

The Power of Placebo in Pediatric Migraine

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Received: July 03, 2017; **Accepted:** July 20, 2017; **Published:** August 04, 2017

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Citation: Francis MV (2017) The Power of Placebo in Pediatric Migraine. J Headache Pain Manag Vol. 2 No.3:11

It is exciting news for clinicians who treat headaches all over the world that many new abortive anti-migraine drugs are on the horizon like CGRP receptor antagonists and antibodies against CGRP. But for preventive therapy, previously prescribed medications face questions of efficacy in the pediatric age group. Non pharmacological treatment for pediatric migraine include education, life style modification and trigger avoidance, bio behavioral therapy and acupuncture. Powers et al. [1] recently published a study on the trial of amitriptyline, topiramate and placebo for pediatric migraine in the New England Journal of medicine. A multi central randomized double-blind placebo controlled trial including patients aged 8 to 17 years with episodic migraine. The trial was stopped following an interim analysis showed no difference between groups and futility of trial continuation. The conclusion is that there are no differences in the reduction of headache frequency or disability in children and adolescents treated with amitriptyline and topiramate as compared with placebo. This study results are noteworthy and highlights the importance of considering non-pharmacological approaches to headache management in children. Powerful placebo responses are indicators that non-pharmacological treatment options are attractive in recurrent headaches in children. This author has documented [2] strong placebo effect of spectacles (upto 73% in children with more than 50% improvement and 32% with complete relief) especially when recurrent headaches involve peri orbital regions or prolonged eye focusing is one of the triggers precipitating headaches. 2422 children aged 5 to 15 years were studied over a period of 7 years. Inclusion criteria were history of abortive/prophylactic treatment failure, fed up with different drug regimens, subsiding with drug treatment but recurring, past history of someone in the family got better with spectacle wear and adverse effects of current drugs. Strict trigger avoidance especially common triggers in this region of India, topical anti-inflammatory creams like diclofenac and regular mild to moderate exercises were additional measures which were found to be beneficial in these groups of children and adolescents [3]. Thus, the conclusion was that, constant wearing of placebo spectacles along with trigger avoidance and topical anti-inflammatory creams were excellent non pharmacological (non-oral) options in pediatric migraine.

What is this Placebo Effect? What Evidence do we have?

Placebo (I will please) therapy is similar to a duplicate medical analysis in which patient is made to belief that treatment is being conducted. It has been considered as a reliable treatment to achieve countless recoveries from chronic headaches and other serious life-threatening diseases. Adverse effect by the Nocebo effect (In Latin Nocebo means I will harm) can be caused by placebo effect, inert substances, bad behavior or negative context. Many data states that the conditions with an analgesic analysis activate the endogenous opioid systems. Context is nothing but the words uttered by doctors and nurses, the smell of a drug, the sight of hospitals and room layouts, spectacles and similar appliances or the touch of a needle or a complex apparatus. Particularly, the administration of a dummy painkiller therapy along with the relevant verbal instructions (such as “your pain is going to decrease”) can reduce pain by the application of opioid receptors. Levine et al. [4] found that endogenous opioids mediate placebo analgesia. Nowadays, it is known that opioid and non-opioid components are comprised in placebo analgesia, considering the method used to induce the placebo effect [5]. We are starting to comprehend some of the workings of opioid-mediated placebo analgesia and research states that the patients who reacted to a placebo administration displayed higher concentrations of peak beta endorphins in the CSF related to patients who did not react to the placebo. For the intervention of opioid–reliant placebo analgesia, an opioid neuronal network in the cerebral cortex and brain stem may be responsible [6] and this network associates with a declining pain regulating pathway that directly or indirectly associates the cerebral network to brain

stem. The ACC (Anterior Cingulate Cortex) and OrbC (Orbitofrontal Cortex) project to the PAG (Periaqueductal Gray) which in turn, regulates the action of RVM (Rostro Ventromedial Medulla) and these brain regions along with other nuclei in the brain stem are excess in opioid receptors and can show a significant role in placebo analgesia. Actually, context- related cognitive cues can stimulate this opioid network in the cerebral cortex and the brain stem. This hypothesis is supported by a brain imaging study with Positron emission tomography [7].

Studies also show that placebo analgesia involving opioid has side effects and is followed by complicated cascade of events that affect the cardiovascular system [8]. After placebo treatment, occurrence of withdrawal symptoms is seen. After the discontinuation of the Women's health initiative study of hormone replacement therapy for menopause, it was found that women were administered with placebo for an average of 5.7 years [9]. Moderate to severe withdrawal symptoms were reported by 40.5% of those on placebo compared to 63.3% of those on hormones. Thus, it is very clear from above studies that there is an intimate relationship between the context and endogenous opioid network.

Everyone is not reactive to placebos. Neither everyone reacts to placebo nor to an active drug. Various investigations including clinical trials implied placebo effects, showed in about 50% of people with recurrent headache like migraine. Yet, the effective rate may be 0% up to nearly everyone relying upon the severity of pain and the context. Placebo effect has been detailed in other chronic illnesses rather than pain. In Parkinsonian patients, the release of dopamine in the striatum [10] is triggered, and some empirical data states that serotonin is responsible for the placebo response of depressed patients [11]. Gastric and duodenal ulcers [12] and allergic disorders (different clinical trials conducted all over the world and personal observations in oculo nasal allergy) too are vulnerable to placebo treatment. The compilation of data in the area of pain with those in other pathological conditions will aid the understanding of the complex mechanisms that link mind, brain and body.

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