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Role of Placebo and Nocebo Effect

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***Abstract*: Placebo effect is considered as an effect which improves patient's health because of his belief in the treatment or drug but has no medical effects. This is mostly related with psychology of the patient and results in improvement of health even on using non clinical treatment. On the other hand, nocebo effect deteriorates the health of the patient due to the negative belief system. In this review paper, we have considered different theories and how placebo effect is beneficial in treatment of various health conditions arising due to psychological factors. Placebo effect has proved to be useful in curing depression, pain, insomnia, fatigue and most recently it has shown positive results in treatment of Corona patients too.**

***Index Terms:* Placebo, Nocebo, Pharmacological approach, Motor Control, Opioid Mechanism, COVID-19.**

I. INTRODUCTION

The term placebo has been used in English language since 13th century and had wide range of meanings. The commonest amongst them was 'to flatter' or 'flatterer' but its association with medicine began in latter part of 18th century and the evidence of the phrase placebo effect came to be known in 19th century only. Wolman, B. B. (1989). It has been derived from Latin word placere meaning I shall please/satisfy or I will do good, and nocebo has been derived from word nocere, meaning I will hurt/harm. Placebo is generally used to reduce medications and is believed to create a positive effect on the patient and improves their health though the placebo itself has no active ingredient. For e.g. Experiments have shown that when an individual is told he has been given very effective medicine but he has been given sugar coated pill, he starts improving and shows desirous results because of this. Thus, the effect can't be attributed to properties of Placebo rather it is associated with the belief of the person. Nocebo explained by Colloca, L. & Miller, F.G. (2011) is rather negative effect and may be considered reverse of Placebo effect. Studies have shown when patient is given sugar pill and is informed that the given medicine has harmful side effects, then the person starts showing those symptoms. It can happen when doctor suggests negative results of surgery and it creates negative impact on health. Thus, it worsens health of the patient.

It is considered as a controversial topic. It has been observed that a lot of tablets, supplements and oils are considered to have no effect. On the other hand, few medicines have the positive effect due to the faith of people in that medicine though they don't do anything by themselves. So, this created interest within the present topic. We need to know whether the placebo effect works? If yes, then How? How placebo effect is related to weight loss, blood pressure, anti-wrinkle creams and so on. Can Placebos be considered better than real drugs? These are some of the questions which we need to understand to save our time and money.

Different theories have been proposed to explain Placebo and Nocebo effects and we have to look on different mechanisms depending on the conditions. Research studies have shown that Placebo effect is psychobiological phenomenon. The commonest theory is that person's own belief system is responsible to create positive desired effects or negative symptoms. There can be improvement of symptoms, and asthma, anxiety, fear, depression, pain etc. can be reduced which has been studied by various researchers (Berg-Smith, S. M., Kemeny, M. E., Kline, J. N., Panettieri, R. A., Rose, R. M., & Rosenwasser, L. J., 2007; Benedetti, F. & Colloca, L., 2005; Benedetti, F., Colloca, L., Lanotte, M. & Lopiano, L., 2004; Loeser, J. D., Melzack, R., 1999; Bandura, A., Gauthier, J., Gossard, D., O'Leary, A. & Taylor, C. B., 1987; Amanzio, M., Benedetti, F., Maggi, G. & Poll, A., 2001).

Treatment is based on the fact that how psychosocial conditions affect therapeutic outcome. We need to eliminate specific action of that drug, and stimulate similar circumstances. When a person takes a pill (the placebo), even if it is not having any active ingredients, and thinks, it will react positively, body starts

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responding positively and produces chemicals and hormones accordingly and produce similar effects as active ingredient.

Many studies have been done mainly in the field of antibiotics, analgesics used to relieve pain, in osteopathy, to study about motor disorders and check immune system etc. Studies have shown that there is interaction between neuronal systems and brain activity.

Lot of scientific and public interest has developed in recent times in placebo effects due to their studies on humans and since the effects of belief provide an entry point for study of internal control of various processes i.e., sensory, affective, and peripheral which has been discussed by various researchers.

Calne, D. B., de la Fuente-Fernandez, R., Ruth, T. J., Schulzer, M., Sossi, V., & Stoessl, A. J., (2001); Smith E. E. & Wager, T. D. (2003); Barrett, L. F. & Wager, T. D, (2004); Liberzon, I., Phan, K. L., Taylor, S. F. & Wager, T. D., (2003); Jonides, J., Reading, S. &. Wager, T. D., (2004) in their studies showed how the thoughts and beliefs affect the brain processes and the health of the person and work as regulators for perceptual and motor processes.

II. The Pharmacological approach

Byrne, W. L., Lipman, J. J., Mays, K. S., Miller, B. E., Miller, M. N., & North, W. C. (1990). have shown that in case of chronic pain patients, higher concentration of endorphins was present in the Cerebro Spinal Fluid of placebo responders than in placebo non responders.

Benedetti, F &. Colloca, L. (2005) observed that a placebo administration can reduce pain by both opioid and non-opioid mechanisms via expectations/conditioning mechanisms. The respiratory centres may also be inhibited by endogenous opioids. Placebos can also act on 5-HT-dependent hormone secretion, on pituitary and adrenal glands thereby copying the effect of analgesic drug.

Recently, a study carried by Benedetti, F., Lanotte, M., Lopiano, L., Pollo, A., Rainero, I. & Vighetti, S. (2003). showed that due to placebo analgesia administration, heart rate was reduced and was accompanied by reduced β-adrenergic response, which proves that placebo analgesic affects cardiovascular system. Studies have also proved that depending on the conditions, placebo effect can be induced consciously or unintentionally (e.g., hormone secretion). Ader, R. (2003) has reported that immune responses which have been recorded show the role of conditioning in Placebo effect. Benedetti, F., et al. (2003) have reported that in case of immunosuppressive placebo responses, effects of secretion of Growth Hormones and Cortisol secretion were observed as a result of conditioning mechanism.

III. Role of Placebo Effect in Motor Control

Neurobiological mechanisms of Placebo response have been studied and very well explained in patients suffering from Parkinson's disease. These patients are given medicine which has inactive ingredient (placebo) but the patient is informed that he is given antiparkinsonian drug. It has been observed there is positive effect in performance of motor nerves. It has been reported by Calne, D. B., de la Fuente-Fernandez, R., Ruth, T. J., Schulzer, M., Sossi, V., & Stoessl, A. J., (2001) that Positron Emission Tomography (PET) shows motor improvement caused due to placebo effect and releases dopamine in the striatum region.

Benedetti, F., Bergamasco, B., Cavanna, A., Lanotte, M., Lopiano, L., Pollo, A., Rizzone, M., & Torre, E., (2002) have reported in their article that experiments were carried out which proved that where expectations were there, neural changes were very fast. It was observed that the patients who had been implanted with electrodes for deep brain stimulation (DBS), when they expected good motor response then the movement of hand increased.

Also, in patients with DBS, responses of single neuron before and after placebo administration were recorded to see if neuronal changes were related to clinical placebo response (Benedetti, F., et. al 2004). Saline solution was used as placebo along with conditioning of apomorphine. There was reduction in neuronal discharge and bursting activity of subthalamic neurons in case of placebo responders which was not seen in case of placebo non responders. Rigidity decreased in case of placebo responder and there was feeling of well-being.

IV. Role of Placebo in Analgesia – Opioid Mechanism

Endogenous opioids are considered to regulate the immune system actively. Studies have shown that involvement of endogenous opioids in mediation of placebo with expectation of analgesia. Deeter, W. R., Dubner, R., Gracely, R. H., & Wolskee, P. J. (1983) & Amanzio, M. & Benedetti, F. (1999) have reported that pain was further reduced with expectation of analgesia.

Zubieta, J. K. et al (2001, 2002, 2003, 2005) reported that when placebo was introduced with expectation of analgesia it activated opioid neurotransmission and there was decrease in availability of opioid receptors to get bonded with radiolabelled tracer agents.

When a pill was taken with the expectation of positive effects then reward pathways of brain got activated and natural pain killers, endorphins were released which were chemically similar to opiates like codeine, morphine. These got binded to opioid receptors and reduced pain. However, this effect was nullified by naloxone which blocked these receptors and placebo effect could thus be modulated and prevented. (Pinch, B. 2016)

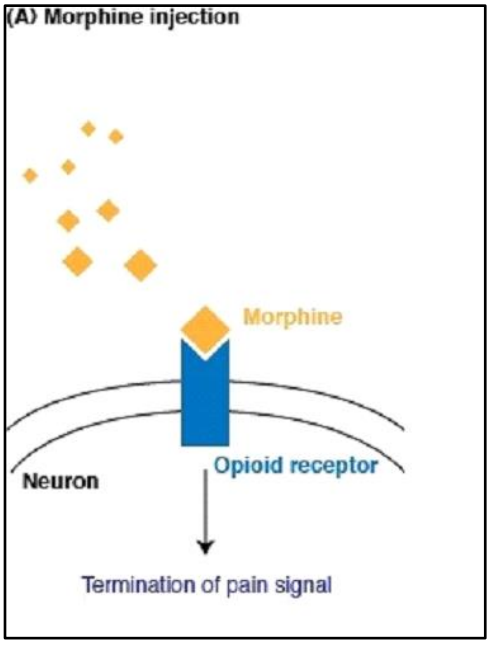

Fig.1(A): Morphine binds with opioid receptors in brain and relieves pain.

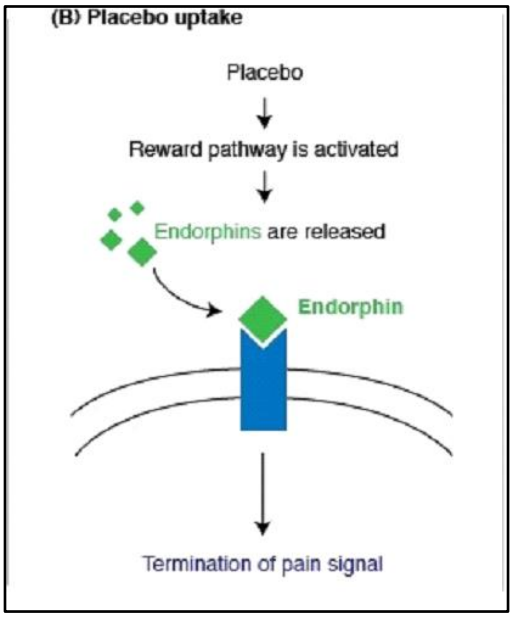

Fig. 1(B): Placebos activate reward pathways and release endorphins which bind to opioid receptors.

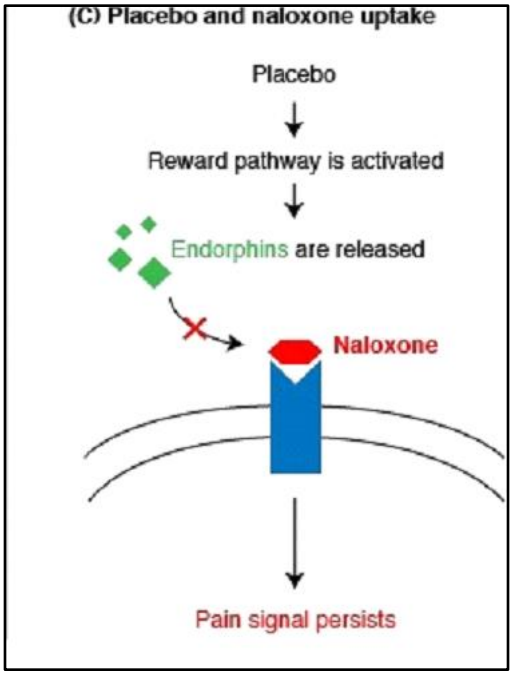

Fig. 1(C): Opioid receptors are blocked by Naloxone, thus preventing binding of endorp hins and inhibiting placebo effect (Pinch, B. & fig by Choi, K. 2016.)

V. Role of Placebo in COVID-19

At present, entire world is facing COVID-19 pandemic spread due to Corona virus, which is believed to emerge from Wuhan, China. This has affected lives of millions of people globally and entire world and medical community is in desperate need for search of medication. It is believed to cause respiratory tract infections which can turn to acute respiratory distress syndrome and may even lead to thrombosis. Still trials for vaccines are going on. Hydroxychloroquine has been commonly used for treatment of malaria, arthritis, some autoimmune diseases like HIV, Hepatitis. Recently, it has been studied for treatment of COVID-19. A randomized clinical trial done by Self, W. H., Semler, M. W., Leither, L. M, et al (2020) have shown that there is lack of efficacy of hydroxychloroquine in the treatment of COVID-19. Immunomodulatory role of Vitamin D is well known but the therapeutic effect of vitamin D supplementation is not known till now in SARS-CoV-2 infection. Recently, studies were carried out by Rastogi, A. et al (November 2020) to find out the role of oral supplementation of cholecalciferol in removal of SARS-CoV-2.

(Trial register number NCT04459247).

Candidates were given (oral nano-liquid droplets) 60 000 IU of cholecalciferol daily for 7 days with therapeutic target 25(OH)D>50 ng/ml (intervention group) or placebo (control group). Patients susceptible to comorbidities and who required ventilation were not considered. 25(OH)D levels were assessed at day 7, and cholecalciferol supplementation was continued for those with 25(OH)D <50 ng/ml in the intervention arm. Different parameters were recorded periodically. Studies have proved that those who have Vitamin D deficiency are more susceptible to this

viral infection and mortality (Illie, P. C., Smith, L. & Stefanescu, S., 2020; Arora, V., Best, T. J., Meltzer, D. O., Solway, J., Vokes, T. & Zhang , H., 2020; Cohen, A. G., Gorohovski, A., Green, I., Merzon, E., Morgenstern, M. F, Tworowski, D. & Vinker, S. 2020). It was observed in above mentioned intervention study with calciferol that requirement of intensive care in hospitalised COVID-19 patients was reduced. It was also seen that respiratory tract infections were less in patients who were given Vitamin D supplements (Martineau, A. R., Jolliffe, D. A., Hooper, R. L., et al. 2017). These studies showed that when vitamin D deficient patients suffering from COVID infection when were given high doses of cholecalciferol, then these patients showed significant reduction in fibrinogen and turned SARS-CoV-2 RNA negative. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection.

In few vaccine trials for COVID-19, candidates were injected with saline solution as placebo. In other groups, they were given actual treatment. For e.g., in case of vaccine developed by University of Oxford for COVID-19, control group was given placebo (septicaemia and meningitis vaccine). Benefit of placebo control will be that it will cause similar reaction (like soreness or muscle pain) and patients will not come to know if they are getting real treatment or placebo. When real vaccine is added to placebo, it helps to keep the trial remain blinded and avoids any kind of bias.

A treatment is considered effective only when it proves to be better than placebo or else it is rejected. However, no standards have been mentioned for placebos which make it difficult to presume about side effects.

The main problem with including something active in the placebo, such as another vaccine, is that it can confuse researchers when they measure side-effects. This problem can be solved by meticulous reporting about the ingredients of placebo.

Conclusion

Studies have proved that placebo effects influence therapeutic outcomes. They help to enhance the efficacy of a treatment. If we have positive belief, and thought process regarding a particular treatment and medication, we will have positive outcomes of the treatment and it will outweigh the risks. So, think positively, to bring a positive change in health.

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