

Placebo Effect on Psychoemotional Status and Clinical Analyses of Armenian Crohn's Disease Patients

Elya S. Pepoyan and Astghik Z. Pepoyan

Abstract—The Zung self-depression scale and Beck Anxiety Inventory were used both to study the depression and anxiety levels of Armenian Crohn's disease patients, and to reveal the relation between emotional status and placebo effect of these patients. On the other hand, the blood cell analyses and gut bacteria investigations were used to assess the placebo effect on ESR, and haemoglobin's and leukocyte's levels as well as gut commensal *E. coli* quantities of these patients.

Despite of registered high levels of depression and anxiety, the high placebo effect on psychoemotional status for investigated patients during the investigations was described. On the other hand, no positive effect of placebo on measurements of ESP and hemoglobin's levels of Crohn's disease patients was revealed.

The importance of use of psychotherapies for optimal outcomes during treatments of Crohn's disease is discussed.

Keywords—Crohn's disease, emotional disorders, placebo, gut microflora and blood composition

I. INTRODUCTION

THE most common condition during gastroenterology practice is functional gastrointestinal disorders (FGID) [17], [5]. As Drossmann noted, psychosocial factors in FGID concern to their effects on gut physiology; their modulation of the symptom experience; their influence on illness performance; their impact on outcome and the selection of the therapeutic approach and these factors are very important [5]. It is necessary to have the exact representation about psychotherapeutic "targets", which can be various types of individual response to illness and social deadadaptation in connection with various forms of illness for the extensive use of psychotherapeutic methods to reach more results during the treatment of gastrointestinal diseases.

Psychological supports are one of the important categories of therapy for FGID, which, can be viewed as a complex interaction of enteric neurochemical abnormalities with psychosocial and environmental factors. If psychosocial factors play no direct role in the diagnosis of most gastrointestinal diseases, psychosocial and socioeconomic factors modify the illness experience and influence the level of pain reporting, and use of medications.

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Generally, in clinical trials, placebos are considered to be control treatments for other treatments but without their specific activity. Recent discussions on placebo treatment in clinical trials suggest that objective effects of placebo may not really exist or, they may be considerably overestimated [11]. Reaction to stress and emotions may indeed play a role in some patients' perceptions of their illness (IBD symptoms), at least partly explaining the placebo response found in clinical trials. Patients having tried a variety of treatments and then enter a clinical trial of a new agent can have an idea that this treatment will be something different, what can makes progress [20]. Medical data supports also the relationship between stress and the immune system. According to Dr. Plevy, 20-30 percent of placebo taking patients with ulcerative colitis not only felt better, but showed evidence of healing of the intestinal lining being examined with endoscopy [20]. He found that the mucosa was actually healed. It's not discussed but there's a lot of literature about the release of neuro-psychiatric hormones that may have direct effects on the immune system and on inflammation. So it is real that the mind can have its effects on the immune system.

Taking into account the above mentioned data we aimed to evaluate emotional disorders of the Crohn's disease (CD) patients as well as their depression and anxiety levels in order to investigate the psychological aspects of this disease. Also we aimed to investigate the placebo effect on laboratory values, including hemoglobin, leukocyte count and ESP and gut commensal *E. coli* qualitative and quantitative changes of CD patients.

II. METHODS

Twenty-six volunteer CD patients were enrolled in our study for the patients' psychoemotional status before and after placebo treatment investigations from different hospitals of Armenia. Five of them were also involved in investigations of placebo in clinical analysis. None of the study participants had been treated with antibiotics, hormones, radiotherapy, or any other immunosuppressive or chemotherapeutic agents for at least 2-3 weeks before the investigation.

The Zung self-depression scale [19] have tested to assess the level of depression for investigated objects, and the Beck Anxiety Inventory (BAI) was developed to address the need for

an instrument that would reliably discriminate anxiety from depression while displaying convergent validity [2]. Except testing patients had been interviewed of their disease.

The questionnaires were used twice: before and after a month of placebo treatment.

Fecal samples were collected in sterile plastic bags and transported to laboratory on ice. Faecal material (1 g) was mixed with 9 ml of phosphate buffered saline (PBS) and vortexed for 2 min. The debris was removed by low-speed centrifugation (700xg, 5min) and the supernatant was serially diluted in PBS. The dilutions were plated on MacConkey agar for preliminary identification of *Enterobacteriaceae*, with further analysis using the selective media and conventional biochemical testing [8].

Taxonomically defined *E. coli* isolates were grown aerobically at 37°C in Luria-Bertani (LB) medium (10g tryptone; 5g yeast extract; 10g NaCl per litre; pH 7,5), solidified with 1.8% agar when necessary.

Blood cell analyses were done according to methodic [6] before placebo administration when the disease was in active phase and after a month of placebo administration.

Placebo was administered twice daily, for 30 consecutive days during the investigations.

III. RESULTS AND DISCUSSIONS

The symptoms of CD have been described since 1612; however, the disease identified in 1932 by Dr. Burrill Crohn and his two colleagues, Dr. Leon Ginzburg and Dr. Gordon D. Oppenheimer finally. CD is a chronic non-specific inflammatory disease, which can affect different segments of gastrointestinal tract comparing with other colitis. The disease often develops in the teenage years, though individuals in their 60s and 70s are also at increased risk. The exact origin of CD is not known yet, but the genetic, autoimmune and environmental versions are more considerable [9]. None evidence of CD to be caused by psychological factors, even relationship between psychological variables and CD suggested since 1949 [1], [4]. It has been shown that severe chronic stress can lead to increased inflammation [10], and a high incidence of psychopathology has been reported in CD patients [7], [10], [16].

As shown our investigations, CD has a very rare frequency of patients in Armenia (3 cases for 1000 000 people). Among twenty-six Armenian patients with CD the mean age of the patients was 47,6 years and we observed male predominance. Histogram of the age of patients showed the characteristic biphasic distribution with two peaks between 20 and 50 years and between 70 and 75 years. Coexisting disorders demonstrated in 10% patients. Only a patient had need of surgical treatment. 62% of patients were from Yerevan, others were from different regions of Armenia. The majority of CD cases are diagnosed in young people (20-50 years) with the predominance of male patients. Generally we noticed that the majority of CD patients were from Yerevan.

Depression and anxiety levels in Crohn's disease patients. The Zung self-depression scale is a short self-administered survey to quantify the depressed status of a patient. There are 20 items on the scale that rate the four common characteristics of depression - the pervasive effect, the physiological equivalents, other disturbances, and psychomotor activities.

There are ten positively worded and ten negatively worded questions. Each question is scored on a scale of 1-4 (a little of the time, some of the time, good part of the time, most of the time). The scores range from 25-100.

The BAI offers advantages for clinical and research purposes over existing self-report measures, which have not been shown to differentiate anxiety from depression adequately. The BAI scale consists of 21 items, each describing a common symptom of anxiety. The respondent is asked to rate how much he or she has been bothered by each symptom over the past week on a 4-point scale ranging from 0 to 3. The items are summed to obtain a total score that can range from 0 to 63.

The results of our investigations show that the studied CD patients were in different depression levels. We grouped the patients into 3 conventional groups: the patients with expression of low depression, patients with moderate depression, and patients with severe depression (Table I). Taking into account also the different anxiety levels of these patients, we grouped them into 9 subgroups finally (Table I).

As showed the results only a patient had severe depression (subgroup 9), and 46,2 % of all patients registered high anxiety (subgroups # 3, 6 and 9).

Anxiety levels in Crohn's disease patients with low depression (1, 2 & 3 subgroups). As the results have shown 34,6 % of patients gathered scores of low depression. However, they indicated that most of time they were more irritable than usual and the response to the statement "I feel useful and needed" was "little of time". The patients of this group had different anxiety levels, and the patients with moderate rate of anxiety composed 66,7% of them (subgroup 2) (Table I). Most patients of this group indicated on the statements "fear of dying", "fear of worst happening" as "bothering a lot".

Anxiety levels in Crohn's disease patients with moderate depression. The largest group of CD patients, composing about 61,5 % of all patients, had moderate level of depression (Table I). These patients also indicated on various fears.

Anxiety levels in Crohn's disease patients with severe depression. As we mentioned above, only a patient had a high score (75) of depression. He also gathered the highest anxiety scores. The patient differs from other 25 patients; he was diagnosed as having neurosis, besides CD.

All interviewed patients complained of the unpredictableness of the symptoms of the disease, which they considered as a depressing factor. Some young patients were eager to consider their illness as ulcerative colitis as they knew it may be cured but such auto-suggestion didn't help them to cope with the illness. During the investigation, we also noted differences between patients with favorable and unfavorable life conditions. The patients with unfavorable life conditions demonstrated high levels of depression and anxiety, and it's a fact that patients with CD need specific healthcare.

Placebo effect assessment. The results of our investigations on placebo effect for CD patients have shown the changes in emotional status of CD patients after the discontinuation of placebo administration (Fig. 1).

TABLE I DEPRESSION AND ANXIETY LEVELS IN CROHN'S DISEASE PATIENTS

Quantity of Patients	Patients Groups								
	Zung score of low depression (less or equal 49)			Zung score of moderate depression (between 50– 69)			Zung score of severe depression (more or equal 70)		
	1	2	3	4	5	6	7	8	9
	Beck score ≤21	Beck score 22-35	Beck score ≥ 36	Beck score ≤ 21	Beck score 22-35	Beck score ≥ 36	Beck score ≤21	Beck score 22-35	Beck score ≥ 36
Before placebo	2	6	1	1	10	5	0	0	1
After placebo	4	8	0	5	6	3	0	0	0

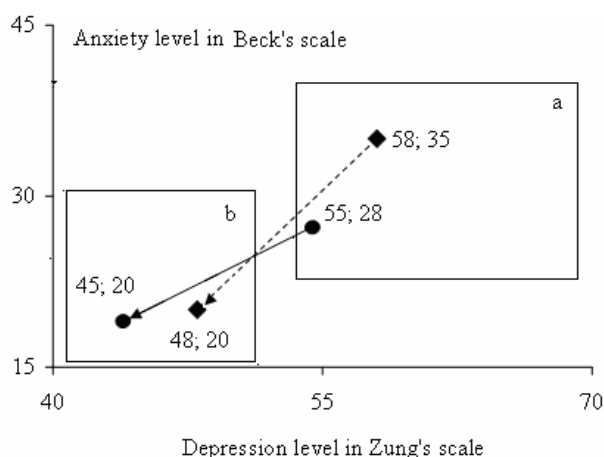


Fig. 1 Anxiety and depression levels of two CD patients: a) before placebo admission and b) taking placebo.

All investigated patients were sure that the “medicament” helps to decrease pain. At the same time, the quantity of patients both with low and moderate expression of depression, who also gathered high scores during the investigations on anxiety level - Beck” score above 36 was decreased (Table I). Emotional changes were obvious also for the patients from the groups of low level of depression. Two of patients gathered moderate scores for depression and anxiety before the placebo admission, and low scores after it (Fig. 1), and were ready for the continuing of treatment in clinics, despite they rejected it before.

The influence of placebo therapy on gut commensal lactose positive *E. coli* and on blood of patients. Recently the relation between gut microflora and CD disease is more being discussed [18], [15], [3].

In our preliminary study we have shown that the 70 % of our investigated patients have had dysbiosis in commensal lactose positive (CLP) *E. coli*. We aimed to investigate the impact of placebo therapy on CLP *E. coli* in gut microflora of CD patients after placebo therapy. On the other hand, taking into account the changes in blood during the CD [3], [14], the laboratory measurements on hemoglobin, erythrocytes’ and

leucocytes’ counts, and erythrocyte sedimentation rate (ESR) were done during our next cycle of investigations.

The results of gut microflora investigations did not found any significant effects of placebo on qualitative and quantitative changes of CLP *E. coli* in gut microflora. At the same time, the measurements in blood confirmed the results of literature data [3]: decreasing in hemoglobin’s and erythrocytes’ counts, increasing in leucocytes count and ESR rate (Table II). However, as the results shown, blood composition remained almost the same after placebo (Table II).

TABLE II THE INFLUENCE OF PLACEBO THERAPY ON BLOOD OF CROHN'S DISEASE PATIENTS

Subjects	Hemoglobin (g/l)	Erythrocyte (mln/1mm ³ n)	Leukocyte (1000 in 1mm ³)	ESR (mm/t)
**Norm	120-160	3,9-5	4-9	2-15
Patient* #1 Before	70,3	2,2	14	43,4
After	70,2	2,1	14,4	43
Patient* #2 Before	92	2,9	11,3	17
After	92,2	2,9	11,2	17
Patient* #3 Before	76,9	2,4	9,2	61,2
After	77	2,3	9,1	59,9
Patient* #4 Before	84	2,8	9,2	27,1
After	84	2,9	9,2	27
Patient* #5 Before	86	2,5	17	42,2
After	86,1	2,5	17	42,1

* Patients before and after placebo treatment

** The norm for male and female; <http://wikipedia.org/>

Thus, we did not detect a significant effect of placebo on both gut microflora and blood composition of CD patients; however we found changes in psychological status of the patients. Our results indicate that placebo treatments in CD may have effects on psychological status more easily and strongly than on clinical bacteriological and blood analysis.

IV. CONCLUSION

Depressive symptoms are an independent modifiable risk factor in many chronic diseases. And because the depression and medical illness commonly coexist and exacerbates one another, and in some disorders (e.g. chronic pain) appear to share biologic pathways, patients with any chronic condition should be screened for depression as part of routine care and both conditions treated for optimal outcomes. The successful management of depression is an important factor of how psychotherapies can affect the outcome of not only quality of life (QOL) for patients, but also medical illness.

The results of our investigations show the significant levels for depression and anxiety in Armenian CD patients, despite the fact, that none of investigated patients was in high level of depression. It has been shown the effect of placebo in the

treatment of CD and the need of psychotherapy for further research. The known "Powerful Placebo" really can make effects on the psychological status of the patients, their perception on illness but no therapeutic effect on the biological status of the organism in CD was shown in our investigation. [20] <http://www.ccfa.org/research/placebo>

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