Celecoxib added to mood stabilizer for treating acute mania: A randomized, double -blind, placebo-controlled trial

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Research

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Abstract

Background: Inflammatory processes in the brain contribute to the aetiopathogenesis of acute mania. Cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib, reduce the production of pro-inflammatory cytokines. The purpose of the present investigation was to assess the efficacy of celecoxib in the treatment of ACUTE MANIA.

Methods: We conducted double-blind, placebo-controlled trial at the Specialty in-patient Clinic of Ibne Sina Hospital [Mashhad University of Medical Sciences, Iran] during March 2014 to August 2014. The study involved 58 patients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for ACUTE MANIA screening to participate in the trial were used for the study. 23 patients were assigned to a study group and were given valprovate sodium 200 mg /BD plus celecoxib 400 mg/day (200 mg BID). The control group included 22 patients who were given valprovate sodium 200 mg /BD plus placebo. Patients were assessed by yung mania rating scale (YMRS) at baseline 0, after 9, 18, and 28 days after the medication started. Data were analyzed by using Statistical Package for Social Sciences (SPSS) 11.5., two-way repeated measures analysis of variance, Fisher's exact test, and T-Test. $P \leq 0.05$ was considered to be statistically significant.

Conclusion: This study suggested that celecoxib can be an effective adjuvant agent in management of patients with ACUTE MANIA and anti-inflammatory therapies should further be investigated in this patients.

Trial registration: Iran clinical trial register: IRCT20200306046708N1 Registered on 2 October 2019.

Background

In recent years, an increasing volume of evidence has shown the role of the inflammatory processes in the pathophysiology of psychiatric disorders, including schizophrenia, depression, and bipolar disorder (1-4)Bipolar disorder, characterized by recurrent episodes of mania, mixed and depression, is the most common major psychiatric disorder that is reported to have a prevalence of 0.5-4.3% in a recent systematic review of patients referred to the first level of care(5) and this prevalence could be higher in secondary and tertiary care levels. Also, according to the recent investigation of world Health organization that was conducted in eleven countries, the prevalence of bipolar disorder have been reported 2.4%(5, 6). As noted, many hypotheses have been proposed about the immunologic-inflammatory processes as part of the pathophysiology of bipolar disorder, as well as different mechanisms of action based on the pathophysiology of mood stabilizers (7, 8) and it has recently been proposed that it may be better to view bipolar disorder as a multi-system inflammatory disease (9)Regarding manic episodes, also various evidence has shown the activation of the inflammatory process. For instance, in two recent studies, inflammatory immune system was significantly more active in patients with mania than the control group (10, 11) and in one of these studies, increase in the immune activity was a predictor of re-hospitalization of patients (11). The results of a recent meta-analysis provided evidence of increased pro-inflammatory,

anti-inflammatory and regulatory cytokines (12). Blood levels of IL6 in acute phase of mania was higher than the control group and compared to the period of remission of symptoms and manic patients with high levels of interferon-gamma was associated with more severe clinical symptoms (based on the Yang mania scale(13). It is also known that mood stabilizers such as lithium, sodium valproate and carbamazepine down-regulate the inflammatory pathways in rat's brain and this effect may contribute to their efficacy in bipolar disorder (14-16). The therapeutic effects of IL6 receptor antagonists have been also proposed in bipolar disorders (17). Celecoxib is an anti-inflammatory drug and selective cox-2 inhibitor. Considering the role of cox-2 enzyme in the synthesis of prostaglandin E2 and that the prostaglandin stimulates biosynthesis of pro-inflammatory cytokines such as IL6 (18), celecoxib stop this process by inhibition of cox-2 enzyme. Despite increase in the number and variety of medications, a considerable number of patients in the acute phase of mania does not respond sufficiently(19, 20). Thus, combined treatment strategies of mood stabilizers with augmentation of atypical antipsychotics in the treatment of acute mania is commonly used. But regarding the widespread side effects of mood stabilizers (21) and the considerable prevalence of metabolic syndrome among bipolar patients who receive atypical antipsychotics (22) and with regard to the role of the inflammatory processes in this disorder, the anti-inflammatory drug “celecoxib” with a favorable profile of side effects without gastrointestinal adverse effects of other NSAIDs (23, 24)can be added as a potentially effective and safe option to the treatment of acute mania.

Therefore, in this study, we intended to evaluate the effectiveness of Celecoxib as adjunctive therapy in treatment of acute mania.

Methods/design

Study design:

This study is a 4-week, Randomized double blind placebo-controlled clinical trial launched at the Specialty in-patient Clinic of Ibne Sina Hospital [Mashhad University of Medical Sciences, Iran] during March 2014 to August 2014.

Participants:

58 Patients were considered for participation in the project if they met Diagnostic and Statistical Manual of Mental Disorders (DSM V) criteria for diagnosis of acute mania(25). The diagnosis was confirmed by a psychiatrist based on structured interview and a minimum score of 20 or above on the Young mania rating scale (YMRS). The patients did not receive any psychotrophic medications, such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), or monoamine oxide inhibitors for 4 weeks preceding entry into the trial. Patients were excluded from the study if they have suffered from known autoimmune disease and diagnosed of infectious diseases for at least 4 weeks prior to the beginning of the study. Also, patients were excluded if they met the criteria for major depressive disorder,

eating disorders, personality disorders, mental retardation, mental disorder due to general medical condition, substance dependence or abuse in the previous three months, history of seizures that would contraindicate the use of the study's medication and receiving electroconvulsive therapy (ECT) and peptic ulcers or a history of gastrointestinal bleeding, and use of any medications identified as contra-indicated with COX-2 inhibitors. Patients were prohibited from initiating psychotherapy after entry into the study. Pregnant women or women not using medically accepted means of birth control were excluded. Patients were required to be free of all psychotropic medications for at least 4 weeks before the study entry.

The protocol was approved by the IRB of Mashhad University of Medical Sciences. The patients and their legally authorized representative provided informed consent in accordance with the procedures outlined by the local IRB and were informed that they could withdraw from the trial at any time. The trial was performed in accordance with the Declaration of Helsinki and subsequent revisions (26). The trial was registered in Iran: IRCT20200306046708N1

Interventions:

The investigator was provided with a sealed randomization code for each available medication number. Blinding was to be broken only if the patient's trial medication would affect specific emergency treatment. Patients were randomized to receive celecoxib or placebo in a 1:1 ratio using a computer-generated code. Patients were randomly given routine treatment for mania plus celecoxib 400 mg/day (200 mg bid) (morning and evening) and routine treatment plus placebo for a 4-week, double-blind (participants, care providers, those assessing outcomes), placebo controlled study. Five patients dropped out over the trial . Three patients from the celecoxib group left the trial due to personal reasons unknown to the authors. One of the patients in the placebo group withdrew from the study due to vomiting and another patient discontinued the trial, because of early discharge

Outcome:

Patients were assessed with the YMRS at baseline (0), and 9, 18, and 28 day after the start of the treatment(3). Examinations of the patients during the treatment period was performed by a trained psychiatrist trained in the use of YMRS. There was more than 50% reduction in YMRS scores as compared to the baseline, as a response to treatment.

Side effects

Side effects were systematically recorded althrough the study and were assessed using a checklist administered by a resident psychiatrist at baseline and 9, 18, and 28 days after the start of treatment.

Statistical analysis

A two-way repeated measures analysis of variance (time-treatment interaction) was used. The two groups as a between-subjects factor (group) and 4 weekly measurements during treatment as the within-subjects factor (time) were considered; this was done for YMRS total scores. In order for interaction to be eliminated, then baseline score was considered as the covariate in the analysis. The two groups at baseline were compared and the outcome of the two groups at 9,18, and 28 days from the start of trial was also compared using an unpaired student's t-test with a two-sided P value. The results are presented as mean±standard deviation (SD). Data were analyzed using commercially available statistical packages (SPSS 11.5. Chicago, IL). In order to compare the demographic data and frequency of side effects between the protocols, Fisher's exact test (two-sided) was performed. All statistical tests were two-sided and were considered statistically significant at $P \leq 0.05$.

Patients with an informed consent entered the study and stated that they could withdraw from the study whenever they did not

Results

Demographic characteristics

Patients (58) were initially examined, among whom4 did not fall within the inclusion criteria and 9 were eliminated due to the exclusion criteria. Therefore, 45 patients were enrolled in the study; 23 were assigned to the celecoxib group and 22 were assigned to the placebo group. The characteristics of the two study groups are summarized in Table 1.

Table 1

Comparing the Characteristics of patients in the two groups

	routine treatment +celecoxib group	routine treatment +pleacebo group	P-Value
**sex	Female: 9(45%) Male: 11(55%)	Female: 15(75%) Male: 5(25%)	0.10
*Age	30.60±8.28	37.90±10.59	0.01
*Marital status	Married: 12(60%) Single: 8(40%)	Married: 12(60%) Single: 8(40%)	1.00
**Number of episode	2.05±1.39	1.70±0.92	0.50
*Past psychiatric history	Yes: 2(10%) No: 18(90%)	Yes: 8(40%) No: 12(60%)	0.02
*Past medical history	Yes: 15(75%) No: 5(25%)	Yes: 13(65%) No: 7(35%)	0.49
*Family history	Yes: 11(55%) No: 9(45%)	Yes: 9(45%) No: 11(55%)	0.75
*: frequency (precent) **: mean ±SD			

There were no statistically significant differences between the groups regarding number of episode.sex, marital status, past medical history and family history. P value ≥0.05

40 patients completed the 4-week trial, while 5 patients discontinued the trial.

Three patients from the celecoxib group left the trial due to personal reasons unknown to the authors. One of the patients in the placebo group withdrew from the study due to vomiting and another patient discontinued the trial, because of early discharge (Figure 1)

Efficacy: ROUTNE TREATMENT +Celecoxib vs. ROUTNE TREATMENT + Placebo

There were no significant differences between the two groups at week 0 (baseline) on the young mania rating scale (t: 0.29, df:38, P:0.76). Table 2

Table 2

mean ±SD in two groups in the course of study

	group	N	Mean±SD	Std. Error Mean	P value
Day0	patient	20	37.1500±6.9	1.56487	0.769
	placebo	20	36.5500±5.70	1.28856	
Day9	patient	20	30.7500±7.99	1.78867	0.743
	placebo	20	29.8500±9.20	2.05871	
Day18	patient	20	25.9500±8.19	1.83314	0.899
	placebo	20	26.3000±9.17	2.05208	
Day28	patient	20	21.1000±7.48	1.67473	0.258
	placebo	20	24.0500±8.72	1.95000	

Precentage response was a significant difference at week 4 as compared to the baseline. In the patient group 50 % in patient group respose to treatment vs 20 % in placebo group response to celecoxib: P: 0.04. (Figue 2)

The difference between the two treatments was not significant as shown by the effect of the group; the between-subjects factor (Greenhouse–Geisser correction; df:1, F:0.38, P:0.84). The behavior of the two treatments was similar across time (groups-by-time interaction, Greenhouse–Geisser correction) F:8.17, df:1, P:0.001.figure 3

Figure show the patient group had a clinical greater reduction in YMRS scores but were not statistically significant different.

We considered Age and numberof episode as a cofonding factor but the result were no changes

Effect size in this study was from 36.8 (CI95%:34.7-38.9) to 22.5 (CI95%:19.9-25.1)

Clinical complications and side effects

About 5 category of side effects were observed over the period of the trial. The difference between the celecoxib and placebo groups in the frequency of side effects was not significant. In this study, the disturbances were examined and there was no significant difference between the two groups in terms of these disturbances. Table2

Table 2

clinical complication and side effect in both group

	Routine treatment +celecoxib group	Routine treatment +pleacebo group	P-value
Headache	2(10%)	3(15%)	0.98
GI disturbance	4(20%)	2(10%)	0.66
Decrease or increase appetite	2(10%)	2(10%)	0.99
Other(Anxiety, Sexual dysfunction)	2(10%)	1(5%)	0.98
Respiratory	1(5%)	1(5%)	0.99

Discussion

To the best of our knowledge, this study is the second clinical 4-week study suggesting the potential use of celecoxib as adjuvant to routine therapy in the treatment of acute mania.

It has been suggested that the clinical efficacy of routine treatments may be enhanced by concurrent administration of agents with anti-inflammatory effects, such as celecoxib(20). There is no doubt that routine treatment are effective in the treatment of acute mania (24) As expected in both groups of patients, during the 4 weeks of treatment, a significant improvement was shown on YMRS. The results of a recent meta-analysis provided evidence of increased pro-inflammatory, anti-inflammatory and regulatory cytokines (12). Blood levels of IL6 in acute phase of mania was higher than the control group and compared to the period of remission of symptoms and manic patients with high levels of interferon-gamma was associated with more severe clinical symptoms (based on the Yang mania scale)(13). In agreement with the hypothesis of this study, the celecoxib group had significantly greater improvement over a 4-week trial.

Because of there was one similar clinical trial research study to evaluate the efficacy of celecoxib in alleviating symptoms of acute mania so the closest research was used

Arabzadeh et al in 2015 were done the efficacy of Celecoxib adjunctive therapy for acute bipolar mania :A significant difference was observed in the change in YMRS scores at the end of study that this result was similar with our study (27)

The results of this study provide support for the enhancement of the treatment by concurrent with celecoxib (25) . Indeed, this study shows that celecoxib as an adjuvant agent for acute mania produces improved outcomes in the form of greater reductions of mania, better response, and higher remission rate like other study The results of this study provide statistically significant support for the enhancement of

the antidepressant effect of the SSRI by concurrent treatment with celecoxib (25) . It has been suggested that celecoxib is a potential adjunctive treatment strategy for OCD in a trial reported by Sayyah et al(28)

Therapy with 400 mg/day of celecoxib was well tolerated and no clinically important side effects were observed. Clinical characteristics of the patients, such as sex,number of episode, did not differ between the groups and cannot explain the differences in the therapeutic outcome.

Limitations of this study, including the relatively small sample size and only a fixed dose of celecoxib, should be taken into account and this shows the need for further research. In addition, as with all NSAIDs, there is a risk of stomach problems when taking celecoxib. Although this is a very rare side effect with celecoxib. It is still possible and the risk increases with prolonged use

Abbreviations

Diagnostic and Statistical Manual of Mental Disorders (DSM-V)

Yung mania rating scale (YMRS)

Statistical Package for Social Sciences (SPSS)

Declarations

Acknowledgment:

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Authors' Contribution:

Farhad Faridhosseini: study concept and design, and writing the article; Najmeh Shahini: data collection, writing the article, and final approval of the article; Ali talaei: writing the article, data collection, and literature review; mahbobeh eslamzadeh and samira ahrari: data collection , and majid khadem: statistical analysis , meysam pourgholamicritical revision of the article, provision of the materials,

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Mashhad university of Medical sciences. Prior to participation, all subjects provide written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

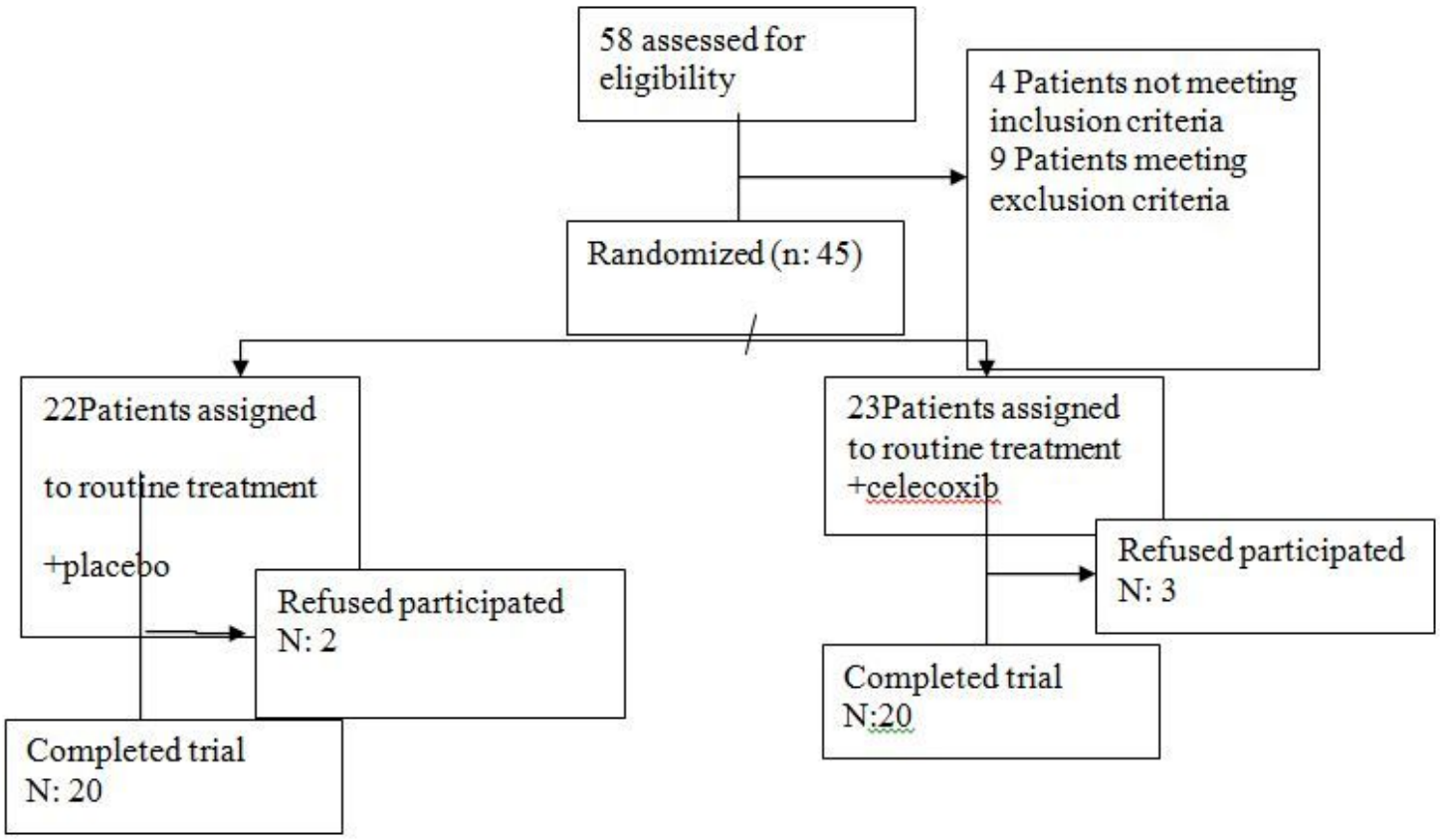

Figure 1

CONSORT diagram showing the disposition of all subjects screened for the study

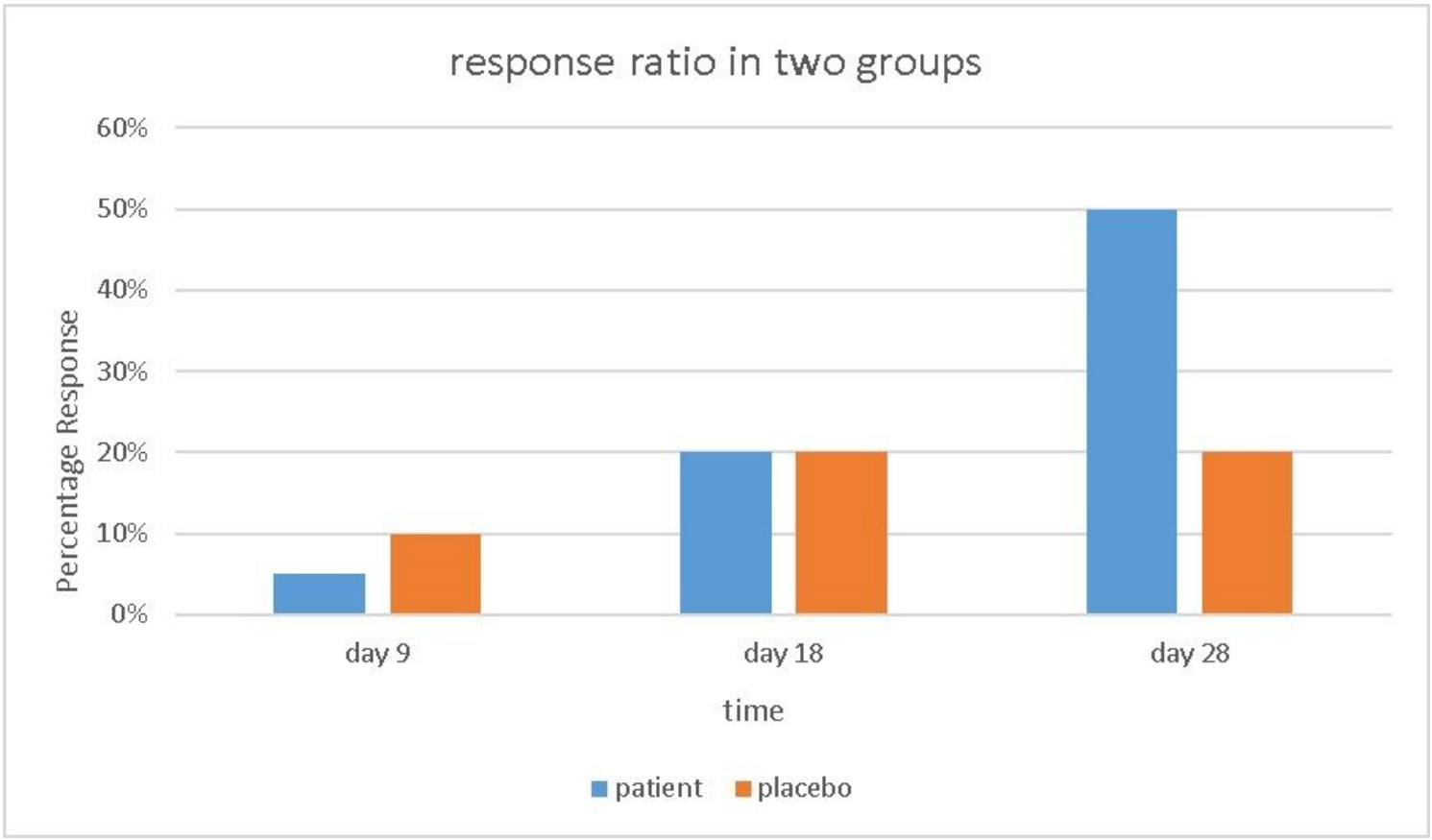

Figure 2

response ratio in two groups

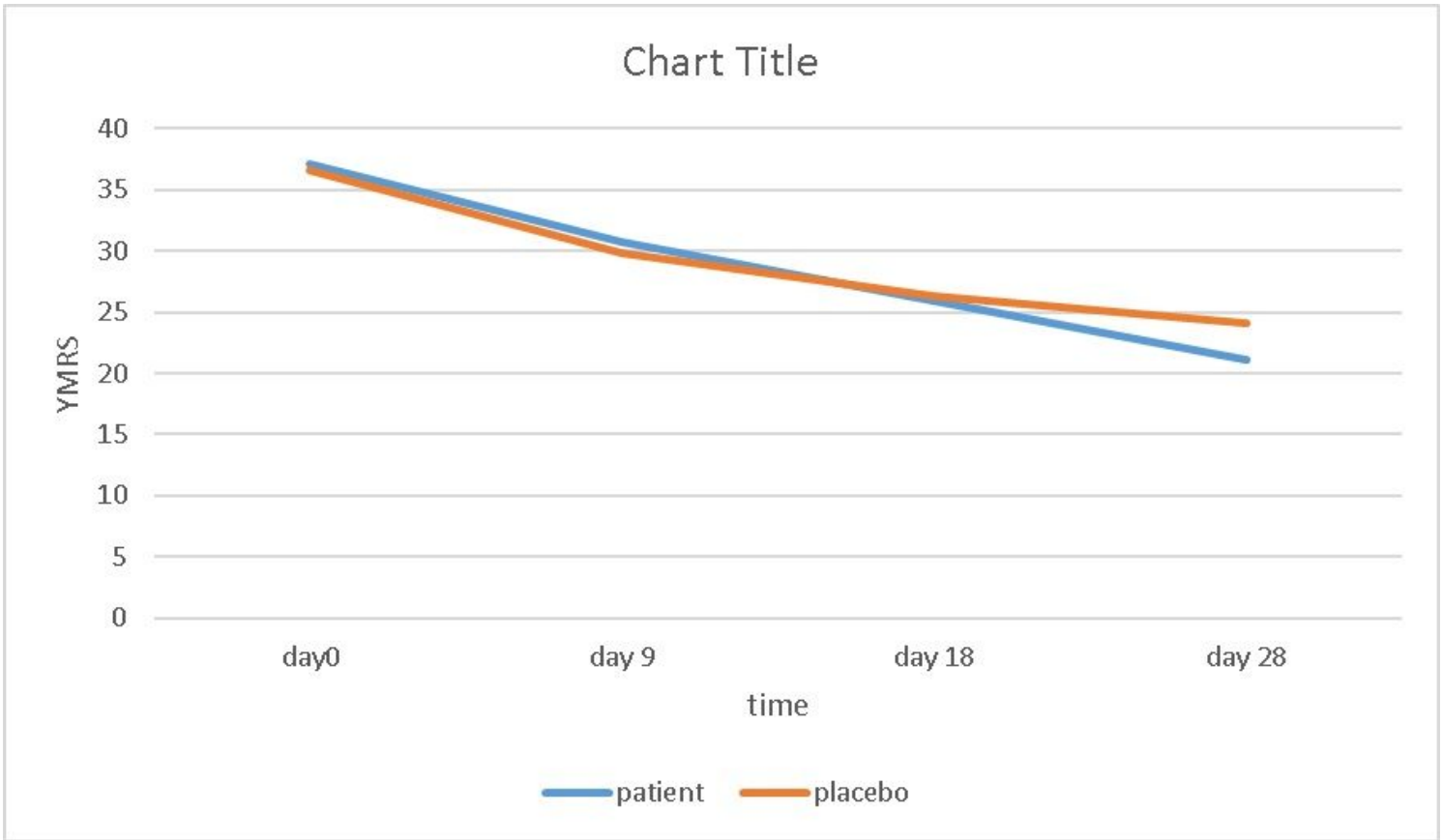

Figure 3

the Plot of the two groups over time

Supplementary Files

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