

Efficacy and Safety of Levamisole Treatment in Clinical Presentations of Patients With COVID-19: A Double-Blind, Randomized, Controlled Trial

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Abstract

Background

In late December 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was identified as the cause of a series of pneumonia cases in China. Levamisole can show clinical benefits in management of COVID-19 by its immunomodulatory effect, but effect in clinical status of patients is unknown. We evaluated the efficacy of levamisole on clinical status of patients with COVID-19 on days 3, 7, and 14.

Methods

This prospective, double-blind, randomized, and controlled clinical trial was performed in 18- to 60-year-old patients with confirmed COVID-19 from late April 2020 to mid-August 2020. Patients were randomly assigned to two groups to receive a 5-day course of levamisole or placebo in combination with routine care.

Results

50 patients with COVID-19 were analyzed: 25 patients were in each group. More than half of the infected patients was men too (60%). On days 3 and 14, patients in Levamisole group had significantly better cough status distribution compared with Placebo ($P=0.034$ and 0.005 , respectively). The difference in fever status on days 1, 3, 7, and 14 between two groups was not statistically significant ($P > 0.05$). There was significant differences between two groups in dyspnea over a median follow-up of 7th ($P=0.015$) and 14th ($P=0.010$) days after receiving the interventions.

Conclusion

The results of the current study have overall demonstrated that patients receiving levamisole had significantly higher odds of having a better clinical status including cough and Dyspnea on day 14 than those receiving placebo, but with an effect-size of unsure clinical importance. The difference in the distribution of fever on days 3, 7, and 14 between two groups was not significant, suggesting that levamisole can efficiently improve the most clinical status of patients with COVID-19 infectious compared to placebo.

Trial registration

The trial was registered as IRCT20190810044500N7 (19/09/2020).

Background

In late December 2019, a novel flu-like human coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 or COVID-19), was identified as the cause of a series of pneumonia cases in

Wuhan, Hubei Province in China (1, 2). The outbreak has rapidly spread, resulting in an epidemic throughout China, as well as other countries around the world. On March 12th 2020, the World Health Organization (WHO) announced the outbreak of COVID-19 as a pandemic (3).

Prevalent symptoms at the beginning of the disease were fever, cough, myalgia, chills, dyspnea and pneumonia. Less common Symptoms include humor, headache, hemoptysis and diarrhea (4). COVID-19 also made troubles such as acute respiratory distress syndrome, RNAemia, acute heart damage, and secondary infection in patients (5). In patients with CoVID-19, the number of white blood cells can vary. Leukopenia, leukocytosis, and lymphopenia are reported problems, although lymphopenia is the most common of all. It is notable that the increased levels of aminotransferase have also been presented in some COVID-19 patients (6).

Because the SARS-CoV and SARS-CoV-2 are very similar, the biochemical interactions and the pathogenesis are likely to be similar (7). The delivery of virus particles into the host cell needs the virus to bind to the angiotensin-converting enzyme 2 (ACE-2) receptors in the type II pneumocytes in the lungs and form a viral endosome through a clathrin-mediated endocytosis (8–10). When the SARS spike protein, a homotrimer of S proteins, binds to the type I integral membrane receptor ACE-2, a pH-independent endocytotic reaction occurs (11, 12). When internalized, the fusion of virus with lysosomes occurs depending on the low endosomal and lysosomal pH (13). Endosomal proteases cathepsin B and L splitted S-glycoprotein into S1 and S2 domains that S2 causes membrane fusion (14). Cathepsin B and L activity is prevented when endosomal pH increased. Viral entrance into the cytoplasm is also dependent on an acidic endosomal pH (15). After releasing the virus into the cytosol, a viral RNA-dependent RNA polymerase is utilized to run the viral replication, exocytosis of virions, and spread to neighboring cells (16). Binding of the SARS-CoV to the ACE-2 receptors triggers an inflammation cascade in the lower respiratory tract. Infection of human cells by SARS-CoV causes inflammatory cascade by virus-infected antigen-presenting cells (APCs). APCs presenting the outsider antigen to CD4+-T-helper (Th1) cells, and releasing interleukin-12 to further motivate the Th1 cell that stimulate B-cells to produce antigen-specific antibodies (17). Although these mechanisms may proceed differently in the novel SARS-CoV-2, the intermediate host of SARS-CoV2 is not known yet. However, few approved prophylactic or therapeutic drugs for COVID-19 diseases are available. Some therapeutic agents are used off-label, alone or in combination. There are several possible suggestions to treat this disease: (1) Inhibitors of viral replication such as Ribavirin, Remdesivir, Favipiravir, Emtricitabine/tenofovir, (2) Inhibitors of viral proteases such as Lopinavir/ritonavir (LPV/r), Darunavir, Danoprevir, Atazanavir, Cobicistat, Noscipine, (3) Inhibitors of viral entry to the host cell such as Chloroquine/hydroxychloroquine, Arbidol, Baricitinib, Ruxolitinib, Recombinant human ACE2, Bromhexine, (4) Immune enhancement agents such as Interferon-alpha (α)-1b/2b, Interferon-beta (β), Programmed cell death 1 (PD-1) blocking antibody, Levamisole, (5) Immunomodulating agents such as Intravenous immunoglobulin, Fingolimod, Thalidomide, (6) Immunosuppressive agents such as Glucocorticoids, (7) Anti-inflammatory agents such as Tocilizumab, Sarilumab, Siltuximab, Eculizumab, Tetrandrine, NSAIDs, (8) Pulmonary vaso-effectors such as Nitric oxide, Sildenafil, Aviptadil, Bevacizumab, Losartan, (9) and other drugs such as Carrimycin and Mepolizumab (18).

Chloroquine (CQ) sulfate and Chloroquine phosphate are classified as anti-malarial drugs. Hydroxychloroquine (HCQ) is used for both anti-malarial activity and for autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus as well (19). The suggested mechanism for anti-viral activity of CQ in SARS-CoV2 is to target low endosomal pH (acidification) required for virus cell fusion, and to interfere with cellular receptors glycosylation. CQ/HCQ also targets the entrance of extracellular zinc to intracellular lysosomes where it interferes with RNA-dependent RNA polymerase activity and replication of coronavirus (20). The molecular mechanism of CQ/HCQ is to inhibit the cytokine storm by suppressing activation of T cells (21). HCQ has shown more potency than CQ against SARS-CoV2, in vitro (22). Gastrointestinal effects, like vomiting and diarrhea, are the most common adverse effects of HCQ and CQ (21). Other less common side effects including muscular weakness, diplopia, dyskinesia, seizures, myasthenic syndrome, sleeplessness, agitation, psychosis, depression, anxiety, and confusion have also been shown (23). Retinopathy and cardiomyopathy are the severe side effects caused by using the drug for a long time (21).

Levamisole as a synthetic low molecular weight compound belonging to the anti-helminthic class of medications can enhance the cellular immunity based on dosage and timing of its clinical administration (24, 25). A previous study had reported that a combination of levamisole and ascorbic acid therapy in-vitro can reverse the depressed helper/inducer subpopulation of lymphocyte in measles virus. The abnormality in lymphocytes could be reproduced by Levamisole treating of normal lymphocytes with measles virus in-vitro. Thus, this compound could also be considered as a suggestive drug for COVID-19 treatment (25, 26).

Methods

This prospective, double-blind, randomized, and controlled clinical trial was performed in 18- to 60-year-old patients with COVID-19 based on clinical signs and radiological manifestations of COVID-19 CT scan for 4 months from late April 2020 to mid-August 2020. Patients were randomly assigned to two groups of 25 controls or intervention by permutation block method.

Sample size

In previous sources, there is no complete study that can be used to calculate the sample size, but if we want to reduce the overall improvement score obtained from the patient's symptoms by 2 points and taking into account the maximum standard deviation of this score by 2.5, 25 patients are required for each group.

Exclusion and inclusion criteria

Patients were included in the study if they met the following criteria: Age 18 to 60 years; Detection of COVID-19 in the last 24 hours; Female patients should not be exposed to pregnancy and should not become pregnant until 30 days after the end of the study; Do not take levamisole during the last five days (due to the half-life of the drug 16 hours); Patients suspected of covid-19 based on clinical signs and

manifestations of CT scan and outpatient candidate; Do not take drugs outside the protocol and no underlying diseases such as diabetes and high blood pressure. Patients were not included in this study if they met the following criteria: Patients hospitalized; Patients with hemodynamic instability; History of cirrhosis, hepatitis and severe liver disease, severe renal failure (creatinine clearance less than 30 ml / min); Patients taking levamisole for other uses such as parasitic infections; Patients with a history of allergic reaction or allergy to levamisole; Patients receiving chemotherapy for cancer and Pregnancy and lactation.

Intervention

Patients were randomly divided into two intervention groups including levamisole with routine care or placebo with routine care by permutation block method. Routine care consisting of hydroxychloroquine 200 mg twice daily for 5 days with acetaminophen 500 mg tablets was used to control fever and diphenhydramine syrup 10 cc every 8 hours to control cough. Patients in the intervention group took roudarou levamisole 50 mg orally three times a day for three days in addition to routine care. Patients in the control group received routine care and placebo (Placebo was prepared in the Pharmaceutics Laboratory of Shahid Sadoughi School of Pharmacy, Yazd).

Measurements

Demographic information, telephone numbers and initial symptoms of patients were first recorded in the prepared questionnaire. Warning signs were explained to patients for re-referral and a pamphlet containing the contents was handed to them. Patients were contacted on the third and seventh days and were asked about their symptoms according to the questionnaire. Other questions include the use of acetaminophen to reduce fever, reduce dyspnea by asking the extent of dyspnea and its relationship to the level of activity, and check cough with the question of reducing cough, not changing cough and increasing cough, whether he needed to see again or not and whether the patient needed hospitalization or not.

Statistical analysis

After collecting the completed checklist, the data were coded and entered into SPSS statistical software version 20 and descriptive data were presented using means, standard deviation, frequency and percentage in the form of tables and graphs. Before analyzing the data, quantitative variables in terms of normality were examined through Kolmogorov-Smirnov analysis.

If the data were normal, t-test and paired t-test were used to compare the improvement between the two treatment methods and over time. We used chi-square test and Fisher's exact test to compare qualitative variables. If the data are not normal, non-parametric equivalent Friedman tests will be used. Significance level was considered 0.05.

Results

Patients' characteristics

Between April 12, 2020, and August 2, 2020, 59 patients were screened, of whom 50 were eligible. 25 patients were assigned to receive Levamisole along with the routine care and 25 to receive placebo and routine care. The mean (\pm SD) age of the patients in this study was 36.68 ± 13.33 years, and 40% of the patients were female. There were no important differences in demographic characteristics between groups. Patients in the two groups were balanced in baseline demographics characteristics (Table 1).

Table 1
Patients Demographic Data

Characteristics	Placebo/Routine Care	Levamisole/ Routine Care	Total
Gender	N (%)	N (%)	N (%)
Male	13 (52.0)	17 (68.0%)	30 (60.0%)
Female	12 (48.0)	8 (32.0%)	20 (40.0%)
Age			
18–29	7 (28.0%)	11 (44.0%)	18 (36.0%)
30–39	7 (28.0%)	8 (32.0%)	15 (30.0%)
40–49	1 (4.0)	4 (16.0%)	5 (10.0%)
50–60	10 (40.0)	2 (8.0%)	12 (24.0%)
Weight			
20–40	2 (8.0)	0 (0.0)	2 (4.0)
40–60	5 (20.0)	3 (12.0)	8 (16.0)
60–80	14 (56.0)	15 (60.0)	29 (58.0)
> 80	4 (16.0)	7 (28.0)	11 (22.0)
Marital status			
Single	6 (24.0)	6 (24.0)	12 (24.0)
Married	19 (76.0)	19 (76.0)	38 (76.0)
Smoking			
Yes	2 (8.0)	4 (16.0)	6 (12.0)
No	23 (92.0)	21 (84.0)	44 (88.0)
N: Number.			

Of 59 patients who consented and were assessed for eligibility, 52 underwent randomization and began the study: 27 entered to levamisole/routine care group and 25 patients continued routine care with placebo (Fig. 1). Of these 52 patients, two patients withdrew from the study, and 50 patients completed it. A CONSORT flow diagram of the study is presented in Fig. 1.

Clinical Improvement during Levamisole Treatment

On days 3 and 14, patients randomized to the levamisole/routine care group had significantly better cough status distribution compared with those randomized to routine care ($P = 0.034$ and 0.005 , respectively). The difference in fever status on days 1, 3, 7, and 14 between the levamisole/routine care and placebo/routine care groups was not statistically significant ($P > 0.05$). There was significant differences between two groups in dyspnea over a median follow-up of 7th ($P = 0.015$) and 14th ($P = 0.010$) days after receiving the interventions that indicating significant improvement in levamisole/routine care group compared to placebo/routine care. Individual patients' clinical improvement in placebo/routine care group compared with levamisole/ routine care is shown on Table 2 in details. Parameters of headache, weakness, dizziness, myalgia and nausea were also assessed on days 1, 3, 7 and 14, which showed no significant difference in both the baseline and during treatment. Among the patients, only one patient needed to be hospitalized, which belonged to the placebo/routine care group and none of the patients died during or after treatment. No adverse effects were reported by any patient in either group.

Table 2
The Most Common Patients' Clinical Status on Study Days 1, 3, 7, and 14

Clinical Presentation	Placebo/Routine Care	Levamisole/ Routine Care	P value
	N (%)	N (%)	
Fever			
Day 1	20 (80.0)	24 (96.0)	0.189
Day 3	20 (80.0)	24 (96.0)	0.189
Day 7	3 (12.0)	0 (0.0)	0.235
Day 14	0 (0.0)	0 (0.0)	> 0.05
Cough			
Day 1	17 (68.0)	22 (88.0)	0.088
Day 3	17 (68.0)	23 (92.0)	0.034
Day 7	17 (68.0)	15 (60.0)	0.556
Day 14	9 (36.0)	1 (4.0)	0.005
Shortness of breath			
Day 1	13 (52.0)	14 (56.0)	0.777
Day 3	13 (52.0)	14 (56.0)	0.777
Day 7	12 (48.0)	4 (16.0)	0.015
Day 14	0 (0.0)	7 (28.0)	0.010

As acetaminophen is the first drug of choice for fever and pain management in patients suffering with COVID-19, acetaminophen requirement was evaluated in both groups. There were no significant differences between two groups in acetaminophen requirement, see Table 3.

Table 3
Acetaminophen Requirement in Patients Suffering with COVID-19

Dose of Acetaminophen	HCQ / placebo	HCQ / Levamisole	Total
	N (%)	N (%)	N (%)
Yes	12 (48.0)	10 (40.0)	22 (44.0)
500 mg tds for 2 days	1 (4.0)	0 (0.0)	1 (2.0)
500 mg tds for 3 days	3 (12.0)	8 (32.0)	11 (22.0)
500 mg tds for 8 days	1 (4.0)	0 (0.0)	1 (2.0)
500 mg tds for 10 days	1 (4.0)	0 (0.0)	1 (2.0)
500 mg tds for a week	5 (20.0)	2 (8.0)	7 (14.0)
500 mg tds for 2 weeks	1 (4.0)	0 (0.0)	1 (2.0)
No	13 (52.0)	15 (60.0)	28 (56.0)

Discussion

The present study is a randomized controlled clinical trial evaluating the effectiveness of levamisole in combination with routine care in patients suffering with COVID-19. The results of the current study have overall demonstrated that patients in levamisole/routine care group had significantly higher odds of having a better clinical status including cough and Dyspnea on day 14 than those receiving placebo/routine care, but with an effect-size of unsure clinical importance. The difference in the distribution of fever on days 3, 7, and 14 between two groups was not significant.

Nowadays the coronavirus COVID-19 pandemic is a global dilemma. Since the main pathogenic mechanism of the disease is unclear, many drugs have been evaluated in an attempt to relieve the symptoms (27). One of the suggestive agents used for systemic treatment of COVID-19 is levamisole because of its wide variety of immunological effects including regulation of neutrophils, macrophages, and T-cell activity. It also modulates the human interferon (IFNs), interleukin-6 (IL-6) and IL-8 (24, 25) and enhances the serum level of immunoglobulin A (IgA) and IgM (28). Previously, in an In-vitro study its combination with ascorbic acid can reverse the depressed helper/inducer subpopulation of lymphocyte. The abnormality in lymphocytes could be reproduced by Levamisole treating of normal lymphocytes with measles virus in vitro. Therefore, levamisole could also be considered as a suggestive drug for the treatment of COVID-19 (25, 26).

As previously reported in China (5), in the current study more than half of the infected patients was men too (60%). Clinical presentations of 41 COVID-19 infected patients were evaluated in Wuhan, China. The results of the study indicated that the common symptoms in Chinese patients were fever (98.0%), cough (76.0%), dyspnea (55.0%), myalgia (44.0%), sputum production (28.0%), headache (8.0%), hemoptysis

(5%), and diarrhea (3%), respectively (5). The most clinical status in the current study were fever (88.0%), cough (78.0%), and dyspnea (54.0%) while less common symptoms were weakness (18.0%), headache (8.0%), dizziness (6.0%), myalgia (6.0%), and nausea (6.0%) at the baseline but there were no significant difference between groups.

Previous investigation found that Immunomodulators play an important role in management of patients infected with COVID-19 (27, 29). Levamisole is a safe and successful immunomodulatory drug, suggesting that in COVID-19 patients, levamisole may also contribute to attenuating the immune response.. In conclusion, our results indicated that levamisole can efficiently improve Clinical Status compared to placebo.

Conclusions

The results of the current study have overall demonstrated that patients in levamisole/ routine care group had significantly higher odds of having a better clinical status including cough and Dyspnea on day 14 than that receiving placebo/routine care, but with an effect-size of unsure clinical importance. The difference in the distribution of fever on days 3, 7, and 14 between two groups was not significant, suggesting that levamisole can efficiently improve the most clinical status of patients with COVID-19 infectious compared to placebo.

Abbreviations

SARS-CoV-2 or COVID-19: Severe Acute Respiratory Syndrome Coronavirus 2 / WHO: World Health Organization / ACE-2: angiotensin-converting enzyme 2 / Th1:CD₄⁺-T-helper / LPV/r:Lopinavir/ritonavir / NSAIDs: Nonsteroidal anti-inflammatory drugs / CQ: Chloroquine / HCQ: Hydroxychloroquine / IL-6: interleukin-6 / IFNs: human interferon / IgA: immunoglobulin A / IgM: immunoglobulin M / CONSORT: Consolidated Standards of Reporting Trials.

Declarations

Ethics approval and consent to participate:

All patients signed an informed consent form prior to participation in the study. All methods were carried out in accordance with relevant guidelines and regulations. This study was approved by the Ethics Committee of Yazd University of Medical Sciences (Ethics ID: IR.SSU.REC.1399.063). This study was also approved in the Iranian Registry of Clinical Trials (IRCT20190810044500N7) at the date of 19/09/2020.

Consent for publication:

Consent for publication was agreed upon in the written consent forms signed by the patients.

Availability of data and materials:

All data generated or analyzed during this study are included in this published article.

Competing interests:

The authors declare that they have no competing interests regarding the publication of this paper.

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Authors' contributions:

F.S., Z.A.M., S.R.M. and I.K. were involved in conception and design of the study. A.R., M.G., and Z.A.M. collected the data. F.S., A.R., A.S., and S.R.M. analysis the data and drafted the first manuscript. All authors read and approved the final manuscript.

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Figures

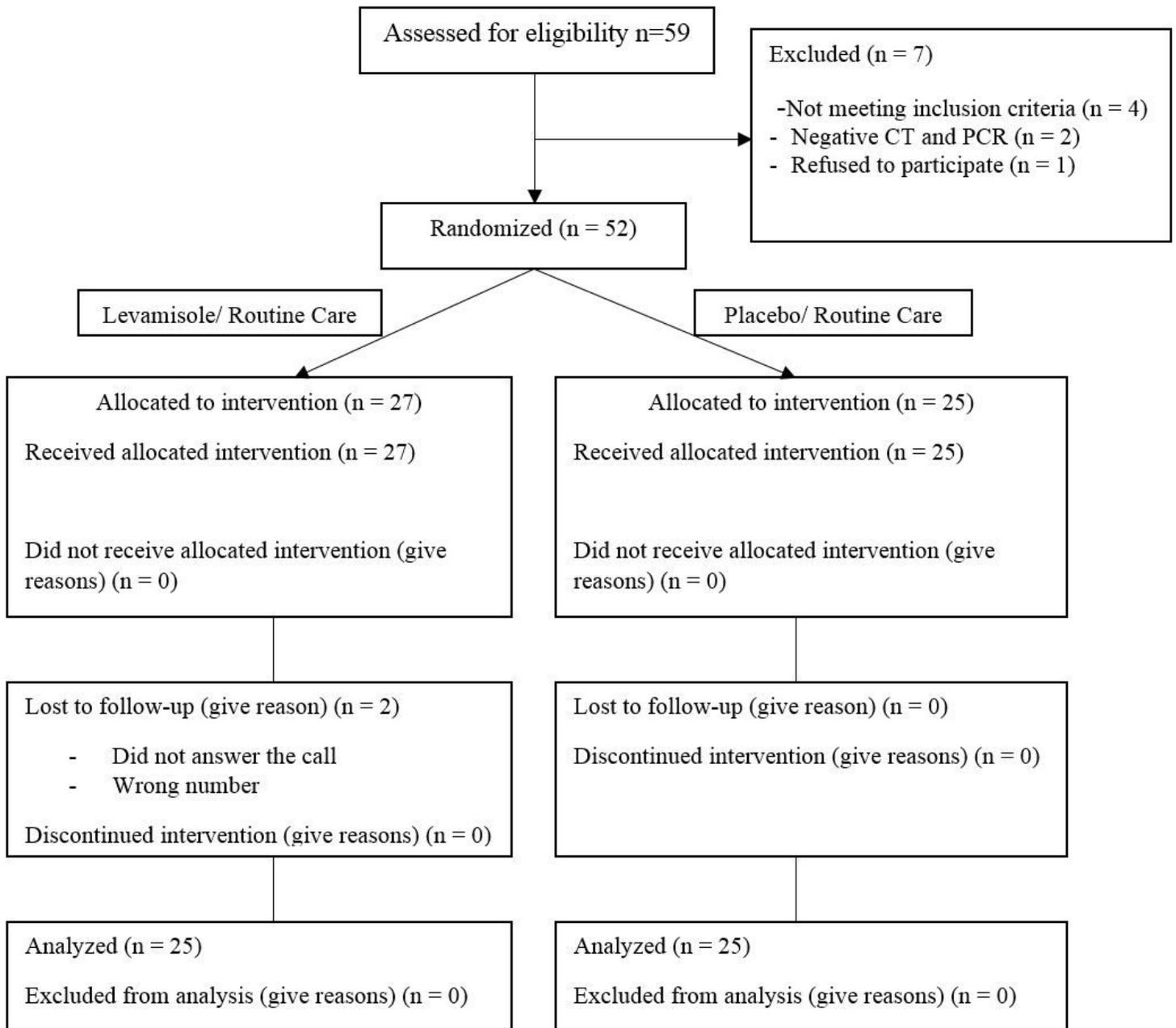


Figure 1

CONSORT flow diagram.

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