Efficacy and Safety of Oral Pentoxifylline in the Treatment and Recovery of Patients with Moderate to Severe COVID-19 Infection Treated with Routine Protocols: A Randomized Controlled Clinical Trial

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May 18, 2023

Abstract

Backgrounds: The absence of a gold-standard treatment for COVID-19 infection encourages clinicians to benefit from multi-potential medications in the treatment of COVID-19. The current controlled randomized clinical trial tried to evaluate the efficacy and safety of pentoxifylline (PTX) as an adjuvant therapy in moderate to severe COVID-19 infection. *Methods:* In this randomized controlled clinical trial, two groups of hospitalized patients with moderate to severe COVID-19 infection were randomized by the block randomization method to either receive standard protocol therapy or standard protocol therapy plus pentoxifylline 400 mg TDS for 14 days. *Results:* The results showed a greater improvement in the proinflammatory biomarkers in the intervention group. Oxygen saturation, hemoglobin, and platelet levels were also improved to a higher level among pentoxifylline recipients. The mortality rate was reported 4% and 32% in the intervention and control groups, respectively. One out 13 patients with severe COVID-19 infection expired in the intervention group, while 20 out of 28 patients expired in the control group, showing about 10 times higher mortality rate compared to the pentoxifylline recipients. *Conclusion:* Pentoxifylline increased the survival rate of COVID-19 patients and played as a preventive role for COVID-related mortality and morbidity such as acute respiratory distress syndrome.

1. INTRODUCTION

Coronavirus is a member of the Coronaviridae family, a coated RNA virus, causing a common pathogenesis between humans and animals [1]. The coronavirus family can cause different forms of disease varying from simple cold and gastrointestinal symptoms to pneumonia and bronchitis or acute respiratory distress syndrome (ARDS) [2-7].

Severe Acute Respiratory Syndrome-related Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome-related Coronavirus (MERS-CoV) were some of the most important epidemics caused by coronaviruses in the form of severe pneumonia leading to ARDS [2, 8, 9]. COVID-19, in compression with other coronaviruses, has been reported to have a high prevalence and rapid transmission ability which caused the current pandemic in a very short time [10].

COVID-19 causes asymptomatic and symptomatic infections; symptomatic patients may present with broad manifestations from dry cough, sore throat, fever, myalgia, and shortness of breath to respiratory failure leading to intubation and mechanical ventilation [11]. In severe cases of COVID-19 infection, progression to sepsis and multiple organ failure has been reported [12-16]. The pathogenesis of COVID-19 infection

combines primary viraemia and secondary inflammation resulting from cytokine storm; in patients with lung involvement this can lead to inflammation and destruction of the alveoli. Therefore, prevention of cytokine storm seems to be rational in the treatment of moderate to severe COVID-19 infection. Some medications such as hydroxychloroquine (HCQ) with anti-inflammatory properties and antiviral medications like lopinavir/ ritonavir have been reported to be effective in the treatment of SARS-CoV-2 [17-19]. Pentoxifylline is a well-known medication with anti-inflammatory properties, prescribing in the treatment of many clinical conditions [14, 19].

The anti-inflammatory effects of Pentoxifylline (PTX) include decreasing in the production of proinflammatory cytokines and inflammatory parameters such as TNF and IFN-gamma IL-6, and IL-1 which help suppress the inflammation [20, 21]. Moreover, PTX enhances the blood flow within narrow arteries, resulting in better circulation and oxygenation [22]. In the current study, the efficacy and safety of PTX in the treatment and recovery of patients with moderate to severe COVID-19 infection was investigated in a randomized controlled clinical trial.

2. Method

2.1. Design and Settings

This was a double-blind randomized clinical trial study that was performed in Rasool Akram Medical Complex and Firoozgar hospital in Tehran on 150 patients with COVID-19. The diagnosis of COVID-19 was made according to the opinion of the relevant physician based on clinical signs and PCR, paraclinical, or laboratory findings. Both hospitals are affiliated to the Iran University of Medical Sciences (IUMS) and observe the same country protocol to treat COVID-19 patients.

2.2. Sampling and Allocation

Sampling method was convenient. Eligible participants were classified by the block randomization method through random allocation software (RAS) and were randomly assigned to one of the groups receiving the intervention (n=50) or the routine treatment regimen group (n=100) (Figure 1).

2.3. Inclusion and Exclusion Criteria

The inclusion criteria were age range between 18 and 90 years, being hospitalized, patients with COVID-19, not being hospitalized in the intensive care unit at the time of entrance to the study, patients without coagulopathy, patients without a history of stroke, ocular and cerebral hemorrhage, women those were not pregnant or breastfeeding, patients without cancer, porphyria, liver and renal dysfunction, having no massive surgery in the past two weeks, history of intolerance or allergy to PTX or any type of Xanthine.

Exclusion criteria were the occurrence of any bleeding or severe side effects during the study such as gastrointestinal intolerance that does not respond to predetermined measures of antidote use, skin drug reactions, heart attack and stroke during the study, unstable vital signs, being intubated under mechanical ventilation, hospitalization in ICU, and patients under the treatment with any therapeutic blood thinner.

2.4. Intervention and Follow-up

The standard treatment for COVID-19 infection is sofosbuvir/daclatasvir + hydroxychloroquine, which both groups receive. Dosage and frequency of use of atazanavir + hydroxychloroquine are as follows: tab sofosbuvir/daclatasvir 400/60 mg oral daily for 7 to 10 days (produced by BakhtarBiochemistry pharmaceutical company, Iran) and oral hydroxychloroquine 400 mg stat then 200 twice daily for 7 to 14 days (produced by Macleod'spharmaceutical company, India). PTX 400 mg TDS was administered to the intervention group for 14 days (produced by Farabi Pharmaceutical company, Iran).

2.5. Paraclinical Data

Laboratory parameters were evaluated by peripheral blood samples of the patient and LDH, CPK, ESR, CRP tests were performed daily for the patient and the course of laboratory changes was monitored. Radiological

examination of the lungs was performed by CT scan twice at the time of admission and at the time of discharge, and differences in radiological findings were recorded and compared.

2.6. Outcome definition

The following checklist was used to define the patient status. This checklist was provided using COVID-19 research team opinions (Expert panel)

2.7. Response to treatment criteria

- Time of symptoms improvement such as cough, shortness of breath, and lethargy
- Improvement of the patient's oxygen saturation without changing the treatment protocol and reduction in the need for oxygen
- Duration of hospitalization of the patient according to the course of improvement of symptoms
- Evaluation of laboratory parameters as serial consisting of LDH, CBC, ESR, CRP, and comparison of parameters at hospitalization, during hospitalization, and at discharge
- Investigation of changes in anti-inflammatory parameters

2.8. Statistical Analysis

After extracting the required data from the patients' records, the data were analyzed using SPSS, version 18. In addition, descriptive data for continuous variables and qualitative statistics were reported as bar charts and tables. The mean difference test (independent t-test) was used to compare the patients. Moreover, Chi-square was utilized comparing both groups of studies for qualitative variables. P value less than of 0.05 was considered significant.

2.9. Ethical consideration

The research followed the tenets of the Declaration of Helsinki. This study was approved by the ethic committee of Iran University of Medical Sciences (ethical code: IR.IUMS.REC.1399.458). Moreover, the study protocol was registered in the Iranian Registry of Clinical Trials (IRCT#IRCT20170809035597N2; https://en.irct.ir/trial/51927). Accordingly, informed consents were obtained from all patients.

3. Results

A total number of 150 patients with moderate to severe COVID-19 disease (supplement table) were enrolled in the current study and after proper randomization, treated based on the current standard treatment protocol. The intervention group, including 50 patients, also received PTX on top of the standard protocol and was compared with the control group. Mean age of all enrolled patients was 61.32±15.59 years (54 ±14.32 vs. 64.99±14.96 in the intervention and control groups, respectively) and a total of 64% of the subjects were male (n=96).

In the baseline assessments for all patients, there were significant differences in CPK, CRP, LDH, AST, systolic blood pressure (BP), pulse rate (PR), age, and temperature between both groups of study ($P<0.05$). Additionally, the mean SO_2 was not different at the admission time (**Table 1**). Primary qualitative assessments at the time of admission, such as headache, dyspnea, chest discomfort, body pain, weakness and fatigue, anorexia, anosmia, diarrhea, history of cardiovascular disease (CVD), drug history, similar symptoms in close relatives, fever, and chills showed significant differences in the intervention and control groups ($P<0.05$) (**Table 2**); however, the drugs reported in the patients' past medical history were reported to have no effect on the mortality of patients in none of the groups (**Table 3**).

Clinical and preclinical assessment on all patients was again performed at the discharge time and the results revealed that platelets (PLT) were significantly increased in the intervention group after the treatment ($P=0.001$). Moreover, PR was reduced significantly in both groups compared to the baseline values ($P<0.005$). Diastolic BP was significantly decreased only in the intervention group posttreatment ($P=0.023$) and not among control patients ($P=0.162$). Moreover, Glasgow coma score (GCS) was significantly reduced

in the control group from 14.85 to 11.62 (P=0.001), which implied a worse prognosis in this group. Furthermore, hospitalization days were reported to be less in the intervention group compared to the control group (7.02 vs. 10.83 days, respectively) (P=0.001) (**Table 4**).

The final assessment of patients' clinical condition showed that 32% of individuals in the control group and 4% in the intervention group were expired (P<0.001, odds ratio=0.08) (**Table 5**). In addition, evaluation of CT score revealed that 1 out 13 patients (7.7%) with severe COVID-19 infection expired in the intervention group, while 20 out of 28 patients (71.4%) expired in the control group, showing about 10 times higher mortality rate compared to the PTX recipients (**Table 6**). Noteworthy, that there were eight patients in the intervention group and 12 patients in the control group that required re-hospitalization; however, the difference between both groups was not significant (P=0.497).

4. Discussion

The current study provides evidence regarding the efficacy and safety of pentoxifylline in the recovery of hospitalized COVID-19 patients. A total number of 150 patients were selected from two hospitals, Rasool Akram Medical Complex and Firoozgar hospital in Tehran, affiliated to the Iran University of Medical Sciences. Both hospitals were tertiary COVID-19 centers and were following the same protocol in the treatment of COVID positive patients. The trial was conducted during the same period (3-month period) of the second wave of the pandemic in both centers. Responsible physicians were also affiliated with the IUMS. All patients were PCR positive for COVID-19 and hospitalized in the infectious floor and not in ICU.

Demographic characteristics of the patients between the intervention and control groups were similar and no significant differences were detected except for the sex in which the number of male patients was significantly greater in the control group (P=.012); the latter might be due to the higher rate of hospitalization and severe forms of COVID-19 infection in males [23, 24].The socioeconomic statuses of all patients were in the same triers of the society. Regarding the severity of the disease, both groups of patients were struggling with moderate to severe COVID-19 infection at the time of admission. The treatment protocol in both centers was the same except for pentoxifylline that was added to the therapeutic regimen for the intervention group.

A statistically significant drop of proinflammatory biomarkers such as LDH, CRP, and ESR as well as non-statistically significant decreases in CPK were reported at discharge in the intervention group; Since PTX is a methylxanthine derivative, it may reduce the severity of cytokines storm and their consequences [25-27]. Noteworthy, that LDH is a hallmark of COVID-19 severity and disease prognosis. Therefore, decreased LDH in the treatment group can imply the ability of PTX in the reduction of tissue damage [28]. AST level was increased in the intervention group at discharge time; noteworthy, that PTX was extremely metabolized by liver cells and this might be the reason for AST build up in patients who received PTX [29, 30].

The infection signs such as fever, pulse rate, and blood pressure declined after the initiation of the standard protocols for the treatment of COVID infection in both groups; however, the course of decline was more significant in the intervention group treated with pentoxifylline.

Oxygenation and O2 saturation were significantly improved compared before and after the treatment in both intervention and control groups. The anti-inflammatory and immunomodulatory properties of PTX decrease the risk of ARDS in COVID-19 patients with significant lung involvement [26, 31, 32]. On top of that, pentoxifylline was reported to be beneficial in controlling the hypercoagulable state resulting from virus-induced injury to the epithelium [26, 31, 33].

Regarding hospitalization, a significant shorter hospital stay was reported in the treatment group; a mean of 7 vs. 10 days in the intervention and control groups, respectively. Thus, PTX may hasten the recovery process in moderate to severe COVID-19 because of the lower need for intubation and less serious dysregulation of the immune response [34]. Moreover, the mortality rate in the treatment group was statistically lower than the control group; only 4% vs. 32% of patients expired in the treatment and control groups, respectively. The reason can be the beneficial effects of PTX on the respiratory system and lowering tissue damage to heart, kidney, liver, and the brain [33].

CT score for the severity of lung involvement was higher in expired patients of the control group. The CT score was suggested by other studies to be directly related to the mortality of COVID positive patients [35, 36]. In the meanwhile, GCS was significantly more declined during the therapy in the control group, which implied the poorer prognosis and higher morbidity in this group [37, 38].

Overall, PTX is considered being a safe modality in the treatment of various medical conditions. The most common adverse effects reported with PTX were gastrointestinal upset (nausea, vomiting, and abdominal pain) and dizziness [39-41]. Finally, regarding the efficacy of medical agents in the treatment of COIVD-19, it is strongly recommended to prioritize vaccination in respect of their possible side effects because some new subvariants may be emerged with severe consequences even more than the primary subvariants [42-45].

5. Conclusion

The mortality rate was reported 4% and 32% in the intervention and control groups, respectively. Moreover, the mean hospitalization days were 7.02 vs. 10.83 in the PTX and control group, respectively. Therefore, pentoxifylline increased the survival rate of hospitalized COVID-19 patients and played a preventive role for COVID-related mortality and morbidity such as ARDS.

Key points/ Highlights

- Pulse rate in both groups reduced significantly compared to the baseline values (P<0.005).
- In the intervention group, diastolic blood pressure reduced significantly (P=0.023) but not in the control group (P=.162).
- Mean SO_2 reduced in both groups, while in the intervention group, the level of SO_2 was higher. Moreover, PLT significantly increased in the intervention group (P=0.001).
- GCS significantly reduced in the control group from 14.85 to 11.62 (P=0.001).
- Hospitalization days were lower in the intervention group compared to the control group (7.02 vs. 10.83 days) (P=0.001).
- Sputum, headache, dyspnea, chest discomfort, body pain, weakness and fatigue, anorexia, anosmia, diarrhea, CVD, drug history, similar symptoms in close relatives, fever, and chills, the two groups were significantly different (P<0.05).
- 32% in the control group and 4% in the intervention group were expired (P<0.001, odds ratio=0.08).
- CT score, 1 out 13 severe patients (7.7%) expired in the intervention group while 20 out 28 severe patients (71.4%) expired in the control group.
- Eight patients in the intervention group and 12 patients in the control group required readmission, which this difference was not significant (p=0.497).

Capsule summery

What is already known on this topic

- hydroxychloroquine (HCQ) with anti-inflammatory properties and antiviral medications like lopinavir/ ritonavir have been reported to be effective in the treatment of SARS-CoV-2.

-Pentoxifylline is a well-known medication with anti-inflammatory properties, prescribing in the treatment of many clinical conditions

What this study adds to our knowledge?

-The mortality rate was reported 4% in sofosbuvir/daclatasvir + hydroxychloroquine + Pentoxifylline group and 32% in the sofosbuvir/daclatasvir + hydroxychloroquine group.

-The mean hospitalization days were 7.02 vs. 10.83 in the sofosbuvir/daclatasvir + hydroxychloroquine + Pentoxifylline group and control group.

-Pentoxifylline increased the survival rate of hospitalized COVID-19 patients.

-Pentoxifylline plays a preventive role for COVID-related mortality and morbidity such as ARDS.

Acknowledgment

The authors would like to express their gratitude to the authorities of Rasool Akram Medical Complex Clinical Research Development Center (RCRDC) especially Mrs Farahnaz Nikkhah for their technical and editorial assistance.

Authors Contribution

Contributions to the current study included AG in the study idea and design, database search, literature review, quality evaluation, conducting the trial, data gathering, designing and drafting the proposal, following up with an ethical committee for approval, and revising the manuscript critically for importance intellectual content. SA in the study idea and design and drafting the manuscript. SS in the study design, literature review, and drafting the manuscript. FS in the proposal preparation and edit. RV in the study design, supervision, statistics and analysis, and drafting the manuscript. TR, ZY, SJ, MR, MJM, MG, and FSHB in conducting the trial, treatment of the patients, and data gathering. All authors have read and approved the final version to be published and agreed to be accountable for all aspects of the work. All authors agreed on the order in which their names are listed in the manuscript.

Abbreviations

Randomized clinical trial (RCT), Pentoxifylline (PTX), Oxygen saturation (SO_2), hemoglobin (Hgb), platelets (PLT) acute respiratory distress syndrome (ARDS), severe acute respiratory syndrome-related Coronavirus (SARS-CoV), Middle East Respiratory Syndrome-related Coronavirus (MERS-CoV),hydroxychloroquine (HCQ), Iran University of Medical Sciences (IUMS), random allocation software (RAS), blood pressure (BP), pulse rate (PR), cardiovascular disease (CVD), glascow coma score (GCS)

Conflict of interest

The authors declare that there is no conflict of interests.

Funding Support

Vice chancellor of Iran University of Medical Sciences

Transparency declaration

Authors declare that the manuscript is honest, accurate, and transparent. No important aspect of the study is omitted.

Data Availability Statement

All data produced in the present study are available upon reasonable request to the authors.

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Figures and Legends

Table 1 : Clinical and paraclinical characteristics at admission time

Table 2 : Clinical and paraclinical characteristics (qualitative variables) by groups

Table 3: Comparison of the final situation for patients according to the received drugs

Table 4 : Clinical and paraclinical characteristics (quantitative variables) at discharge time

Table 5 : Comparison of the final condition for patients receiving two types of medicine in both groups

Table 6 : Comparison of the final situation for patients by CT score between the two groups

Figure1 . CONSORT flow chart showing the flow of patients through the trial

Table 1 . Clinical and paraclinical characteristics at admission time

Variable	Variable	Mean	Std. Deviation	t	P value
Age	Intervention group	54.0000	14.32281	-4.301	<.001
	Control group	64.9900	14.96291		
Temperature	Intervention group	37.3682	.56764	4.966	<.001
	Control group	36.9348	.42619		
Pulse rate	Intervention group	88.3542	13.93830	2.805	.006
	Control group	82.9400	9.26906		
BP Systolic	Intervention group	116.6667	13.38677	-3.395	.001
	Control group	123.9596	11.61009		
BP diastolic	Intervention group	104.7674	158.16400	1.880	.062
	Control group	74.1170	9.50931		
SO2	Intervention group	90.0708	4.27267	0.552	.717

Variable	Variable	Mean	Std. Deviation	t	P value
	Control group	89.4388	7.67385		
GCS	Intervention group	14.8750	.53096	.421	.141
	Control group	14.8400	.44313		
WBC	Intervention group	7.1345	6.74108	-.731	.461
	Control group	7.7565	3.32789		
Leukopenia	Intervention group	1.8667	.34378	-.686	.494
	Control group	1.9053	.29440		
PLT	Intervention group	203473.4694	63364.44447	-.224	.823
	Control group	206777.7778	93153.21541		
HG	Intervention group	12.4813	1.42431	.040	.968
	Control group	12.4646	2.21821		
ALT	Intervention group	64.5918	113.65938	-1.235	.219
	Control group	116.6250	283.17245		
AST	Intervention group	48.8776	28.01089	-5.010	<.001
	Control group	84.3229	45.25053		

Table 2 . Clinical and paraclinical characteristics (qualitative variables) by groups

Variable	Variable	Group	Group	X^2	P value
		Intervention	Control		
Gender	Male	25	71	6.380	.012
	Female	25	29		
DM	Negative	11	33	1.946	.163
	Positive	39	67		
HTN	Negative	14	42	2.947	.086
	Positive	36	57		
History of CVD	Negative	5	29	6.865	.009
	Positive	45	71		
Drug history	Negative	29	40	4.348	.037
	Positive	21	60		
Contact with infected or suspicious people	Yes	30	2	1.556	.385
	No	20	4		
History of travel before symptom manifestation	Yes	10	1	.038	>.999
	No	40	5		
Similar symptoms in close relatives	Yes	32	1	4.959	.071
	No	18	5		
Fever	Yes	32	29	16.923	<.001
	No	18	71		
Chills	Yes	29	12	35.511	<.001
	No	21	88		
Cough	Yes	32	63	.014	>.999
	No	18	37		
Sputum	Yes	5	24	4.189	.041

Variable	Variable	Group	Group	X^2	P value
	No	45	76		
Headache	Yes	27	36	4.433	.053
	No	23	64		
Dyspnea	Yes	23	77	14.415	<.001
	No	27	23		
Chest discomfort	Yes	12	11	4.339	.037
	No	38	89		
Body pain	Yes	28	21	18.564	<.001
	No	22	79		
Weakness and fatigue	Yes	33	29	18.819	<.001
	No	17	71		
Anorexia	Yes	32	22	25.521	<.001
	No	18	78		
Sneeze	Yes	2	1	1.531	.234
	No	48	99		
Rhinorrhea	Yes	2	3	.103	>.999
	No	48	97		
Sore throat	Yes	4	4	1.056	.442
	No	46	96		
Anosmia	Yes	24	8	31.392	<.001
	No	26	91		
Diarrhea	Yes	24	22	10.598	.001
	No	26	78		

Table 3. Comparison of the final situation for patients according to the received drugs

Variable	Variable	Final situation	Final situation	X^2	P value
		Died	Discharge		
Pantoprazole	Positive	3	3	3.200	.264
	Negative	0	2		
Glibenclamide	Positive	6	8	3.591	.088
	Negative	28	108		
Atorvastatin	Positive	2	5	.146	.657
	Negative	32	111		
ASA	Positive	6	15	.486	.574
	Negative	28	101		
Metformin	Positive	7	24	.000	>.999
	Negative	27	92		
Amlodipine	Positive	4	12	.056	.760
	Negative	30	104		
Losartan	Positive	8	24	.126	.812
	Negative	26	92		

Table 4 . Clinical and paraclinical characteristics (quantitative variables) at discharge time

Variable	Group	Before	After	P value
Temperature	Intervention group	37.2677	36.9484	.005
	Control group	36.9676	33.7500	.087
Pulse rate	Intervention group	87.7368	82.8158	.050
	Control group	89.0000	81.6667	.048
BP Systolic	Intervention group	118.4839	112.9032	.063
	Control group	115.1429	118.5714	.390
BP Diastolic	Intervention group	76.9355	69.3548	.023
	Control group	63.7143	72.8571	.162
SO2	Intervention group	89.9838	93.8919	<.001
	Control group	88.2131	93.1475	<.001
GCS	Intervention group	14.8571	14.8333	.902
	Control group	14.8511	11.6277	.016
PLT	Intervention group	201893.3333	282011.1111	<.001
	Control group	204219.7802	206252.8571	.931
HG	Intervention group	12.5571	13.0321	.084
	Control group	12.3230	11.9425	.062
ALT	Intervention group	66.0444	86.8000	.315
	Control group	136.1014	73.9855	.126
AST	Intervention group	48.6444	72.2444	.223
	Control group	89.8088	71.4265	.015
LDH	Intervention group	591.5750	494.0000	.002
	Control group	796.9481	982.0649	.360
CRP	Intervention group	74.6585	19.6512	<.001
	Control group	21.3333	17.4667	.515
ESR	Intervention group	43.5429	31.1143	.002
	Control group	33.0000	42.0000	.177
CPK	Intervention group	174.6800	119.8000	.297
	Control group	465.6316	400.1579	.713

Table 5 . Comparison of the final condition for patients receiving two types of medicine in both groups

Final situation	Group	Group	X^2	P value	Odds ratio
	Intervention group	Control group			
Died N, %	2 (4%)	32 (32 %)	14.909	<.001	0.08
Discharged N, %	48 (96%)	68 (68%)			

Table 6 . Comparison of the final situation for patients by CT score between the two groups

Variable	CT score	Final situation	Final situation	X^2	P value
		Expired	Discharge		
Intervention group	Mild	0 (0)	13 (100%)	25.96	<.001
	Moderate	0 (0)	23 (100%)		
	Severe	1 (7.7%)	12 (92.3%)		
	Critical	1 (100%)	0 (0)		
Control group	Mild	0 (0)	15 (100%)	30.20	<.001

Variable	CT score	Final situation	Final situation	X^2	P value
	Moderate	12 (21.1%)	57 (78.9%)		
	Severe	20 (71.4%)	8 (28.6%)		

Figures:

Figure1 . CONSORT flow chart showing the flow of patients through the trial