Health Economic Evaluation

A randomised controlled trial of effectiveness and safety of Niclosamide as add on therapy to the standard of care measures in COVID-19 management

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ARTICLE INFO

Keywords: Niclosamide
COVID-19
SARS-COV2
Standard of care

ABSTRACT

Background: COVID-19 pandemic has ignited the urge for repurposing old drugs as candidate antiviral medicines to treat novel challenges of viral infections. Niclosamide (NCS) is an anti-parasitic drug of known antiviral potential. Therefore, this study attempts to investigate the antiviral effect and safety of NCS on SARS-CoV-2 caused COVID-19 patients.

Methods: Randomized controlled open label clinical trial encompassed 75 COVID-19 patients treated with standard of care plus NCS were included as experimental group and 75 COVID-19 patients treated with only standard of care therapy as control group. Survival rate, time to recovery, and side effects were the main end points for the assessment of the therapeutic effect and safety of NCS.

Results: No significant difference between the two study groups in the incidence of death Vs recovery within 30 days of follow up\(p = 1\).Median survival time to cure in the NCS addon group was significantly less than controls (5 Vs 7days, Log rank \(p = 0.005\)).All the recoveries took place within 20 days in the NCS add on group, which is 10 days shorter than that in the controls (30 days), NCS add on treatment increased the risk of cure by 60% per day compared to control group (adjusted HR\( = 1.6, p = 0.007\)) after adjusting for the count of comorbidities. Additionally, two or more comorbidities reduced the risk of cure to 33% (\(p < 0.001\)).Male gender increased the risk of cure by 42% (\(p = 0.046\)).Older age group decreased the risk of recovery per day to 0.58 and 0.53 for 50–59 and 60+ years of age. Hypertension (HT) and diabetes mellitus (DM) significantly reduced the risk of being cured per day to 0.56 (\(p = 0.003\))and 0.65 (\(p = 0.039\)) respectively. No significant signals of safety in NCS add on therapy compared to control group.

Conclusion: adding NCS to the standards of care measures increased the risk of the cure and had shorter time to stay in the hospital compared with controls., male gender increased the risk of cure, while older patients >40 years, HT, and DM decreased the risk of cure. Also, NCS add on therapy was relatively safe; hence, NCS is of clinical benefit for freeing hospital beds for more patients in pandemic crisis.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) \cite{1}. The outbreak of COVID-19 has become gradually nationwide with significant impact on public health and this outbreak was declared as a public health emergency on 30 January 2020 by the WHO and need an urgent viral infection identification and intervention as early as possible \cite{2,3}. Several treatment strategies have been evaluated for Covid19 \cite{4–6} but no current evidence from randomized controlled trials to recommend them as antiviral treatment for patients with COVID-19. On October 22, 2020 FDA approved NDA214787 for velkury (Remdesivir) which is indicated for adult and pediatric patients for treatment of COVID 19 requiring hospitalization \cite{7} however WHO recommends

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https://doi.org/10.1016/j.amsu.2021.102779

Received 8 August 2021; Received in revised form 23 August 2021; Accepted 2 September 2021
Available online 4 September 2021

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against the use of remdesivir in COVID-19 patients [8].

Niclosamide was discovered in 1958. It is on the World Health Organization’s List of Essential Medicines. Niclosamide is an anti-parasitic medication used to treat tapeworm infestations. This includes diphyllobothriasis, hymenolepiasis, and taeniasis. In addition, Niclosamide may have broad clinical applications for the treatment of diseases other than those caused by parasites. These diseases and symptoms may include cancer, bacterial and viral infection, metabolic diseases such as Type II diabetes, NASH and NAFLD, artery constriction, endometriosis, neuropathic pain, rheumatoid arthritis, scleroderma, and systemic sclerosis [9]. It is an FDA approved anthelmintic drug with low cost and low in vivo toxicity profile [10]. Recent drug repurpose screening identified NCS as an antimalar, antibacterial and antiviral agent [11,12]. Compelling body of evidences also suggest NCS possess broad spectrum antiviral properties including SARS-CoV (IC50 = 1.56 μM) [13,14].

Recently, it was also reported that NCS exhibited in vitro antiviral activity against SARS-CoV-2 (IC50 = 0.28 μM) [15]. When treating human subjects with a 2g oral dose of NCS, the maximum serum concentration was shown to be 0.25–6 μg/ml (0.76–18.3 μM). Hence, it is feasible to reach the effective IC50 of NCS on SARS-CoV-2 (0.28μM) by using the current dosage limits. However, the half-life of NCS is short, 6–7 h [16]. Hence, to attain plasma concentrations of NCS close to the SARS-CoV-2 IC50 with less fluctuations, a daily oral dose of NCS 1g three times a day is needed.

The potential antiviral mechanism of NCS against SARS-CoV2 can be 1) blocking endocytosis of SARS-CoV2 [17] and 2) preventing auto-phagy of SARS-CoV-2 by inhibition of S-Phase kinase associated protein 2 (SKP2) [18]. Therefore; NCS can be a potential drug candidate for COVID-19 therapy.

This study was designed to assess the effectiveness and safety of Niclosamide as an addon therapy to the standard measures in COVID-19 management compared to standards of care therapy group.

2. Patients and methods

2.1. Trial design

This pilot randomized controlled open label study was conducted at Alkarkh and Alforat hospitals in Baghdad city from January 2021 to April 2021. The study was performed according to the Declaration of Helsinki and its amendments, and the Guidelines for Good Clinical Practices issued by the Committee of Proprietary Medicinal Product of the European Union. Ethical approval was taken from Iraqi Ministry of Health- Arab Board of Health Specialization in Iraq and the study was registered with the number of 20201541 at December 31, 2020T. Also, this study was registered in Research Registry UN: researchregistry7040. And in the Clinical Trials.gov website under identifier number: NCT04753619. Informed signed consent was obtained from the participants to admit the study. The work has been reported in line with CONSORT criteria [19].

2.2. Participants

Eligible patients to be included in the study were Patients with age above 18 years and of any gender, definite diagnosis of COVID-19 according to the WHO classification criteria [18]. Patients symptomatic for no more than three days for mild-moderate cases, no more than two days after being severe cases, and no more than one day after being critical cases, and finally patients Understand and agree to comply with planned study procedures.

Patients were excluded from the study if they refused to enroll in the study, had hypersensitivity or severe adverse effects to niclosamide, had renal impairment (serum creatinine > 2 mg/dl), or hepatic impairment (Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) > 3 times upper limit of normal, and pregnant women or women desire to become pregnant, breast feeding women.

2.3. Intervention

Patients were recruited from inpatients and outpatients according to the WHO classification criteria of severity of the disease. Study groups were divided into two groups:

Niclosamide Add-on group: NCS 2 g orally loading dose chewable then 1g every 12 h were given in the first day, then on the 2nd day: 1g < 3 for 7 days. That is to say, only in the first day 4 g/m² then on the second day 3 g/d in 3 divided doses for 7 days. If the participant requires mechanical ventilation over the course of the study, NCS may be administered via nasogastric (NG) or oroogastric (OG) tube and, if possible, should be administered with a scheduled nasogastric (NG) or oroagastric (OG) feeding.

In the control group, the patients received only standard of care which included all or some of the following, according to the clinical condition of each patient:

- Acetaminophen 500 mg on need.
- Vitamin C 1000 mg twice/day.
- Zinc 75–125 mg/day.
- 12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h for the next 4 days
- Favipiravir course of therapy (1600 mg twice daily in the first day then 600 mg twice daily for up to 10 days total)
- Vitamin D3 5000IU/day.
- Azithromycin 250 mg/day for 5 days.
- Oxygen therapy/CRAP if needed
- Dexamethasone 6 mg/day or methylprednisolone 40 mg twice per day, if needed.
- Mechanical ventilation, if needed.

2.4. Outcome measurements

Primary outcomes: To assess the percentage of recovered patients and evaluated by physician’s judgment on clinical recovery from the time of assessment over 30 days. The physician will check for the following: Fever: axillary temperature ≤37.2 °C or oral temperature ≤36.6 °C or oral temperature ≤37.2 °C; Respiratory rate: ≤24/minute on room air; Oxygen saturation: >94% on room air; Cough: mild or absent on a patient reported scale of severe, moderate, mild, absent,) and elevated D-dimer, C reactive protein, ferritin, thrombocyte, PT, aPTT, and fibrinogen were associated with a poor outcome in COVID19. These parameters will be checked on day 1 and day 3.

Secondary outcomes: To study the time to recovery in days over 30 days, and to assess type of side effects and number of participants who developed these adverse events over 30 days.

2.5. Sample size

To find the true and significant difference between the NCS add on group and controls in the recovery, we need A total sample size of at least 143 participants to get an effect size of 30% and alfa error of probability of 0.05 with a statistical power (1-β) of 80%.

2.6. Randomisation

This study is randomized using simple randomization method with 2 arms study trial of 1:1 allocation (75 Niclosamide group vs. 75 control group). The randomization process, patient’s records for disease progression, recovery, and clinical or laboratory testing were supervised by third party authority from Ministry of Health.
2.7. Binding

This study was open label non blinded study.

2.8. Statistical analysis

Statistical analyses were done using IBM SPSS version 21 computer software (IBM Statistical Package for Social Sciences) in association with Microsoft Excel.

Frequency distribution for selected variables was done first. Followed by exploring the associations between 2 categorical variables using crosstabulations. The statistical significance of such associations was assessed by Chi-square (χ²) test of homogeneity or Fisher’s exact test (when the condition for a valid chi-square test are not met). The log rank test was used to assess the statistical significance of difference between two survival curves. The Kaplan Meier survival analysis was used to calculate the mean and median survival time for two dichotomous outcomes (death and cure after treatment) in addition to calculating the cumulative rates. The Cox-regression model was used to calculate the adjusted Hazard Ratio for the risk of cure after treatment per unit time for a set of predictors. We assumed the level of statistical significance at P < 0.05. All analyzed tests were bilateral.

3. Results

3.1. Participant flow

A total of 200 patients infected with COVID-19 were screened for eligibility to be included in the study. Of those 50 patients were excluded: 2 of them were pregnant, 2 patients had elevated liver enzyme more than 3 times the normal reference range, one patient was <18 years age, 15 patients had heart failure, 10 patients had sepsis, 8 patients had liver failure, 7 patients had renal failure, 5 patients had rheumatoid arthritis on hydroxychloroquine and sulfasalazine. The remaining 150 patients were randomized to 75 Niclosamide add on group and 75 standards of care therapy group. All of the patients in both groups completed the study as in Fig. 1.

3.2. Baseline characteristics

The current study evaluated the outcome of treatment in two study groups within a maximum of 30 days study period. Table 1 shows that there were no obvious or statistically significant difference in age, gender, BMI, disease severity classification and count of comorbid conditions. However, those who started treatment earlier constituted a higher proportion (69.3%) of the intervention group compared to controls (52%).

3.3. Outcome measurement

3.3.1. Effectiveness of NCS add on therapy

As shown in Table 2, no difference was observed between the two study groups in the incidence of mortality (4%) within 30 days of follow up period for each.

3.4. Death as an outcome of treatment

As shown in Table 3 and Fig. 2, the NCS add on treatment was
Table 1
Baseline characteristics of niclosamide add on group and control group.

| Age group (years) | Study group (Intervention Vs Control) | P      |
|------------------|--------------------------------------|--------|
|                  | Control (Standard Therapy) | Intervention (Add on Niclosamide) |        |
|                  | N %                     | N %               |        |
| <40              | 21 28.0                  | 22 29.3           | 0.56   |
| 40-59            | 34 45.3                  | 28 37.3           |        |
| 60+              | 20 26.7                  | 25 33.3           |        |
| Total            | 75 100.0                 | 75 100.0          |        |
| Gender           |                        | 0.74 [NS]         |        |
| female           | 34 45.3                  | 36 48.0           |        |
| male             | 41 54.7                  | 39 52.0           |        |
| Total            | 75 100.0                 | 75 100.0          |        |
| Obesity categories |                        | 0.65 [NS]         |        |
| Lean (<25)       | 19 25.3                  | 17 22.7           |        |
| Overweight (25–29.6) | 33 44.0              | 33 44.0           |        |
| Obese grade-I (30–34.9) | 14 18.7             | 13 17.3           |        |
| Obese grade-II (35–39.9) | 5 6.7                | 10 13.3           |        |
| Obese grade-III (40+) | 4 5.3                 | 2 2.7             |        |
| Total            | 75 100.0                 | 75 100.0          |        |
| Disease severity |                        | 1[NS]             |        |
| Mild             | 25 33.3                  | 23 33.3           |        |
| Moderate         | 25 33.3                  | 25 33.3           |        |
| Severe           | 25 33.3                  | 25 33.3           |        |
| Total            | 75 100.0                 | 75 100.0          |        |
| Count of comorbid conditions | 0.63 [NS] |        |        |
| None             | 28 37.3                  | 25 33.3           |        |
| Only one         | 16 21.3                  | 21 28.0           |        |
| 2+               | 31 41.3                  | 29 38.7           |        |
| Total            | 75 100.0                 | 75 100.0          |        |
| Timing of treatment inception referring to disease symptoms (<1 week duration) | 0.03 |        |        |
| 1 week +         | 39 52.0                  | 52 69.3           |        |
| <1 week          | 36 48.0                  | 23 30.7           |        |
| Total            | 75 100.0                 | 75 100.0          |        |

Table 2
The difference between the two study groups in the incidence of death Vs recovery within 30 days of follow up.

| Outcome of treatment | Study group (Intervention Vs Control) | P      |
|----------------------|--------------------------------------|--------|
|                      | Control (Standard Therapy) | Intervention (Add on Niclosamide) |        |
|                      | N %                     | N %               |        |
| Recovery             | 72 96.0                  | 72 96.0           | 1[NS]  |
| Death                | 3 4.0                    | 3 4.0             |        |
| Total                | 75 100.0                 | 75 100.0          |        |

Table 3
The difference in mean survival time between the two study groups considering death as an outcome.

| Study group (Intervention Vs Control) | Mean survival time (days) | SE |
|--------------------------------------|---------------------------|----|
| Control (Standard Therapy)           | 29                        | 0.531 |
| Intervention (Add on Niclosamide)    | 30                        | 0.313 |

P (Log rank) = 0.98[NS].

Table 2
The difference between the two study groups in the incidence of death Vs recovery within 30 days of follow up.

| Timing of treatment inception referring to disease symptoms (<1 week duration) | Study group (Intervention Vs Control) | P      |
|-----------------------------------------------------------------------------|--------------------------------------|--------|
|                                                                             | Control (Standard Therapy) | Intervention (Add on Niclosamide) |        |
|                                                                             | N %                     | N %               |        |
| 1 week +                                                                    | 39 52.0                  | 52 69.3           | 0.03   |
| <1 week                                                                     | 36 48.0                  | 23 30.7           |        |
| Total                                                                       | 75 100.0                 | 75 100.0          |        |

As shown in Table 5, the NCS add on treatment was associated with a significantly lower median survival time (average duration of symptoms after starting treatment to cure = 5 days) compared to the control group (7 days). The NCS add on group takes less period to recover on average. After 5 days of treatment an obviously higher incidence of cure (60%) was observed in the NCS add on group compared to controls (40%). This amounts to 33% higher risk of cure with the NCS add on group. All the recoveries took place within 20 days in the NCS add on group, which is 10 days shorter than that in the controls (30 days), Table 6.

3.5. Cure as an outcome of treatment

As shown in Table 5, the NCS add on treatment was associated with a significantly lower median survival time (average duration of symptoms after starting treatment to cure = 5 days) compared to the control group (7 days). The NCS add on group takes less period to recover on average. After 5 days of treatment an obviously higher incidence of cure (60%) was observed in the NCS add on group compared to controls (40%). This amounts to 33% higher risk of cure with the NCS add on group. All the recoveries took place within 20 days in the NCS add on group, which is 10 days shorter than that in the controls (30 days), Table 6.

3.6. Multivariate modelling

The net and independent risk of being cured after treatment per unit of time (day) for each item in a set of predictors was assessed using a Cox-Regression model. The list of predictors used include age, gender, disease severity, effect of intervention, timing of treatment inception referring to disease symptoms and count of comorbidity conditions. Only two of these predictors were retained by the Backward selection method as significant. Being on NCS add on treatment increased the risk of cure by 60% (HR = 1.6) per day compared to control group, after adjusting for the count of comorbidities. Having only one comorbidity condition would reduce the risk of cure to 0.73 compared to those with no comorbidity, while having two or more comorbidities reduce the risk of cure to 0.33, Table 7.

A second model was developed to adjust for two specific comorbidities, namely: Hypertension (HT) and diabetes mellitus (DM), Table 8. Only five of these predictors were retained by the Backward selection method as significantly affecting the probability of cure after treatment. Being a male increase the risk of cure by 42% compared to females after adjusting for the type of treatment, age and the two comorbidities. Being on the intervention treatment increased the risk of cure by 63% (HR = 1.6) per day compared to control group, after adjusting for the other predictors included in the backward selection model. Older age group decreased the risk of recovery per unit time to 0.58 and 0.53 for 50–59 and 60+ years of age compared to those less than 40 years of age. Each of hypertension and DM significantly reduce the risk of being cured per unit time to 0.56 and 0.65 respectively.

3.7. Safety of niclosamide as add on therapy

As shown in Table 9, the most common side effects in NCS add on group was headache in 10 patients (13.3%), then fatigue in 9 patients (12.0%), diarrhea in 7 patients (9.3%), skin rash in 6 patients (8%), and abdominal pain in 2 patients (2.7%). However, these reported side effects were not significantly different between the tested groups (Table 3). This indicates the safety of NCS among COVID-19 patients.

4. Discussion

This study was designed to assess the effectiveness and safety of NCS as an add on therapy to the standard measures in COVID-19 management compared to standards of care therapy group.

To our knowledge; it is the first study regarding this aim. For patients with high risk, it is mandatory to search for new or old drugs to be used to lower morbidity and/or mortality of COVID-19 patients. Moreover, COVID-19 patients, especially those who need hospitalization, demand a...
lot of medical and respiratory supportive care with parenteral fluids, antibiotics, anti-inflammatory and maybe invasive respiratory intuba-
tion. Severe/critical patients may reside more than a month in hospitals.
During pandemic, finding drugs that can lower time of hospitalization is
important as medical systems all over the world were close to collapse

because of huge number of hospitalized COVID-19 patients in respira-
tory care units. In this endeavor, repurposing old drugs that have poten-
tial to lower this burden in SARS-CoV-2 pandemic is necessary. One

| Study group (Intervention Vs Control) | Median Survival time (days) | SE |
|--------------------------------------|----------------------------|----|
| Control (Standard Therapy)           | 7                          | 0.76 |
| Intervention (Add on Niclosamide)    | 5                          | 0.33 |

P (Log rank) = 0.005.

Table 4
The Kaplan Meier cumulative probability (incidence) of death after selected follow up periods for the two study groups.

| Study group (Standard Therapy) | Cumulative probability of death (%) | Cumulative survival probability (%) | SE |
|-------------------------------|------------------------------------|-----------------------------------|----|
| Control after 5 days of treatment | 2.7                                | 97.3                              | 1.9 |
| Control after 10 days of treatment | 4.0                                | 96.0                              | 2.3 |
| Intervention after 10 days of treatment | 1.3                                | 98.7                              | 1.3 |
| Intervention after 18 days of treatment | 2.7                                | 97.3                              | 1.9 |
| Intervention after 25 days of treatment | 4.0                                | 96.0                              | 2.3 |

Table 5
The difference in mean survival time between the two study groups considering cure as an outcome.

| Study group (Intervention Vs Control) | Adjusted HR | P  |
|--------------------------------------|-------------|----|
| Control vs Intervention               | 1.60        | 0.007 |
| Count of comorbid conditions          | 0.73        | 0.15 [NS] |
| Two or more comorbid conditions       | 0.33        | <0.001 |

P (Model)<0.001, NS, not significant.
of the candidates of repurposed drugs to treat COVID-19 patients is NCS.

The current study revealed that NCS did not enhance the survival rate of COVID-19 patients compared to the standard of care control group. Up to 3/75 (4%) patients from NCS and 3/75 (4%) patients from control group died and all of them were presented as severe COVID-19 cases. However, NCS use in this study provided evidence that it is useful in reducing significantly the time needed to recovery when compared to control group, (5 days in NCS add on group versus 7 days in controls) This is an important finding of accelerating recovery of COVID-19 patients and it is crucial to intensive care units during pandemic crisis of such fatal and demanding respiratory and multi-organ disease.

Another observation of note after multivariate modelling using cox regression analysis are being on NCS add on treatment increased the risk of cure by 60% per day compared to control group (adjusted HR = 1.6), after adjusting for the count of comorbidities. Additionally, Having only one comorbid condition would reduce the risk of cure by 73% (adjusted HR = 0.73) compared to those with no comorbidity, while having two or more comorbidities reduce the risk of cure to 33%

Moreover, a second model was developed to adjust for two specific comorbidities, namely: Hypertension (HT) and diabetes mellitus (DM). Being a male increased the risk of cure by 42% compared to females after adjusting for the type of treatment, age, and the two comorbidities. Older age group decreased the risk of recovery per unit time to 0.58 and 0.53 for 50–59 and 60+ years of age compared to those less than 40 years of age. In addition, HT and DM significantly reduced the risk of being cured per day to 0.56 and 0.65 respectively.

Another finding was no observable and significant signals of adverse events in NCS add on therapy compared to control group. This may indicate that NCS can be a possible adjuvant therapy to the treatment of COVID-19 patients.

Niclosamide could be a candidate for host-directed antiviral therapies. Strategies for controlling viral infections are mainly of two approaches: agents that target the virus directly or agents that target the host. Niclosamide has been reported as a potential agent for host defense during viral infections. It was reported that NCS inhibited SARS-CoV replication and protected Vero E6 cells from cytopathic effects after virus infection. Niclosamide’s effect on anti-viral host defense mechanisms was first reported by Jurgeit et al. They used a monoclonal antibody mabJ2 to stain viral dsRNA in infected cells as a readout for imaged-based screening. They screened a library of 1200 known bioactive compounds and identified NCS as a potent, low micromolar inhibitor of pH-dependent human rhinoviruses (HRV) and influenza virus. The mechanism of action proposed was related to niclosamide’s protonophore activity and its ability to act as a proton carrier.

More to the antiviral effect of NCS found in the current study, interestingly NCS succeeded in reducing the time to recovery for COVID-19 patients with co-morbidities, about 5 days, far more than the reduced time to recovery in COVID-19 patients without comorbidities, only 1 day. Hence, NCS seems beneficial for moderate and severe COVID-19 cases especially those with risk factors and co-morbidities who are most prone to complications and death.

It was reported that NCS as having anti-Chikungunya virus activity through reducing Chikungunya virus entry and transmission. Moreover, NCS was found to be a potent inhibitor of the replication of Zika virus, a mosquito-borne flavivirus, is a growing public health concern following a large outbreak that started in Brazil in 2014. In addition, repurposing of NCS has been proposed for the treatment of other pulmonary conditions, such as asthma and cystic fibrosis. It has potent bronchodilating effects, and inhibits excessive mucus production. Due to its effects on intracellular Ca2+ levels, NCS also inhibits the release of proinflammatory cytokines such as IL-8, and possibly also other cytokines, which could be of utmost importance to curb the cytokine storm frequently observed in hospitalized Covid-19 patients. Another fortunate aspect is the antibacterial activity of NCS that could be most welcome in fighting potential pulmonary superinfections.

This study has some limitations: first, open label study with short time; second, small sample size and done in single center. However this study, up to the best of our knowledge, was the first study that evaluated NCS effectiveness and safety as add on therapy to the standard care of measures in COVID-19 patients.

5. Conclusion

This study showed that adding NCS to the standards of care measures increased the risk of the cure and had shorter time to stay in the hospital compared with controls. After adjustment of selected predictors of cure, male gender increased the risk of cure, while older patients >40 years, HT, and DM decreased the risk of cure. Also, NCS add on therapy was relatively safe. These findings may suggest using NCS as an add on therapy to protocols used for treatment of COVID-19. However, these results are needed to be validated in a larger prospective follow up study.

Ethical Approval

Ethical approval was taken from Iraqi Ministry of Health- Arab Board of Health Specialization in Iraq and the study was registered and approved with the number of 20201541 at December 31, 2020T.

Funding

None.

Author contribution

All authors(contributed in concept or design of the study.)
Mohammed Fauzi Maulood and Hashim Ali Hashim contributed in data collection, Ahmed S. Abdulamir & A.S. Abdulamir et al. contributed in writing the paper and approval of the final version of the paper. Sattar Jabari Saad and Manal K. Abdulrrazaq contributed in writing the paper and approval of final version.

Consent
All patients signed written informed consent for participation in the study.

Registration of research
Research registry UIN: researchregistry7040. At the website: www.researchregistry.com/browse-the-registry#home/?view_2_search = researchregistry7040. &view_2_page = 1.

Guarantor
Faiq I. Gorial.

Provenance and peer review
Not commissioned, externally peer-reviewed.

Declaration of competing interest
None.

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