AIMS Medical Science

AIMS Medical Science, 10(2): 118–129.
DOI: 10.3934/medsci.2023010
Received: 03 October 2022
Revised: 06 April 2023
Accepted: 23 April 2023
Published: 28 April 2023

http://www.aimspress.com/journal/medicalScience

Protocol

Hydroxyurea and pyridostigmine repurposed for treating Covid-19 multi-systems dysfunctions

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Abstract: Early in the COVID-19 pandemic, medical care providers at an acute illness hospital received increasing numbers of post-acute advanced COVID-19 patients from referring hospitals where they were showing no signs of improvement after receiving treatments from standard Emergency Use Authorization (EUA)-type protocols. The care providers turned to repurposing medications to treat these patients and added hydroxyurea, a medication commonly used for treating sickle cell anemia, to the hospital's COVID-19 treatment protocol and began to see notable clinical improvements. As the pandemic continued and new concerns arose concerning COVID-19 complications, those same care providers again turned to repurposing drugs. Focusing on the neuromuscular effects seen in COVID-19 patients, care providers turned to medications used to treat chronic neuromuscular conditions. Post-acute advanced Covid-19 patients initially received an abbreviated course of hydroxyurea followed by titrated doses of pyridostigmine. Positive responses were noted with cognition, diminished oxygen demands, progressive decrease in ventilator support, improved swallowing, and mobility. The authors suggest repurposed drugs could have great utility for treating COVID-19. It is recommended larger, COVID-19 clinical trials be completed to include hydroxyurea and pyridostigmine for validating the outcomes and clinical observations seen in these presented cases.

Keywords: Covid-19; drug repurposing; acute care; hydroxyurea; pyridostigmine

1. Introduction or history

The coronavirus disease 2019 (COVID-19) pandemic first began upon its discovery in China in December 2019 [1]. Initially the major concerns were the viruses attack on the respiratory system of each patient [2]. Medical care providers rushed to treat patients and provide adequate oxygen assistance during recovery [2]. As the COVID-19 pandemic continued, physicians worldwide were reporting additional concerns with neurological muscular disorders both during COVID infection and post COVID recovery [3].

Currently there is not a worldwide protocol for treating COVID-19 [4]. Although the introduction of a vaccination for the virus has decreased the number of fatalities associated with the virus, there are still reports of people contracting the virus [5]. Additionally, the COVID-19 virus has mutated multiple times and has the ability to continue to do so, supporting the need to continue to focus on treatment options to improve outcomes [6].

One medication that has been used worldwide to treat COVID-19 is convalescent plasma, however many studies have found no significant data to support the use of the medication [7]. Early in the pandemic in April 2020, authors posted a summary of ten clinical patients who received convalescent plasma [7]. The ten patients improved but further studies were recommended with larger trials [7]. One of the larger studies completed at a later date with a larger number of patients compared COVID-19 patients treated with convalescent plasma to a control group [8]. The study found no association between the medication and lower mortality or improved disease progression [8]. Another study conducted by the National Institute of Health was discontinued in February 2021 when the use of convalescent plasma in high-risk outpatients with COVID-19 showed no prevention of disease progression [9].

Another medication that has been commonly used to treat COVID-19 is remdesivir. Studies did support the use of remdesivir to be more beneficial and to shorten the recovery time of inpatients with Covid-19 [10]. However, as the medication was used more, other trials showed the side effects associated with remdesivir led to some patients having to discontinue the medication before adequate time for recovery [11].

As the pandemic continued, ivermectin was another medication that generated interested among practitioners. When put through a clinical trial of high-risk patients with mild to moderate COVID-19 infections, ivermectin did not prevent the patients from advancing to severe stages of the disease [12].

During the pandemic, a specialty hospital in central North Carolina began using hydroxyurea as part of their treatment protocol for severe COVID-19 patients. Upon seeing positive outcomes, the results were reported in the hopes of sharing the protocol and the idea of repurposing hydroxyurea with care providers to increase the percentage of those who recover from COVID-19 [13].

The hospital chose to try hydroxyurea after conflicting observations were made between the patients' imaging and poor oxygen levels. The lower oxygen levels patients were demonstrating did not correlate with the radiographic and computed tomography images which were showing decreased congestion in the lungs. This led providers to believe the low oxygen levels were a result of compromised gas exchange at the capillary levels rather than lung congestion and abnormalities. Hydroxyurea was chosen because of its ability to increase the amount of fetal hemoglobin (Hb F) in the red blood cells therefore increasing hemoglobin oxygen bonding. This assists with oxygen exchange at the capillary levels and helps ensure sufficient oxygen levels. More commonly used to

assist sickle cell anemia patients with maintaining appropriate oxygen levels, the providers hypothesized the medication could be used to achieve the same effect in COVID patients [13].

After witnessing the positive results from incorporating the hydroxyurea into the treatment protocol for COVID-19 patients, care providers at the same hospital wanted to find a way to improve neurological muscular outcomes in recovering, post-ventilated COVID-19 patients and again turned to repurposing current medications.

2. Clinical observations

In 2021, the Journal of Critical Care Medicine published an article, "The use of hydroxyurea in the treatment of COVID-19: A combination of clinical findings and data analyses." The paper presented nine cases of severe COVID-19 patients being treated with a specialty hospital's protocol using hydroxyurea. Hydroxyurea is historically used as a maintenance drug for sickle cell patients. The cases dated back to the initial stages of the COVID-19 pandemic, April 2020. All nine cases involved patients who were previously unsuccessfully treated at other facilities using varying treatment methods including convalescent plasma, antibiotics, steroids, remdesivir, and other methods commonly used for the treatment of COVID-19. The patients ranged in age from 51–76 and were both male and female. Prior to contracting COVID-19, no other major comorbidities were reported. After being treated with the specialty hospital's hydroxyurea protocol, all nine cases resulted in patients fully recovering and reverting back to pre-COVID respiratory status. The average time from beginning of the hydroxyurea treatment protocol and tube removal was 14 days [13].

The facility continued to use the protocol and additionally expanded to using hydroxyurea on both an inpatient and outpatient basis, with slight variances in the protocol. As of July 2022, 1,683 outpatients have been treated with the protocol, with 1,681 full recovering and two expiring. For inpatients, as of July 2022 approximately 190 patients have been treated with the hydroxyurea COVID-19 protocol with an estimated 90% survival rate. Additionally, hospitals throughout the world have adapted similar protocols with hydroxyurea being the main component, including an Intensive Care Unit in Florida and a hospital in Australia. The medical care providers also correlated with other teams to provide a similar protocol to outpatient COVID-19 patients that still featured hydroxyurea as the primary medication.

Beginning in January 2022, the same specialty hospital modified their treatment protocol for new admissions of severe COVID-19 patients. This was initiated by a patient who was referred to the hospital with advanced COVID-19 associated with suspected severe neurotoxicity induced by a curare-like drug that had been prescribed by the referring facility. The drug, vecuronium, was prescribed to address the patient's violent reaction to being intubated while on a ventilator. Pyridostigmine was prescribed by the specialty hospital to address the suspected neurotoxicity. This had positive results with addressing the patient's violent reaction to being intubated and it additionally showed significant improvements in many of the patient's COVID-19 related dysfunctions including swallowing difficulties, cognitive issues, high oxygen demands, and mobility dysfunctions. The patient made a full recovery despite being dependent on a ventilator for several weeks following a complex COVID-19 pneumonia diagnosis and other organ complications while in an acute ICU setting. After this observation, care providers cautiously proceeded to modify the facility's COVID-19 protocol (which included hydroxyurea) and added pyridostigmine. As with the previous patients used initially for the original treatment protocol, the new protocol was used on patients who had been treated for COVID-

19 at other facilities with little to no improvement. The family members and/or health care proxies for these patients were not yet ready to move the patients from curative treatment to palliative treatment so they were sent to the specialty hospital in hopes of continuing treatment to allow more time for signs of improvement.

The clinical observations provided all involve severe COVID-19 patients. One reason the patients were sent to the specialty hospital is because it has a chief focus of weaning medically intricate patients from mechanical ventilation. The specialty hospital is a licensed long-term care acute facility with expertise in the recovery of critical illness. Patients are typically referred to this hospital who have survived an injury or illness but are not showing adequate or any improvement and have a need for continued, substantial medical care.

The patients observed were admitted to the specialty hospital between October 2021 and April 2022. All patients had previously demonstrated severe side effects resulting from COVID-19 infection and had shown minimal and/or no improvement at the referring facilities. Treatments from the referring facilities included remdesivir, breathing tubes, percutaneous endoscopic gastrostomies (PEGs), dexamethasone, ivermectin, acyclovir, and tocilizumab. There was a combination of both vaccinated and unvaccinated patients. None of the observed patients had received post-vaccination boosters.

The protocol used on the observed patients included:

(1) hydroxyurea, 500 mg PO BID X 7 days
(2) solumedrol, 60 mg IV BID, continued until discharge but slowly tapered to oral administration
(3) folic acid, 2 mg daily X 7 days
(4) anticoagulation medicine, heparin, enoxaparin sodium or apixaban, continued until discharge
(5) fish oil, Omega 3, 300 milligrams per gram, 6 g daily, continued until discharge
(6) amantadine,100 mg daily
(7) sertraline, 25 mg daily with allowance up to 75 mg
(8) melatonin, 3 mg at bedtime
(9) acyclovir if needed when viral encephalitis and/or stomatitis was suspected
(10) pyridostigmine—dosage varies based on the patient's vitals—mild bradycardia is desired because it will decrease the systemic doses of chronotropic agents such as amiodarone and diltiazem, resulting in decreased toxicities from these medications

-baseline dose is 60 mg TID, slowly tapered down after discharge

-if the pulse does not respond and drop significantly, the dose will be increased to 120 mg TID, then tapered

-for some patients, 90 mg TID is sufficient to see the desired decrease in pulse

Twelve patients were observed including both males and females, between the ages of 47 and 76. All patients were intubated and dependent on tube feedings at the time of admittance to the specialty hospital. The average number of days between a patient's admittance to the specialty hospital and discharge was 47 days.

The average duration of the illness for patients prior to beginning treatment with pyridostigmine was 69 days. The average time for discharge after starting the modified COVID 19 protocol including pyridostigmine was 20 days. Eleven of the twelve patients were decannulated prior to being discharged and one was decannulated two days after being discharged to an inpatient rehabilitation facility. Six months post discharge, no patients reported any complications or rehospitalizations. Table 1 provides

a summary of all presented case studies of patients receiving the specialty hospital's modified COVID-19 treatment protocol that includes pyridostigmine in addition to hydroxyurea.

3. Theory

Initially, the primary focus of the specialty hospital's COVID-19 treatment protocol was the use of hydroxyurea. The protocol has resulted in numerous cases of recovery, and to improve outcomes of other, muscular related side effects of COVID-19 the primary focus of these case study reviews was the modification of that protocol to include pyridostigmine. Thus far in the COVID-19 pandemic, neither hydroxyurea nor pyridostigmine are medications commonly used in COVID-19 treatment protocols [14].

It has been noted through clinical observations COVID-19 patients sometimes demonstrate complications with respiratory musculature, muscarinic receptors, and/or nicotinic receptors [15]. Some patients struggling with COVID-19 recovery will demonstrate both peripheral and central nervous system dysfunction symptoms such as difficulty swallowing and difficulty breathing without assistance [16].

With the increasing number of patients suffering from these symptoms, health care providers involved with these case studies began to consider drugs used for the maintenance of chronic neuromuscular diseases. Specifically, pyridostigmine was added to the hospital's protocol.

Pyridostigmine is most commonly used as a maintenance drug in the treatment of myasthenia gravis [17]. Myasthenia gravis is a chronic disease that results in weakness of the skeletal muscular system [18]. Although it can affect any muscles, the most common ones affected are those of the face and throat, resulting in eye drooping, double vision, and difficulty swallowing [18]. With myasthenia gravis, antibodies interfere with neurotransmission at the level of the alpha7-nicotinic acetylcholine receptors (a7NAChR) that reside where the nerves and muscles are joined [18]. When the antibodies disrupt these receptors, nerve impulses can no longer pass through to cause the desired and/or necessary muscle contractions in that particular area [18]. In most cases, immunoglobulin G1 (IgG1) and immunoglobulin G3 (IgG3) antibodies are what attacks the a7NAChRs, therefore causing the lack of impulses that leads to muscle weakness [19]. When the unstimulated acetylcholine is detected, acetylcholinesterase quickly hydrolyzes it [19]. Acetylcholinesterase is an enzyme secreted by the muscles [19].

Medical providers who were focused on improving the quality of life for neuromuscular disorder patients determined if acetylcholinesterase could be inhibited, it helped improve the muscle strength of those patients [20]. Pyridostigmine hinders acetylcholinesterase, therefore preventing the breakdown of acetylcholine [20]. This results in increased muscle strength in patients with myasthenia gravis [20].

Table 1. Summary of presented case studies of patients receiving specialty hospital's modified COVID-19 treatment protocol to include pyridostigmine in addition to hydroxyurea.

	Age	Sex	Duration of illness prior to beginning COVID-19 treatment protocol with pyridostigmine	Diet on admission	Days until discharge total (based on admission to specialty hospital)	Days until discharge since beginning pyridostigmine	Decannulated prior to discharge?	Diet on discharge	Complications
1	50	M	139	Tube feedings	123	49	Y	D2 thin	None
2	68	M	84	Tube feedings	78	41	Y	D1 thin	None
3	47	M	52	Tube feedings	24	2	Y	NPO	None
4	47	F	51	Tube feedings	23	4	Y	D3 thin	None
5	50	M	81	Tube feedings	24	2	Y	D3 thin	None
6	49	M	59	Tube feedings	42	12	Y	D2 thin	None
7	62	F	33	Tube feedings	15	9	Y	Regular	None
8	55	M	85	Tube feedings	54	21	Y	D3 thin	None
9	64	M	117	Tube feedings	99	33	Y	D2 thin	None
10	76	M	53	Tube feedings	31	23	Y	D2 thin	None
11	70	F	50	Tube feedings	39	27	Y	NPO	None
12	57	F	22	Regular	17	15	N/A	Regular	None

Note: M: Male; F: Female; D1 thin: Level 1 dysphagia diet (pureed food); D2 thin: Level 2 dysphagia diet (minced food); D3 thin: Level 3 dysphagia diet (chopped food); NPO: Nothing by mouth (no food allowed orally).

Through consultations with a biochemist, Dr. Maryna Skok of the Palladin Institute of Biochemistry in Kiev, Ukraine, was instrumental for the clinical team to validate some of their theories related to the addition of pyridostigmine to the treatment protocol. Dr. Skok has an extensive history with research, publications, and new discoveries involving nicotinic acetylcholine receptors, medical care providers found more correlation between the potential of improved patient outcomes for COVID-19 patients if treatment included a focus on improving neuromuscular issues [21]. This ultimately led the care providers to add pyridostigmine to the COVID-19 treatment protocol that included hydroxyurea.

Prior to adding it to the treatment protocol, the side effects of pyridostigmine were evaluated thoroughly. The most common side effects of pyridostigmine are non-life-threatening and include sweating, diarrhea, nausea, vomiting, drooling, epiphora, abdominal cramping, erythema of the face, and erectile dysfunction [22]. In rarer cases, patients may experience muscle twitching, cramping, or weakness. As with all medications, unknown severe allergy to a substance can result in anaphylaxis upon initial treatment [22].

All twelve cases provided featured patients who were unable to breathe independently due to respiratory muscle weakness and fully dependent on PEG tube feedings due to esophageal muscle dysfunction. With the ten case studies provided, after being treated with the new protocol that included both hydroxyurea and pyridostigmine, significant improvement was seen in the swallowing and respiratory functions of the patients. All patients were able to be decannulated and breathe without mechanical support. Nine of the ten patients were able to begin taking food by mouth. All patients were able to be discharged either home or to an inpatient rehabilitation facility, which is the specialty hospital's goal for their severe illness patients.

The repurposing of drugs for treatment purposes is not an uncommon practice. As previously mentioned, the same physicians previously repurposed hydroxyurea, a drug commonly used for sickle cell patients, to treat COVID-19 patients due to its ability to assist with gas exchange at the capillary level [13].

Most cases of drug repurposing resulted from observations made by medical practitioners or those who were highly knowledgeable of the mechanisms of action of the repurposed medications [23]. One of the first drugs that became well-known for being repurposed was sildenafil, also known as Viagra [23]. Sildenafil was originally used to treat pulmonary arterial hypertension, but in the 1990s during clinical trials it was discovered the effect it had on erectile difficulties [23]. Since then, the drug has been accepted globally as one of the most common treatments for erectile dysfunction, while still being used to treat hypotension in some patients [23].

Both positives and negatives exist to the practice of repurposing drugs [24]. One positive is the ability to hasten treatment ideas by using repurposed drugs [24]. Since the repurposed drug has already been on the market and undergone numerous clinical trials to receive approval from the proper entities (such as the Food & Drug Administration in the United States of America), a lot of the required data has already been acquired [24]. New drugs must undergo intense clinical trials and review before they are approved for treatment purposes, which can take a substantial amount of time [24]. The risks of drugs already in use have already been discovered and evaluated [24]. Additionally, already having this data allows practitioners to focus on already known side effects of the drug and take the necessary precautions when prescribing the medication for the new purpose [18]. Also, in contrast with newly approved drugs, many of the repurposed drugs have been on the market for decades, which also allows practitioners to be aware of the risk of side effects resulting from long term use of the medication [24].

In contrast to the positive aspects to repurposing drugs, one negative is not all approval requirements can be skipped [24]. As with any medication, using it outside of the normally accepted diagnostic use and patient population could introduce new risks and side effects, so testing and data must be evaluated to determine the probability of new risks and/or side effects [24]. Additionally, the economic impact on the pharmaceutical industry cannot be ignored [24]. Traditionally, pharmaceutical companies earn more profit with new medications compared to the profit they make on most repurposed drugs [24]. If repurposing drugs were to become an extremely customary practice, the financial effects it has on pharmaceutical companies could be detrimental [24]. However, in contrast, using more affordable and readily available medications could have a positive impact on health care cost for patients and providers [24].

Research budgets can also be benefited by utilizing repurposed drugs [24]. As more illnesses and injuries are found to be treatable through repurposing drugs, this would allow research dollars to be redistributed to areas where repurposing drugs is not an option, therefore allowing more resources for discovering new medications and treatments in those areas [24].

4. Conclusions and prospects

As the COVID-19 virus continues to spread and mutate, medical care providers are finding more associated complications that must be treated [25]. These complications now include a concern for the neuromuscular health and wellbeing of patients [25]. The neuromuscular complications affecting respiratory muscle functions result in serious difficulties when attempting to wean patients from dependence on mechanical ventilation [26]. Additionally, the neuromuscular complications are also causing esophageal muscle dysfunction, making it difficult for patients to swallow and ingest food [27].

After reviewing the presented cases as well as evaluating findings from other studies involving the treatment of neuromuscular disease, it is suggested that both hydroxyurea and pyridostigmine could be a potential pharmaceutical component to add to the treatment of COVID-19 patients. In addition to the physical benefits, it has also been suggested that this medication combination could potentially help combat the COVID-19 “brain fog” phenomenon that has also become a new concern for medical care providers [28].

Others have also noted the potential cardioprotective effects that could result from pyridostigmine. One study reviewed the effects of acetylcholine treatment in patients with hypoxia/reoxygenation (H/R) injury from cardiac damage. Once the acetylcholine treatment was started and re-oxygenation began, cell viability improved, and a significant increase was found in the mass and density of the mitochondria as well as the mitochondrial DNA copy number. Additionally, positive developments were noted in ATP synthesis and membrane quality. The authors of the study proposed that by supporting acetylcholine levels in the body, the acetylcholine in turn worked as nourishment for the mitochondria. This helped protect the mitochondria from deficiencies that could result from the H/R injury [29].

Furthermore, since the initial step of repurposing hydroxyurea as a COVID-19 treatment, medical practitioners at the specialty hospital have also noted other potential favorable responses with hydroxyurea in patients with myocarditis, acalculous cholecystitis, and some bone marrow abnormalities. This has motivated the medical practitioners to continue giving high consideration to the repurposing of medications when looking for more successful treatments.

Other researchers and medical care providers have also expressed the positive results from using hydroxyurea to treat COVID-19 patients. In one article by Moftah and Eswayah, although it was not able to provide resulting data as supporting evidence, the study did emphasize the potential of hydroxyurea to reduce the risk of thrombotic events in COVID-19 patients, and possibly others [30]. One common cause of mortality and morbidity in COVID-19 patients is cytokine release syndrome [31]. Cytokine release syndrome causes increased release of proinflammatory mediators which increases the D-dimer level that indicates high potential for thrombotic events, such as pulmonary embolisms [31]. The authors argue that, since hydroxyurea can help control circulatory levels of key cytokines through its anti-inflammatory capabilities, it can serve as a supportive therapeutic agent for COVID-19 patients [30]. As mentioned in both this article and the Foster et al. article, hydroxyurea also induces the production of fetal hemoglobin production [13]. Moftah and Eswayah theorize with both of these capabilities combined, hydroxyurea can also serve as a protective agent against thrombotic events in COVID-19 patients [30].

The capability of a hydroxyurea as a protective agent against severe COVID-19 infection has also been theorized. Another group of researchers published an article presenting observations of 30 sickle cell disease patients who were diagnosed with COVID-19 [26]. The authors noted those sickle cell patients who were taking hydroxyurea prior to being diagnosed with COVID-19 ultimately displayed less severe symptoms than the patients who were not already taking hydroxyurea prior to their diagnosis [32].

Another article also focused on repurposing hydroxyurea as a potential, temporary solution to the shortage of blood. For patients requiring regular blood transfusions, access to the necessary care and/or blood can be difficult to obtain [33]. Hydroxyurea's capability of inactivating certain enzymes (specifically ribonucleoside diphosphate) and fetal hemoglobin induction, it enhances the body's ability to efficiently use blood and can lengthen the amount of time between blood transfusions [33]. The article suggested hydroxyurea can be used as a supplemental drug for those needing regular blood transfusions to extend the time between their transfusions therefore serving as a potential solution to the limited blood supply issue [33].

Both pyridostigmine and hydroxyurea are affordable drugs that are efficiently manufactured. With a long history of treatment use for diseases such as sickle cell anemia and myasthenia gravis respectfully, the side effects for both medications have proven to be minimal in most cases. Years of use and data support the benefits outweighing the risk when using both medications. For pyridostigmine, the clinical observations summarized presented here represent a small number, so the authors recommend a larger scale study be completed using pyridostigmine as a treatment component for COVID-19 patients. This study should focus on evaluating the neuromuscular changes in those patients to determine if pyridostigmine assists with eliminating dependence on mechanical ventilation, dysphagia, and other neuromuscular issues. Furthermore, more data would also assist with finding other potential uses for pyridostigmine in addition to maintenance treatment for myasthenia gravis patients. For hydroxyurea, since the previously mentioned article was published summarizing similar clinical observations, the numbers have increased drastically, providing more validity to the original article's theory. However, the authors still recommend a larger scale study be completed focusing on hydroxyurea as well to provide more data concerning the potential use of hydroxyurea to improve COVID-19 prognosis as well as find other potential uses for the medication.

If further research finds pyridostigmine does improve the neuromuscular outcomes for COVID-19 patients, it would be efficient to use the drug in other trials. Pyridostigmine is an affordable

medication with minimal side effects that is easily manufactured. This would make it an ideal candidate for pharmaceutical drug trials focused on repurposing current medications.

Acknowledgments

The authors would like to express immense gratitude to Maryna Skok D. Sci at the Palladin Institute of Biochemistry of the National Academy of Sciences of Ukraine in Kyiv for her invaluable contributions and continued dedication to the field of research. Her extensive research with α7nicotinic acetylcholine receptors have greatly contributed to our appreciation of patient clinical outcomes and given us more validation for continued efforts to share important concepts related to multi systems pathophysiologies with COVID-19.

The authors would also like to acknowledge Anupama Matcha MD,MPH, Farouque Khan MD, Chun Li NP, Ms. Priya Varghese NP, David Best MD, and Weston Saunders MD for their amazing contribution and dedication to helping critically ill patients with repurposed drugs, which greatly contributed to the possibility of this article.

Conflict of interest

The authors declare no conflict of interest.

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