



Pharmacological Effort and Medication Approaches for the Management of COVID-19 Pandemic in Nepal .

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Abstract:

COVID-19 pandemic has created a long-lasting effect on different aspects of peoples' life. Several efforts were made by Nepal for the management of the COVID-19 surge. This study intended to compile the pharmacological efforts adopted for the prevention and management of COVID-19 during its pandemic in Nepal. A comprehensive study was performed from 10th May to 25th May 2021. Altogether, 25 documents, three guidelines, and 30 articles were assessed and analysed in this study. The major pharmacological steps for the prevention of COVID-19 were seen through vaccination campaigns, the development of guidelines, and the use of repurposed drugs (Remdesivir, corticosteroids, anticoagulants etc). Significant pharmacological steps were seen in the prevention and treatment of COVID-19 in Nepal during the pandemic. With the limited resources, Nepal's action against COVID-19 seemed to be impressive; however, more efforts are demanded to combat similar situations in the future.

Keywords: COVID-19; Nepal; Pharmacology; Vaccines.

1. Introduction

COVID-19 has impacted almost every sector globally. Various pharmacological agents have been investigated in several clinical trials and observational studies as possible treatments for Coronavirus Disease 2019 (COVID-19), but the findings are inconsistent and often conflicting, making it difficult for clinicians to assess which treatments are genuinely effective.[1] Following the World Health Organization's declaration of COVID-19 as a pandemic on March 11, 2020, the Nepalese government took several measures to avoid and mitigate the effects of the coronavirus.[2] However, there is a dearth of literature assessing the pharmacological measures adopted in Nepal during the COVID-19 pandemic.[2,3,4] Therefore, this review was

performed to study the pharmacological approaches that were adopted for the prevention, treatment, and mitigation of the COVID-19 pandemic which will help to figure out how effectively the country could fight against COVID-19 amidst of pandemic. This review will be very useful to compare the efforts taken by other countries as well as will be helpful for the preparedness in combating similar situations in the future.

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2. Methods

An expert team of 5 members with clinical expertise were formed to perform an extensive review. The work was divided evenly among the team members based on the individual expertise. A comprehensive review on pharmacological efforts in the prevention and treatment of the COVID-19 in Nepal was carried out from 10th May to 25th May 2021.

The key words: "Pharmacological efforts", "COVID-19", "Vaccines", "Prevention",

"Treatment" were used to search the literature. The literatures were filtered using Boolean expressions "AND" and "OR". Altogether, 25 documents, 3 guidelines and 30 articles were assessed and analyzed in this review.

3. Results

A. Allopathic Approaches

Allopathic approaches include the efforts made for prevention, mitigation and treatment of COVID-19 through vaccination and medications. (Table 1)

Table 1. Milestones of Pharmacological Efforts for the Prevention and Treatment of COVID-19 in Nepal.

June, 2020	Development of "Interim clinical guidelines for care of patients with COVID-19 in healthcare settings" by Nepal Medical Council
11th August, 2020	Approved Emergency use of Remdesivir injection for COVID-19 infection in designated hospitals only
21st October, 2020	Revision of the "Interim clinical guidelines for care of patients with COVID-19 in healthcare settings"
15th January, 2021	Approval of COVID-19 Vaccine COVISHIELD produced by the University of Oxford and AstraZeneca and manufactured by the Serum Institute of India.
27th January - 4th March, 2021	The first-phase of a nation-wide Covishield vaccination program against corona virus.
3rd February, 2021	Publication of code on "Emergency use of Drug or vaccine 2077"
16th February, 2021	Emergency Use approval of covid-19 vaccine (Vero Cell), inactivated vaccine manufactured by Beijing Institute Biological Products Co. Ltd. (BIBP) (under Sinopharm).
6 th March, 2021	Nepal received 348,000 doses of COVID-19 vaccine under COVAX facility
7th - 15th March, 2021	Covishield vaccination program at second phase
18 th March, 2021	The World Bank had announced that its broad approved \$ 75 million (NRs. 8.72 billion) loan to Nepal to procure COVID-19 vaccine and to strengthen the health system to support the vaccination efforts, and to procure other supplies.
19 th March, 2021	Conditional permission granted for Emergency Use Authorization of COVAXIN vaccine manufactured by Bharat Biotech International Limited, India.
7 th - 28 th April, 2021	First-phase Vero Cell vaccination program
20 th April, 2021	Emergency use Authorization of Sputnik-V COVID-19 Vaccine; a Gam-COVID-vac Combination vector vaccine manufactured by FSBI N.F. Gamaleya National Research Center of Epidemiology and Microbiology of Ministry of Health of Russia.
4 th May, 2021	3000 vials of Remdesivir injection (Bemsivir injection) from Beximco pharmaceutical limited, Bangladesh was imported by Hermo Medi concern Pvt. Limited, Kathmandu, Nepal
6 th May, 2021	4000 vials of Remdesivir injection (Ninavir injection) from Incepta pharmaceuticals limited, Bangladesh was imported by Ayan Health Care Pvt. Limited
10 th May, 2021	2000 vials of Remdesivir injection (Remcor injection) from ACI Limited, Bangladesh was imported by Ways International Pvt. Limited.
12 th May, 2021	Published guidelines on Management of Patients during shortage Created by COVID 19 Surge
16 th - 25 th May, 2021	Second-phase Vero Cell vaccination program

Vaccination

Nepal launched COVID-19 vaccination program from January 27, 2021.[5] For prevention of COVID-19, the Indian government provided one million doses of CoviShield in a grant. In the first phase, the vaccines were targeted to the health workers, FCHV, security personnel, sanitation workers, elderly people living in care homes, and prisoners.[5] Other COVID-19 vaccines Vero cell

and Sputnik were approved for Emergency Use in Nepal.[6,7] However, until May 2021 only CoviShield vaccines and Vero cell vaccines were used in Nepal. **(Table 2)** A total of 438,000 populations received their first dose in the first phase (27th January to 5th March) and around 1.3 million people were vaccinated in the second phase (7th to 15th March). [8, 9]

Table 2. Information related to COVID 19 Vaccines Approved for Emergency Use in Nepal till 24th May 2021

	CoviShield	Vero Cell	Covaxin	Sputnik-V
Vaccine type	(Recombinant, Viral vector) a weakened version of an adenovirus from chimpanzees	inactivated SARS-CoV-2 Vaccine	Whole-Virion Inactivated SARS-CoV-2 Vaccine	SARS-CoV-2 glycoprotein S
Vaccine Efficacy	70% after first dose and 90% after second dose [10]	For symptomatic and hospitalized diseases (all age groups combined): 79% Few older adults (over 60 years) were enrolled in clinical trials, so efficacy could not be estimated in this age group [11].	81%	91.6% after two doses [12]
Vaccine Manufacturer	Serum Institute of India & Oxford-AstraZeneca	BIBP (under Sinopharm)	Bharat Biotech International Limited, Hyderabad, Telangana, India	FSBI N.F. Gamaleya National Research Center of Epidemiology and Microbiology of the Ministry of Health of Russia.
Date of approval for Emergency Use	15 th January 2021	17 th February 2021	19 th March 2021	20 th April 2021
Population covered	1 st dose: 438,000 2 nd dose: 370,000	1 st dose: 289,000 2 nd dose: ongoing	not used till May 2021	not used till May 2021
Dose	2 (4-12 weeks apart)	2 (3-4 weeks apart) [11]	2 (4 weeks apart)	2 (heterologous) given 21 days apart [12]
Storage condition	2 to 8°C [10]	2 to 8°C	2 to 8°C	-18.5°C (liquid form) 2 to 8°C (dry form)

Pharmacological efforts for the treatment of COVID-19 in Nepal during its Pandemic.

Treatment guidelines and protocols for the prevention and treatment of COVID-19 were prepared globally by several healthcare organizations and regulatory bodies. All the therapeutic options that were used for the treatment of COVID-19 were repurposed drugs

globally, and so was done in Nepal. Nepal Medical Council (NMC) developed a clinical guideline and revised it twice for care of patients with COVID-19 in health care settings based on the global evidence of various studies. [13] **(Table 3)** The guideline was revised in different timelines according to new evidence generated from scientific studies of different nations.[14]

Table 3. Detail of medicines that were used to treat Patient with COVID-19 (Nepal Medical Council Clinical Guidelines)

S. No.	Drugs Name	Guideline of June 2020[13]	Revised Guidelines of 12 th May , 2021[14]
1	Antiviral and Immunomodulators		
1.1	Remdesivir*		
	Indication	<ul style="list-style-type: none"> - Patients with moderate COVID-19 if they have two or more risk factors for developing severe illness - Patients with severe and critically ill COVID-19 	<ul style="list-style-type: none"> - Patients with severe disease who are within the first 10 days from symptom onset, but have rapidly progressing hypoxia in spite of systematic corticosteroid use, or - For immune-compromised patients requiring low flow oxygen, or - Severe infection requiring ICU admission who are not on ventilators.
	Doses	- 200 mg on day 1, and 100 mg once daily on subsequent days parenterally (IV) for 5 days course for moderate to severe cases and 5-10 days courses for critically ill cases	NA
1.2	Tocilizumab (not registered in Nepal till this report prepared)		
	Indication	NA	Patients with severe or critical COVID-19, who have rapidly increasing oxygen needs and systemic inflammation despite use of systemic corticosteroids.
	Doses	NA	NA
2.	Corticosteroid		
2.1	Dexamethasone OR Prednisolone or Methylprednisolone, or Hydrocortisone		
	Indication	<ul style="list-style-type: none"> - Patients with severe ARDS with high ventilatory support - Septic shock, adrenal crisis or co-morbidities such as COPD exacerbation or asthma exacerbation if required 	Start early when SpO ₂ is less than 93% on room air in outpatient settings. <i>Not recommended for mild to moderate disease when SpO₂ is ≥ 93%.</i>
	Dose	- NA	Dexamethasone: 6mg/day or Prednisolone 40mg once a day, or oral Methylprednisolone 32 mg once a day depending on availability.
2.2	Inhaled Corticosteroid		
	Indication	NA	Adults with mild to moderate disease within 7 days from onset of symptoms
	Doses	NA	Budensonide 800 mcg twice a day and can be discontinued upon resolution of symptoms or if patient is started on systemic steroids.
3	Empiric antibiotics		
	Indication	Patients with moderate COVID-19, when bacterial super-infection is suspected Patients with severe or critically ill or septic shock secondary to COVID-19, when bacterial superinfection or viral coinfection is suspected.	Not recommended in the absence of clear evidence of bacterial infection.

4	Anticoagulation Agent (AC): Enoxaparin, Dalteparin, Fondaparinux		
	Indication	<ul style="list-style-type: none"> - Treatment of Venous thromboembolism (VTE) for adults with COVID-19 hyper coagulopathy - Case of rising D-dimer (>6 times the normal limit) - Worsening hypoxia not fully explained by worsening chest x-ray - In case of high suspicion of DVT/pulmonary embolism or thrombosis of central venous or arterial line 	NA
	Dose	<ul style="list-style-type: none"> - Based on creatinine clearance level of the patient; whether > 30 ml/min or < 30 ml/min. - Based on the indication; either prophylaxis or treatment of venous thromboembolism (VTE). 	NA
5	Sedation and Neuromuscular Blockage		
	Indication	- Patient with ARDS secondary to COVID-19.	NA
	Dose	- Sedation and intermittent boluses of neuromuscular blocking agents can be given in case of ventilator dyssynchrony.	NA
6	Vasopressors: Norepinephrine, Vasopressin, Epinephrine and Dopamine		
	Indication	- Septic Shock secondary to COVID-19	NA
7	Nonsteroidal anti-inflammatory drugs (Paracetamol)		
	Indications	- Temperature-lowering agent and analgesic	NA
8	Dry nebulization: Metered-Dose Inhaler (MDI)		
	Indications	<ul style="list-style-type: none"> - Acute airflow obstruction - Patients with moderate to severe airflow obstruction 	NA
	Dose	<ul style="list-style-type: none"> - Salbutamol (100mcg) 4 puffs - Ipratropium (20mcg) 4 puff (if available) - Every 10-20 minutes for 1st hour then every 4 - 8 hours-prn, subsequently 	NA

B. Ayurvedic Approach

An interim guideline "Ayurveda and Alternative Medicine Guidelines of Preventive Measures and Management Protocol for COVID-19 in Nepal" was developed by Ministry of Health & Population, Department of Ayurveda & Alternative Medicine, Teku in collaboration with Nepal Ayurvedic Medical Council, Naradevi and Ayurvedic Campus and Teaching hospital, Kirtipur was issued on 15th Baishakh, 2077.[17] The *Zingiber officinale*, *Curcuma angustifolia*, *Tinospora cordifolia*, *Azadirachta indica*, *Ocimum basilicum*, *Mentha arvensis*, *Allium sativum*,

Cinnamomum zeylanicum, *Phyllanthus emblica* were commonly used herbal plants.[17] These species are also listed by the Ministry of Health & Population of Nepal, Department of Ayurveda & Alternative Medicine, Teku, Kathmandu, as an alternative medicine to boost the immunity power of people.

The herbal medicine remedies for COVID-19, like broad-spectrum antivirals, protease inhibitors as well as boosting the immunity were reviewed. *Tinospora cordifolia*, *Glycyrrhiza glabra*, *Swertia chirayita* (Roxb. ex Fleming) H. Karst, *Ocimum sanctum* L, *Zingiber officinale* Rosc, *Curcuma*

longa, *Allium sativum* L, *Withania somnifera* (L.) Dunal, *Moringa oleifera*, *Zanthoxylum armatum* DC, *Cinnamomum zeylanicum*, *Phyllanthus emblica* possess antiviral properties which are locally available in Nepal.[17]

4. Discussion

This review encompasses pharmacological steps of Nepal in the prevention and treatment of COVID-19 starting from the pandemic till 25th May, 2021. Nepal witnessed a second wave of COVID-19 pandemic during April and May with 6,531 deaths and 520,461 (RT-PCR) infected cases on 24th May, 2021.[18] Nepal strived to combat the COVID-19 pandemic through vaccines that were approved for Emergency Use by WHO and other countries and through the use of different medicines that were being used globally to reduce symptoms associated with COVID-19.

Nepal was among the first countries to receive the COVID-19 vaccine earliest through COVAX facility. During first and second wave of pandemic, Nepal's vaccine diplomacy might have served as a model for many countries that had not begun vaccination against COVID-19 in those days, especially low- and middle-income countries (LMICs).[19] Altogether 728,296 (2.5% of the total population) were fully vaccinated in Nepal while 4.7% of the world's population were vaccinated as of 16th May, 2021 data.[20] Since the emergence of this novel virus, scientists from all over the world were working harder than ever to manufacture the vaccines that would help to halt the spread of COVID-19. A total of 15 vaccines were given to the general population in the world until May 2021.[21] Out of them, 4 vaccines were registered for emergency use in Nepal; and 2 vaccines i.e., CoviShield and Vero Cell were being administered to the targeted population during the first and second wave of the pandemic. In USA, nearly 40% of the people were vaccinated till 22nd May, 2021[20] and the trend in number of cases and deaths were decreasing in US based on the report of CDC.[22] So, the high coverage of COVID-19 vaccines was taken as the major key to prevent and control the spread and

deaths related to COVID-19.

Although, Remdesivir was approved for usage during the early stages of the pandemic, WHO eventually advised against its use.[23] However, the use of remdesivir continued in Nepal till the second wave.[24] The prospective observational study conducted in Nepal by NHRC found that the majority of patients with a severe COVID-19 infection had a better outcome with the use of remdesivir.[25] A recovery trial also showed that the adults who were hospitalized with COVID-19 and had lower respiratory infection had a shorter recovery time with the use of remdesivir compared to the control group.[26]

Although the safety and efficacy of corticosteroids along with the combination of antiviral therapy were not studied meticulously in clinical trials, the treatment guidelines developed by National Institute of Health (NIH) recommended the use of Corticosteroids (Dexamethasone, Methylprednisolone, Prednisone and Hydrocortisone) based on the results of the recovery trial performed in United Kingdom in which, corticosteroid therapy reduced the risk of mortality and mechanical ventilation duration.[27] Likewise, in a recovery trial, the use of dexamethasone resulted in lower 28-day mortality in the patients who were in mechanical ventilation or in oxygen therapy.[28]

Furthermore, interleukin-6 inhibitors (Tocilizumab) use was recommended in the severe COVID-19 patients having rapidly increasing oxygen needs and with systemic inflammation despite use of systemic corticosteroids in the recent guideline though was not registered in Nepal during this review. [29]

It had become quite challenging for Nepal to combat the surging pandemic with the existing resources and infrastructures. Altogether four vaccines i.e., CoviShield, Covaxin, Sputnik-v and Vero Cell were approved for Emergency Use in Nepal as of May 2021 and two vaccines: CoviShield and Vero cell were launched in the country. Efforts were carried out to import more vaccines in following days for the rest of the population. However, there was a shortage of some basic medicines including paracetamol in

those days. To overcome this problem, Nepal Chemists and Druggists Association, Jhapa district branch office wrote a letter to the Department of Drug Administration, Biratnagar on 13th May, 2021 to manage the shortage of 22 medicines in the Nepalese market. [30]

To sum up, Nepal had taken imperative measures for the prevention and treatment of COVID-19 pandemic which was wreaking havoc in the country. The major steps included: launching of vaccination program, development of both allopathic and ayurvedic guidelines, clinical trials of repurposed drugs like remdesivir, and favipiravir. Thus, Nepal struggled extensively to tackle the first and second wave of COVID-19 surge with its existing limited resources.

5. Conclusions

Nepal's major pharmacological efforts for prevention were seen largely through vaccination programs. Despite being a low and middle-income country, Nepal succeeded to launch the two COVID-19 vaccines: CoviShield and Vero Cell, and 1.88% of the population were fully vaccinated till May 2021 which was quite appreciative. Medicines like remdesivir, favipiravir, tocilizumab, etc. were used in Nepal for symptomatic treatment of COVID-19 in an allopathic approach while ayurvedic approaches were also adopted for the prevention and cure of COVID-19 in the country based on the guideline. Nepal had fought its battle against COVID-19 vigorously with all the available evidence, resources, manpower, and infrastructures.

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