Pharmacology and Therapeutic Features of COVID - 19 Infection in Hodeidah , Yemen, before the Availability of Specific Antivirals and Vaccines

ABSTRACT

Background : The symptoms and signs of coronavirus diseases 2019 (COVID-19) present at illness onset vary, but over the course of the disease, most persons with COVID-19 will experience the following: fever , cough, fatigue, anorexia, shortness of breath, hypoxia, sputum production, and myalgia . During the first year (2020), there was no effective cure for COVID-19 infection and the most common treatment for patients was supportive therapy. Ministry of Public Health and Population in Yemen presented national guideline that is extracted from other countries and World Health Organization (WHO).

Objective : Therefore, in this research, we discuss the pharmacological and therapeutic approaches for management of COVID-19 during its early period of rampage, using availability of medicines in Yemeni local pharmaceutical marketing. On the other hand, the efficacy of therapeutic was monitored.

Methodology: 505 patients with COVID-19 from Hodeidah showed that respiratory infection illness illness can range from mild to critical. Mild to moderate was 386 case (78.93 %) , severe cases (dyspnea, hypoxia, or lung involvement on imaging) was 73 cases (15.13 %) and critical cases (respiratory failure, shock, or multiorgan system dysfunction) was 28 cases (5.93 %). The major criteria for cases admission namely clinical examination, case definition , clinical investigation, radiological finding, hematological finding , and molecular biology assay namely real – time - polymerase chain reaction (RT- PCR). The pharmacological and therapeutic properties of supportive therapy of COVID - 19 included " antipyrtic agent , analgesic agent, glucocortocoid (dexamethasone), anticoagulant agent (enoxaparin) , bronchodilator agent (sulbtamol), anti-cough (acetylcysteine), antibiotics broad specturm to treat the secondary infection namely azithromycin , ceftriaxone , piperacillin and tazobactam , vancomycine , meropenam , and moxifloxacine). In addition, oxygen therapy is the major treatment that used in treatment of severe and critical cases. Also , vitamins (C and D_3) and mineral namely zinc were pecribed and

proton pump inhibitor (PPI) (pantaprazol) , anti-emetic (ondansetron). Fluid therapy namely ringer lactate or normal saline are used in management of COVID – 19.

Results : The results showed that the age of the patients included in this study between 3- 92 years with 1.5 : 2.0 male: female. 49 patients were admitted in COVID – 19 isolation department of CTMID. 25/49 cases (54.34%) were recovered with national guideline , the average of RR pre - treatment was 30 ± 5 breath / minute and reduced to 23 ± 2 breath / minute post – treatment with significantly statistically different ($p< 0.05$) . On the other hand , the clinical symptoms namely difficult in breathing, co[a]ugh , fevere , and headache reduced to absent absolutely (100 %) . In addition , the results showed that the average of WBC pre - treatment was 20 ± 4 (×10 9/L) and reduced to 7 ± 2 (×10 9/L) post – treatment with significantly statistically different ($p< 0.05$) . Also , lymphocytes decreased with COVID -19 infection to 2 % with aveage (10±5%) and improved post - treatment to 20 % . In addition, neutrophil increased to 95 % with aveage (80±15%) and improved to 70 % post-treatment . the average of WBC pre - treatment was 20 ± 4 (×10 9/L) and reduced to 7 ± 2 (×10 9/L) post-treatment with significantly statistically different ($p< 0.05$). The outcome finding of management that 386 cases (76.43 %) of mild and 54 cases (11.04 %) of severe were recovered at home, 19 cases (3.88 %) of severe and 6 cases (1.22 %) of critical were recovered at isolation center . On the other hand , 1 case of severe and 21 cases of crtical COVID[were] died .

Conclusion :In spite of lack of specifific antiviral drugs,the approach of pharamcology and therapeutics had good impact at level of mild to moderate cases,[and severe case] while severe and crititical cases need[s to develop at level critical case] more intensivecare (ICU) including mechanical venitlation procedure.

Keywords: COVID-19, Pharmacology , Therapeutic , Hodeidah, Yemen

1. INTRODUCTION

"Since December 2019, the world faced a new pandemic caused by a virus in the Coronaviridae family, namely SARS-CoV-2, disrupting global public health and world economies. COVID-19, the disease caused by SARS-CoV-2, is a viral infection that affects the respiratory system, resulting in respiratory syndrome". [1]"COVID-19

is considered the most serious of pandemics since 1918 when the "Spanish flu" (H1N1) emerged".[2] "Before 2021, there were no drugs or vaccines proven to treat or prevent infection caused by SARS-CoV-2"[3]. "However, numerous studies were being conducted"[3,4]. "At the end of December 2019, the dramatic story of COVID-19 began and new species of the virus from the Coronaviridae family emerged in the city of Wuhan, China"[2,5]. "As of April 10, 2020, there were cases confirmed infection in Yemen and to spread in different area of Yemen. The signs and symptoms of COVID-19 present at illness onset vary, but over the course of the disease, most persons with COVID-19 will experience the following: Fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting and diarrhea". [6-8]. Symptoms differ with severity of disease such as fever, cough and shortness of breath are more commonly reported among hospitalized patients than non-hospitalized. This study reviews the therapeutic strategies to deal with the disease before effective vaccines and antiviral drugs against the causative virus became availave,and only symptometic, supportive and prevention were at our disposal.

Table (1) : Pharmacological Properties of Support Therapy used in Treatment of COVID-19 Patients, Hodeidah, Yemen

Medicines Used	MOA	Side Effects	Monitoring	Antidote
Paracetamol	Paracetamol has a central analgesic effect that is mediated through activation of descending serotonergic pathways.	Nausea, vomiting, constipation	Temperature Pain and fever relief , Caution must be observed due to liver toxicity at high doses of paracetamol.	N-acetylcysteine (NAC)
Azithromycin	Prevents bacteria from growing by interfering with their protein synthesis. It binds to the 50S subunit of the bacterial ribosome, thus inhibiting translation of mRNA	Anorexia, nausea, vomiting, and diarrhea are common	Concomitant use of hydroxychloroquine with azithromycin as the association can lead to a higher risk of QT interval prolongation and cardiac arrhythmias [10].	No specific antidote
Ondansetron	5-HT_3 antagonists	Headache, dizziness, and constipation	ECG (if applicable in high-risk or elderly patients); potassium, magnesium. Monitor for signs of serotonin syndrome; monitor for decreased bowel activity.	No specific antidote
Enoxaparin	low-molecular-weight heparin inhibit activated factor X	Hypochromic anemia, thrombocytopenia, hemorrhage, bleeding complications.	Measuring factor Xa inhibition (anti-factor Xa activity).	Limited experience suggests that 1 mg of protamine sulfate may be used to partially neutralize 1 mg of enoxaparin.
Pantoprazole	Proton pump inhibitors (PPIs)	Diarrhea, headache, and abdominal pain Reduction in oral cyanocobalamin absorption		

Dexamethasone	Dexamethasone bind to the DNA of glucocorticoid properties to modify transcription proteins inhibiting leukocyte infiltration to the site of inflammation, interfering with the effect of inflammatory mediators, suppress humoral responses and reduce edema and/or scarring of tissues.	Metabolic Effects Adrenal Suppression,Peptic ulcer, Nausea,dizziness,and weight loss in some patients. Hypomania or acute psychosis. Increased intraocular pressure and glaucoma. Benign intracranial Hypertension. Growth-suppressing. Sodium and fluid retention and loss of potassium. Potential adverse events: Increased risk for infection Hyperglycemia. Peripheral edema . Increased appetite Insomnia, irritability, delirium	A thorough history and physical examination should be performed to assess for risk factors.	No spesific antidote
Ceftriaxone	Inhibition of cell wall synthesis	Rash, pruritus, fever, eosinophilia, urticarial, anaphylaxis, colitis, diarrhea, nausea and vomiting, pseudomembranous colitis.	Therapeutic: Culture and sensitivities, serum levels, signs and symptoms of infection, white blood cell count Toxic: Urinalysis, BUN, SCr, AST and ALT, skin rash, Neutropenia and leukopenia, Prothrombin time in patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy.	No specific antidote.
Ceftazidime	Inhibits bacterial cell wall synthesis	Pain, swelling, burning, or irritation around the IV needle; nausea, vomiting, diarrhea, stomach pain; or vaginal itching or discharge.	As ceftriaxone	No specific antidote
Piperacillin and Tazobactam	Piperacillin, a broad spectrum, semisynthetic penicillin exerts	The same for the parent compound	As ceftriaxone	No specific antidote

	bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam, a beta-lactam structurally related to penicillins, is an inhibitor of many beta-lactamases, which commonly cause resistance to penicillins and cephalosporins. Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.			
Acetylcysteine	Acetylcysteine exerts its mucolytic action through its free sulfhydryl group, which opens the disulfide bonds and lowers mucus viscosity	Bronchospasm , Disagreeable odor. Drowsiness. Fever. Coughing up blood. Increased volume of bronchial secretions.Irritation of tracheal or bronchial tract.	Asses patient for nausea, vomiting and skin rash. Reassess LFTs for possible hepatotoxicity every 4 to 6hours,	
Moxifloxacin	It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell replication Targeting the bacterial DNA gyrase (type II topoisomerase) and topoisomerase IV thus inhibiting bacterial DNA synthesis and leading to cleavage of bacterial DNA and rapid bacterial death.	Diarrhea , dizziness, headache nausea , stomach cramps	Therapeutic: Culture and sensitivities, signs and symptoms of infection Toxic: Urinalysis, BUN, SCr, AST and ALT, Physicial examination: encephalopathic changes Monitor for QT prolongation	
Fluconazole	Interruption of the conversion of lanosterol to ergosterol via binding to fungal cytochrome P-450 and subsequent disruption of fungal membranes.	Headache ,diarrhea, nausea or upset stomach ,dizziness, stomach pain,vomiting, changes in the way food tastes, severe rash in people with lowered	Periodic liver function tests and renal function tests	No specific antidote.

		immunity		
Meropenam	It inhibits bacterial cell wall synthesis like other β-lactam antibiotics.	A skin rash, constipation, diarrhea, headache, nausea and vomiting	Therapeutic: Resolution of clinical signs of infection (fever, decreased white blood cell count), Culture and sensitivity, CBC w/differential, urinalysis, temperature Toxicity: Hepatic and renal function tests during therapy	
Morphine	Morphine acts primarily as a μ-opioid receptor agonist, binding to μ receptors in the brain, on terminal axons of primary afferents in the spinal cord, and elsewhere Opioids produce their effect by acting as agonists at various opioid receptors found in the brain, spinal cord, and sites outside the central nervous system (CNS).	Constipation, feeling or being sick, vomiting, feeling sleepy or tired dizziness and a sensation of spinning (vertigo) confusion, headaches, itchiness or rash Respiratory depression, sedation, nausea/vomiting, constipation, physical dependence, and opioid use disorder.	Respiratory depression	Naloxone
Midazolam	Benzodiazepines, increase the efficiency of GABAergic synaptic inhibition.	Headache, nausea, vomiting, cough, drowsiness, hiccups, and over-sedation	Vital signs Respiratory depression	Flumazenil
Vitamin D3 cholecalciferol	Is a fat-soluble vitamin helps body absorbs calcium, and phospharus	Hypersensitivity reactions such as angioedema or laryngeal edema, nusea and vomiting	A blood test is recommended to monitor blood levels of 25(OH)D three months after beginning treatment.	Supportive treatment
Vitamin C (ascorbic acid)	A water-soluble vitamin Antioxidant and free radical scavenger that has anti-inflammatory properties	Individuals who have a history of kidney stone formation and those who experience iron overload should exercise caution before using supplemental vitamin C.		
Zinc	It is a naturally occurring mineral	nausea, vomiting, diarrhea		

Table (2) : Pharmacokinetics Properties of Support Therapy used in Treatment of COVID-19 Patients, Hodeidah, Yemen

Medicines Used	Absorption	Distribution	Metabolism	Excretion
Paracetamol	Absorbed from the GIT peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion	Distributes rapidly and evenly throughout most tissues and fluids and has a volume of distribution of approximately 0.9L/kg. 10 to 20% of the drug is bound to red blood cells	Metabolized in the liver (90-95%) and excreted in the urine mainly as the glucuronide and sulphate conjugates	Excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged
Azithromycin	Rapidly absorbed and well tolerated orally. It should be administered 1 hour before or 2 hours after meals.	Penetrates into most tissues except(CSF) and phagocytic cells extremely well, with tissue concentrations exceeding serum concentrations by 10- to 100-fold.	Not inactivate cytochrome P450 enzymes	
Ondansetron	Completely and rapidly absorbed from GIT after oral administration	Widely distributed (volume of distribution approximately 160L) and binds moderately (70 to 76%) to plasma proteins;	Extensive hepatic metabolism	Eliminated by renal and hepatic excretion.
Enoxaparin	Full-dose enoxaparin therapy is 1 mg/kg subcutaneously every 12 hours. Bioavailability is 92%.	Volume of distribution of anti-factor Xa activity is about 6 L.	NA	Elimination half-life based on anti-factor Xa activity is about 4.5 hours after S.C. administration.
Pantoprazole	Well absorbed, undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%.	The apparent volume of distribution (V) is approximately 11.0 to 23.6 L, and the serum protein binding is ~98%	Extensively metabolized in the liver through the cytochrome P-450 system, predominantly by CYP2C19 demethylation with subsequent sulfation	The serum elimination half-life of about 1.1 hours
Dexamethasone	Following 20 mg dose of dexamethasone median time to	Dexamethasone is about 77% bound to human plasma proteins in	Dexamethasone is metabolized by CYP3A4.	Renal excretion of dexamethasone is less than 10% of total body clearance.

	peak concentrations (Tmax) (range: 0.5 to 4 hours).	vitro.		Less than 10% of dexamethasone is excreted in the urine.
Ceftriaxone	Parenteral route of administration Rapidly and completely absorbed following intramuscular administration.	C_{max}: 123-151mcg/L Volume of distribution: 10.7L		33- 67 % is excreted in the urine as unchanged drug, and the remainder is secreted in the bile and ultimately is found in the feces as microbiologically inactive compounds.
Ceftazidime	Administered I.V. and I.M.	Distributed widely into most body tissues and fluids, including the gallbladder, liver, kidneys, bone, sputum, bile, and pleural and synovial fluids; unlike most other cephalosporins, ceftazidime has good CSF penetration; it crosses the placental barrier. Ceftazidime is 5% to 24% protein-bound.	Not metabolized.	Excreted mainly in urine by glomerular filtration; small amounts of drug appear in breast milk. Elimination half-life is about 11/2 to 2 hours in patients with normal renal function; up to 35 hours in patients with severe renal disease. Hemodialysis or peritoneal dialysis removes ceftazidime.
Piperacillin and Tazobactam	Piperacillin/Tazobactam 4 g/0.5 g Powder for Solution for Infusion. The peak piperacillin and tazobactam concentrations after 4 g / 0.5 g administered over 30 minutes by intravenous infusion are 298 µg/ml and 34 µg/ml respectively.	Both piperacillin and tazobactam are approximately 30% bound to plasma proteins. widely distributed in tissue and body fluids including intestinal mucosa, gallbladder, lung, bile and bone.	Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite, which has been found to be micro-biologically inactive.	Piperacillin and tazobactam are eliminated by the kidney via glomerular filtration and tubular secretion.
Acetylcysteine	Most inhaled acetylcysteine acts directly on mucus in the lungs; the remainder is absorbed by pulmonary epithelium. After oral administration, drug is absorbed from the GI tract.	Unknown	Hepatic. Acetylcysteine undergoes rapid deacetylation in vivo to yield cysteine or oxidation to yield diacetylcystine.	Unknown
Moxifloxacin	Well absorbed from the gastrointestinal tract. Absolute oral bioavailability is	Volume of distribution is 1.7 to 2.7 L/kg% 50% bound to serum proteins, independent of drug	Approximately 52% or oral or intravenous dose is metabolized via glucuronide and sulphate	Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged drug (~20% in

	approximately 90%. Food has little effect on absorption.	concentration.	conjugation. The cytochrome P450 system is not involved in metabolism. The sulphate conjugate accounts for 38% of the dose, and the glucuronide conjugate accounts for 14% of the dose.	urine and ~25% in feces).
Fluconazole	The bioavailability of orally administered fluconazole is measured to be above 90%. It is extensively absorbed in the GIT when an oral dose is taken	Well distributed to various sites, including CNS, saliva, sputum, blister fluid, urine, normal skin, nails, and blister skin. CNS levels of drug approach 50% to 90% of that of serum. Fluconazole is 12% protein-bound.	Primarily metabolized hepatically.	Primarily excreted via the kidneys. More than 80% of an administered dose is excreted unchanged in the urine. Excretion rate diminishes as renal function decreases.
Meropenam	Administered I.V	Distributed into most body fluids and tissues, including CSF. It's only about 2% bound to plasma protein.	Thought to undergo minimal metabolism. One inactive metabolite has been identified.	Excreted unchanged primarily in urine. Elimination half-life of drug in adults with normal renal function and children age 2 and older is about 1 hour and 1.5 hours in children age 3 months to 2 years.
Morphine	Variably absorbed (about 30%) following oral administration. More reliably absorbed from rectal, SC, and IM sites. Following epidural administration, systemic absorption and absorption into the intrathecal space via the meninges occurs.	Widely distributed. Crosses the placenta; enters breast milk in small amounts. Protein Binding: Premature infants: <20%; Adults: 35%.	Metabolized by the liver.	Active metabolites excreted renally
Midazolam	Benzodiazepines Midazolam is available by oral, rectal, intranasal, intramuscular (IM), and intravenous (IV) routes.	In adults and pediatric patients older than 1 year, midazolam is approximately 97% bound to plasma protein, principally albumin.	Biotransformation of midazolam is mediated by cytochrome P450-3A4.	Elimination of the parent drug takes place via hepatic metabolism of midazolam to hydroxylated metabolites that are conjugated and excreted in the urine.
Vitamin D3			The three main steps in vitamin D	

cholecalciferol			metabolism, 25-hydroxylation, 1α-hydroxylation, and 24-hydroxylation are all performed by cytochrome P450 mixed-function oxidases (CYPs). These enzymes are located either in the endoplasmic reticulum (ER) (e.g., CYP2R1) or in the mitochondria (e.g., CYP27A1, CYP27B1, and CYP24A1).	
Vitamin C (ascorbic acid)	Vitamin C absorption occurs through small intestine (distal intestine) by active transport mechanism.	Vitamin C is widely distributed in all the body tissues.	Vitamin C metabolites (oxalate salts) and unmetabolized vitamin C are excreted by kidneys. Few percentage of vitamin C is excreted through feces.	The urinary excretion of vitamin C is dose dependent.
Zinc	Zinc is absorbed throughout the whole small intestine	distributed to the peripheral tissues, including skeletal muscle (60%), bone (30%), skin (5%), and other tissues (5%)		Zinc is lost from the body through the kidneys, skin, and intestine.

(9-16)

2. METHODOLOGY

2.1. Study design

This was a case series study based on medical file about monitoring the efficacy and safety of national guideline based on using laboratory and clinical outcome in COVID – 19 outbreak in Hodeidah, Yemen. The study was conducted during the period 1st June 2020 to 30th September 2020.

2.2. Study area

This study was carried out in COVID -19 Isolation Department, Center of Tropical Medicine and Infectious Diseases (CTMES) , Authority of Public AL- Thawara Hospital , Hodeidah . The study included all patients that were admitted and treated in isolation department and patients were treated at home. Note : The area is vector – borne diseases endemic , therefore the malarai and dengue were diagnosed to manage the coinfection [17-24] .

2.3. Study population

The study included 505 patinets 386 cases (76.43 %) of mild and modearte cases) ; 70 cases (13.86 %) of severe were treated at home. On the other hand , the pharamcological profiles were applied on 21patients of severe illness (4.16 %) and 28 patients (5.54%) of critical illness were treated at isolation department. 49 patients (9.7 %) needed admission in an intensive care unit (ICU).Note : The biomedical parameters were monitored carefu[a]lly in severe and criticak cases only (49 cases).

2.4. Diagno[i]sis of COVID-19

The major criteria for cases admission namely clinical examination, case definition , clinical investigation, radiological finding, hematological finding. On the other hand , the cases was confirmed using molecular biology assay namely real – time - polymerase chain reaction (RT- PCR) [25-31].

2.5. National guideline

The national guideline treatment of COVID -19 for management of mild , moderate , severe , and crtical cases were desribed in Table 3. [32-33].

2.6. Pharmacological and Therapeutics Approach

The pharmacological and therapeutic properties of supportive therapy of COVID - 19 included " antipyrtic agent to reduce the fever, analgesic agent to reduce the pain, glucocortocoid (dexamethasone) as anti-inflammatory agent, anticoagulant agent (enoxaparin) to prevent the small embolism formation in lung, bronchodilator agent (sulbtamol), anti-cough to reduce productive and non- productive cough (acetylcysteine), antibiotics broad specturm to treat the secondary infection namely azithromycin , ceftriaxone , piperacillin and tazobactam , vancomycine , meropenam , and moxifloxacine). In addition, oxygen therapy is the major treatment that used in treatment of severe and critical cases. Also , vitamins (C and D_3) and mineral namely zinc are used to support the immune system. Finally , proton pump inhibitor (PPI) to prevent the gastric stress (pantaprazol) , anti-emetic (ondansetron). Fluid therapy namely ringer lactate or normal saline are used in management of COVID – 19.

2.7. Statistical analysis

The differences between the females and males groups were analysed by using Excel 2010 and Statistical Process Social Sciences (SPSS) version 15 to calculate the descriptive analysis and paired t- test at $\alpha = 0.05$ that were used to explore the effectiveness of national guideline treatment of COVID -19 pre and post-treatment in Hodeidah city, Yemen.

Table (3): National guideline of COVID-19 Patients, Hodeidah, Yemen [32-33]

Medicines Used	Mild cases	Moderate	Severe	Critical
Paracetamol Tablet 500 mg	three times a day (6 days)	three times a day (6 days)	-	-
Paracetamol I.V 1000 mg			three times a day (14 days)	three times a day (14 days)
Azithromycin 500 mg	Once dose for 6 days	Once dose for 6 days	once a day (6 days)	once a day (6 days)
Ondansetron I.V. 8 mg / 4 ml			If necessairy	If necessairy
Enoxaparin Subq. 60 mg			Once dose for 14 days	Once dose for 14 days
Pantoprazole I.V.			Once dose for 14 days	Once dose for 14 days
Dexamethasone I.V.			+	+
Ceftriaxone 1 g		+	twice a day (6 days)	twice a day (6 days)
Ceftazidime 1 g		+	twice a day (6 days)	twice a day (6 days)
Piperacillin and Tazobactam				+
Acetylcysteine			three times a day (3)	three times a day (3)
Moxifloxacin 400 mg I.V.			once a day (6 days)	once a day (6 days)
Fluconazole 150 mg			+	+
Meropenam 1 g			+	+
Morphine				+
Midazolam				+
Vitamin D3 cholecalciferol			once a day (14 days)	once a day (14 days)
Viatmine C Tablet 1000 mg	Once dose for 14 days	Once dose for 14 days		
Vitamine C Injection			once a day (14 days)	once a day (14 days)

3. RESULTS

3.1. Clinical response

The results showed that the age of the patients included in this study between 3- 92 years with 1.5 : 2.0 male: female. 90 patients were admitted in COVID – 19 isolation department of CTMID. 25/46 cases (54.34%) were recovered with national guideline , the average of RR pre - treatment was 30 ± 5 breath / minute and reduced to 23 ± 2 breath / minute post – treatment with significantly statistically different ($p< 0.05$) . On the other hand , the clinical symptoms namely difficult in breath, co[a]ugh , fevere , and headachic absent abso[u]lutely (100 %) .

Table 4 . Monitoring the level of oxygen saturation and respiratory rate (RR) pre and post - treatment (X ± SD ; n:49)

Parameters	Pre - treatment	Post - treatment	*p*-value
Oxygen satauration (%)	75 ± 10	92 ± 2	$p< 0.05$*
Repiratory Rate (perth/minute)	30 ± 2	25 ± 1	$p< 0.05$*
Blood Pressure (mmHg)			
• [Systolic] Diastolic	80 ± 10	82 ± 10	$p> 0.05$
• [Diastolic]Systolic	120 ± 20	122 ± 10	

* : Significant *p* – value less than 0.05

3.2. Laboratory response

3.2.1. Hematological parametrs

The results showed that the average of WBC pre - treatment was 20 ± 4 (×10 9/L) and reduced to 7 ± 2 (×10 9/L) post – treatment with significantly statistically different ($p< 0.05$) (Table 5). On the other hand , the WBCs count, which had reached a peak of 34 (×10 9/L) as maximum value . Also , lymphocytes decreased with COVID -19 infection to 2 % with aveage (10±5%) and improved post - treatment to 20 % . In addition, neutrophil increased to 95 % with aveage (80±15%) and improved to 70 % post treatment . the average of WBC pre - treatment was 20 ± 4 (×10 9/L) and reduced to 7 ± 2 (×10 9/L) post – treatment with significantly statistically different ($p< 0.05$).

Table 5 . Monitoring the level of WBC and differential count pre- and post-treatment (X ± SD: n:49)

Parameters	Pre - treatment	Post - treatment	*p*-value
WBC ($\times 10^9$/L)	20 ± 4	7 ± 2	$p< 0.05$*
Neutrophils (%)	80 ± 15	50 ± 15	$p< 0.05$*
Eosinophils (%)	Normal	Normal	$p> 0.05$
Basophils (%)	Normal	Normal	$p> 0.05$
Lymphocytes (%)	10 ± 5	25 ± 5	$p< 0.05$*
Monocytes (%)	Normal	Normal	$p> 0.05$

* : Significant *p* – value less than 0.05

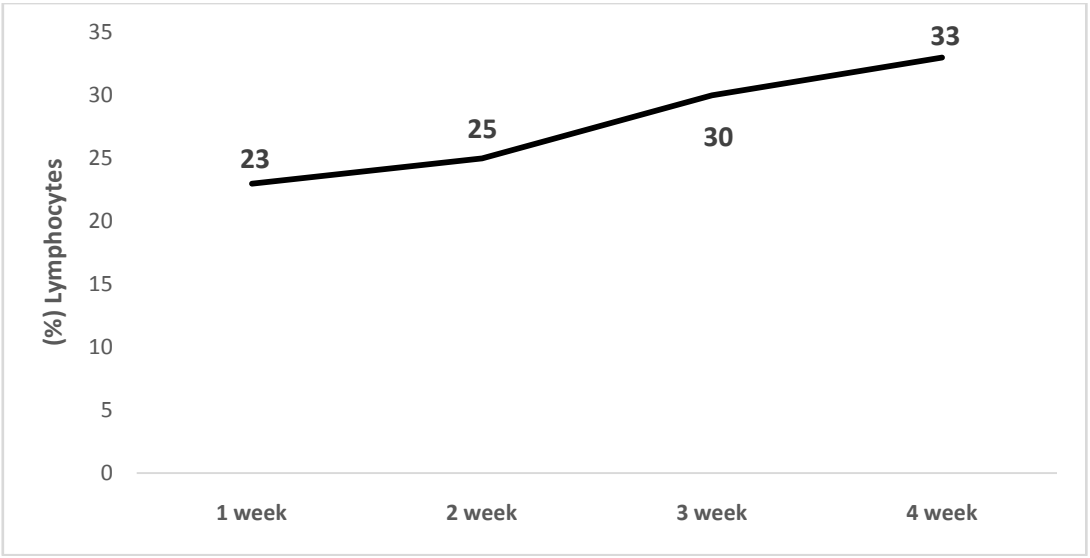

Figure (1) : Kinatic of lymphocytes pre – within and post – treatment of mild and moderate cases

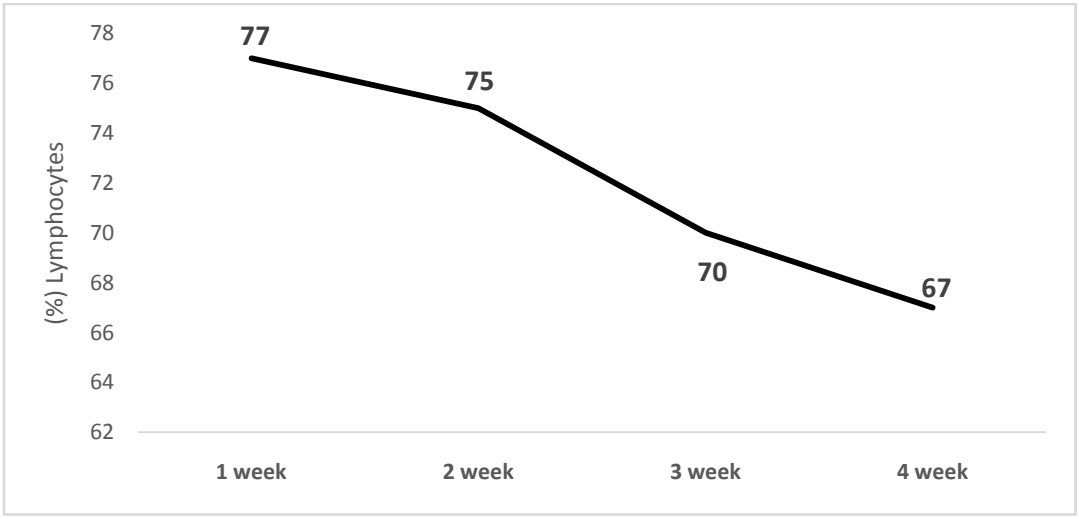

Figure (2) : Kinatic of neutrophils pre – within and post – treatment of mild and moderate cases

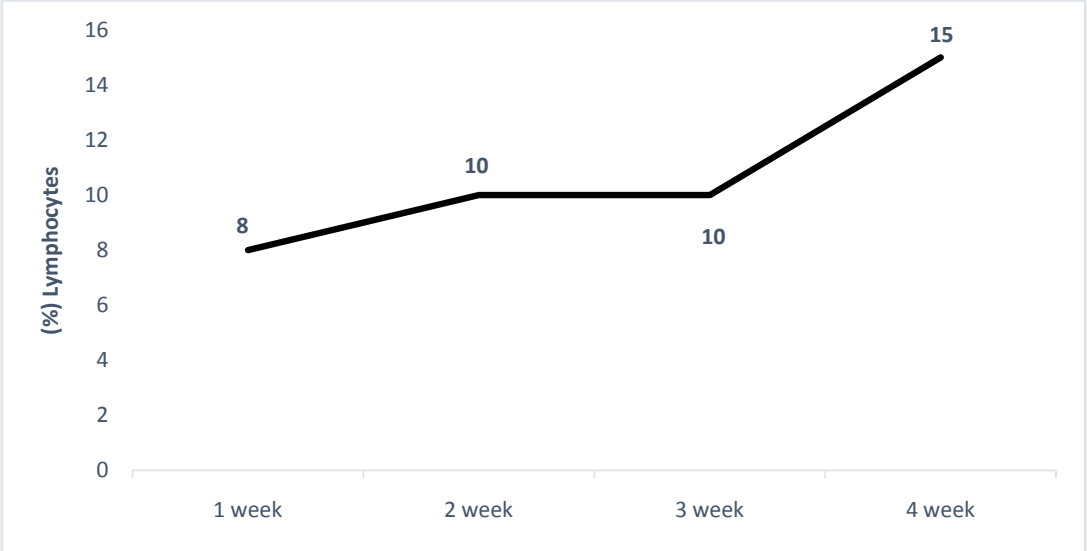

Figure (3) : Kinatic of lymphocytes pre , within and post – traetment of severe cases

Figure (4) : Kinatic of neutrophils pre , within and post – traetment of severe case

3.2.2. Biochemical parameters

The results showed that the average of blood glucose pre - treatment was 370 ± 200 mg/dl and reduced to 140 ± 40 mg/dl post - treatment based on insuline therapy with significantly statistically different ($p< 0.05$) (Table 6). On the other hand , the blood glucose, which had reached a peak of 550 mg/dl as maximum value . Also , albumin decreased with COVID -19 infection to 1.5 g/dl with average (2.2± 0.5 g/dl) and improved post - treatment to 3 ± 0.5 g/dl ($p< 0.05$) (Table 7). In addition, CRP increased to 46 mg/L % with aveage (26±10 mg/L) and very slow[e]ly decreaed[kinetic] post – treatment (23±8 mg/L) ($p> 0.05$). The liver enzyme (Table 7), serum creatinine (Table 9) and serum electrolytes (Table 10) were not correlated to COVID-19 infection , therefore , these parameters were not chan[a]ged post – treatment (Tables 7 , 9 and 10).

Table 6 . Monitoring the level of blood glucose pre and post - treatment (X± SD; n:49)

Parameters	Pre - treatment	Post - treatment	*p*-value
Blood glucose (mg/dl)	370 ± 200	140 ± 40	$p< 0.05$*
* : Significant *p* – value less than 0.05			

Table 7 . Liver function test pre and post - treatment (X± SD , n:49)

Parameters	Pre - treatment	Post - treatment	*p*-value
GOT	45.42±26.31	44.31±20.25	$p> 0.05$
GPT	45.38 ± 29.31	43.40 ± 29.31	$p> 0.05$
Albumin	2.2 ± 0.5	3.100 ± 0.5	$p< 0.05$*
Note : The liver enzymes need long time to change (cohort) while the albumin level was improved **: :** Significant *p* – value less than 0.05			

Table 8 . Immunological marker (CRP) response pre and post - treatment (X± SD ; n:49)

Parameters	Pre - treatment	Post - treatment	*p*-value
CRP mg/dl	16 ± 10	15 ± 10	$p< 0.05$*
Note : The CRP needs long time to change (cohort) ; * : Significant *p* – value less than 0.05			

Table 9 . Renal function test pre and post – treatment (X± SD; n:49)

Parameters	Pre – treatment	Post – treatment	*p*-value
Creatinine mg /dl	0.5 – 1.5	0.4 – 1.6	$p> 0.05$

Table 10 . Electrolytes assay pre and post treatment (X± SD ; n:49)

Parameters	Pre - treatment	Post - treatment	*p*-value
K^+	5.19±4.67	5.19±4.67	$p> 0.05$
Na^+	135.35±5.49	134.44±4.55	$p> 0.05$
Cl^-	100.28±6.31	99.12±5.33	$p> 0.05$

3.3. Outcome

The outcome finding of management that 386 cases (76.43 %) of mild and 54 cases (11.04 %) of severe were recovered at home, 19 cases (3.88 %) of severe and 6 cases (1.22 %) of critical were recovered at isolation center . On the other hand , 1 (0.19%) case of severe and 21 cases (4.15 %) of crtical COID died.

DISCUSSION

"Clinicians namely Intesive Care Unit (ICU) , tropical medicine, and clinical pharmacologist are frequently asked to monitor the effects of national guideline treatment with the objective of ensuring safe and effective therapy. Already in monitoring of supportive therapy care includes therapeutic response bilogically and clinically"[(34)]. Our study monitored the efficacy of national guideline traetment based hematological parameters and clinical response to treatment was used namely .

"Findings of the present study showed that almost all the WBCs of COVID-19 patients sampled from Hodeidah Yemen (collected systemically from COVID-19 patients) were found to be more than normal values . These results were estimated according to direct hematological analyzer that was validated using a classical approach for the assay of WBC and related parameters. This approach gives enough guarantees for the results that will be generated by this method during blood analysis"[(35-36)].

"Monitoring efficacy of supportive therapy care and response to treatment of COVID-19 infection can be assessed using biological and clinical parameters of improvement include symptoms and signs (eg, a decrease in fever, tachycardia, cough , respiratory rate), (eg, decreasing WBC count and neutrophil % within normal range , and increase lymphocytes to normal range. Although hematological criteria namely WBC , neutrophil , and lymphocytes are commonly used as economical indicators in assessing response to infectious disease therapy in Hodieidah outbreak management, WBCs improvement can frequently lag behind clinical improvement. In our study of hematological and clinical follow-up of patients with COVID-19, clinical cure was observed in 128/149 cases (85.90 %) after 14 days of follow-up of patients. During the study period,there were no drugs or other therapeutics presently approved by the U.S. Food and Drug Administration (FDA) to prevent or treat COVID-19. Current clinical management includes infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support

when indicated"[37]. In Yemen, the pharmacological and therapeutic approaches for management of COVID-19 were using available[of] medicines in local pharmaceutical marketing.

"Although systemic corticosteroids for the treatment of viral pneumonia or ARDS were not recommended, dexamethasone treatment is recommended by the National Health Service in the UK and the National Institutes of Health (NIH). In the US for patients with COVID-19 who [are] require supplemental oxygen but are not mechanically ventilated. Dexamethasone is not recommended in patients with COVID-19 who do not require supplemental oxygen or hospitalization"[38-40].

"The Infectious Diseases Society of America (IDSA) guideline panel suggests the use of glucocorticoids for patients with severe COVID-19 where severe is defined as patients with SpO2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). The IDSA recommends against the use of glucocorticoids for those with COVID-19 without hypoxemia requiring supplemental oxygen. The World Health Organization (WHO) recommends systemic corticosteroids rather than no systemic corticosteroids for the treatment of people with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence)"[41-42] . "The WHO suggests not to use corticosteroids in the treatment of people with non-severe COVID-19 (conditional recommendation, based on low certainty evidence). Dexamethasone reduced deaths by approximately one third in patients requiring ventilation and by one fifth in those requiring oxygen"[31]. "Among patients hospitalized with mild-to-moderate COVID-19, the use of azithromycin, did not improve clinical status at 15 days as compared with standard care"[43].

"For pain management during COVID-19, the paracetamol used safely to alleviate symptoms of COVID-19 such as fever, headache, and acute or chronic pain. However, caution must be observed due to liver toxicity at high doses of paracetamol"[10] . "Of importance, in current pain practice, opioids are generally used as only part of a treatment plan, which includes physical therapy, pain psychology, interventional procedures, and other ancillary therapies. Because COVID-19 patients have a higher incidence of venous thromboembolism and anticoagulant therapy is associated with reduced ICU mortality, it is suggested that patients should receive thromboprophylaxis. Moreover, in the case of known thrombophilia or thrombosis,

full therapeutic-intensity anticoagulation (e.g., enoxaparin 1 mg/kg twice daily) is indicated"[44] .

"Different countries recommended the use of chloroquine in management of COVID – 19 but WHO stoped its using"[45]. Our study did use Chloroquine in CTMID, Authority of Public AL Thawarah Hospital , Hodeidah, Yemen. Chloroquine (500 mg every 12 hours), and hydroxychloroquine (200 mg every 12 hours) were proposed by Gautret et al[46]."The study showed that hydroxychloroquine was significantly associated with viral load reduction until viral disappearance and this effect was enhanced by the macrolides azithromycin. In vitro and in vivo studies, indeed, have shown that macrolides may mitigate inflammation and modulate the immune system. In particular, these drugs may induce the downregulation of the adhesion molecules of the cell surface, reducing the production of proinflammatory cytokines, stimulating phagocytosis by alveolar macrophages, and inhibiting the activation and mobilization of neutrophils [11]. However, further studies are needed for recommending the use of azithromycin, alone or associated with other drugs such as hydroxychloroquine, outside of any bacterial overlaps. Again, attention must be paid with the concomitant use of hydroxychloroquine with azithromycin as the association can lead to a higher risk of QT interval prolongation and cardiac arrhythmias and chloroquine can also induce QT prolongation"[11].

"In patients with confirmed COVID-19 pneumonia, community-onset bacterial co-infection is uncommon, so the empirical treatment of antibiotics for patiens 18 and older with with suspected community-acquired pneumonia was azithromycin as oral for moderate or severe pneumonia, in case of unsuitable we used moxifloxacin. However, intravenous antibiotics for moderate or severe pneumonia, we used ceftriaxone, if it is not suitable we used moxifloxacin. A recent in silico study demonstrated that the fluoroquinolones, ciprofloxacin and moxifloxacin, exert strong capacity for binding to SARS-CoV-2 main protease (Mpro), indicating that fluoroquinolones may inhibit SARSCoV-2 replication"[47] .

Antibiotics are given for people 18 and older with suspected hospital-acquired pneumonia, as emprical treatment. Oral antibiotics for non-severe pneumonia, when there is not a higher risk of resistance to azithromycin[,] and moxicloxacin, comprise two options, the intravenous antibiotics for severe pneumonia (for example, symptoms or signs of sepsis or ventilator-associated pneumonia) or when there is a higher risk of resistance, the options included piperacillin with tazobactam: 4.5 g three

times a day, increased to 4.5 g four times a day if infection is severe, or Ceftazidime: 2 g three times a day if the above options are unsuitable for moxifloxacin.

"The emergence of the COVID-19 pandemic has affected individuals and society on multiple levels. The overall focus has been on preventing the spread of the disease and discovering treatment options. However, the psychological impact of the illness should not be overlooked. Patients face multiple stressors due to the COVID-19 crisis including but not limited to fear of becoming infected and of infecting others, especialy family members, inadequate access to testing, disrupted regular medical care, financial losses, distress related to social distancing and quarantine, and uncertainty of the duration of the pandemic"[48] . "Some reports raise concerns of a long-lasting mental health impact as a consequence of the pandemic. It is anticipated that patients infected with COVID-19 may suffer from mood dysregulation, anxiety, anger, and worsening of any preexisting mental illness"[49]. With long hospitalizition and the potential need to intubation and mechanical ventilation, light sedation is required to reduce risk of post –intensive care unit syndrome and adverse outcomes.

4. CONCLUSION

The approach of pharamcology and therapeutics had good impact at level of mild, moderate and severe cases, while[it needs to develop] at level of critical cases (ICU), it needs to develop more elaborate equpments, namely mechnical venitlation procedure.

Ethical Approval and Consent

The study was integrated within the clinical practice. Patients received simple explanation for the aim of the study. If agreed to participate verbally, biological and clinical data were collected and interview was conducted. Confidentiality of the collected data was achieved by keeping data record in a locked room with limited access to the research team only. according to Center of Tropical Medicine and Epidemilogy Studies – Hoediad University (CTMES – HU , Yemen declaration.

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