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Use of Enoxaparin with Corticosteroid Dexamethasone in the treatment of COVID-19 patients in Iraq

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Abstract

As of March 2022, more than 6 million people have died globally as a consequence of the extremely infectious viral disease produced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread quickly around the world when the first instances of this mostly respiratory viral infection were initially recorded in Wuhan, Hubei Province, China, in late December 2019. As a result, the World Health Organization (WHO) was forced to declare it a worldwide pandemic on March 11, 2020. One of the most serious complication is cytokine storm which is term describe several disorders of immune dysfunction characterized by constitutional symptoms, systemic inflammation, and multiorgan dysfunction that can lead to multiorgan failure if inadequately treated. Aim of the study Comparison between inflammatory mediators in COVID 19 PATIENTS on dexamethasone and enoxaparin VS patients on dexamethasone only; Study the anti-inflammatory effects of enoxaparin; estimate the prognostic significance of IL6 & IL8 in COVID 19 patients. Methods: Total 70 iraqi patients with confirmed , severe COVID-19 infection admitted to RCU was done into two groups , 45 patients on dexamethasone and enoxaparin (group II) and 25 patients on dexamethasone only (group I). blood sample from each group collected in the first day and seventh day of admission. Results: The levels of all studied parameters in patients received mono treatment of dexamethasone showed significant reduction in the levels of CRP and LDH and a significant increase in the level of lymphocytes in the seventh day comparing with the results obtained in the first day whereas all other parameters showed non-significant differences in their levels between the seventh and first day . Patients received a combination therapy of dexamethasone and Enoxaparin showed significant reduction in the levels of D-dimer, LDH, IL-6 and IL-8 with significant elevation in the levels of lymphocytes at the seventh day of treatment in comparison with the levels of these parameters in the first day. Conclusion Percentage of patients recovered after receiving the combination therapy were (73.3%) which is higher than that for patients receiving only dexamethasone. With interested correlation between treatment and the recovery of patients , the anti-inflammatory action of enoxaparin in addition to its anti-coagulant effect.

Keywords

COVID-19 patients; Enoxaparin; Corticosteroid Dexamethasone

Corona virus is spherical or pleomorphic, single stranded, enveloped RNA and covered with club shaped glycoprotein. Coronaviruses are enveloped positive sense RNA viruses ranging from 60 nm to 140 nm in diameter with spike like projections on its surface giving it a crown like appearance under the electron microscope (Singhal et al., 2020).

Coronavirus Disease-2019 (COVID-19) in Iraq

After the first cases of this predominantly respiratory viral illness were first reported in Wuhan, Hubei Province, China, in late December 2019,SARS-CoV-2 rapidly disseminated across the world in a short span of time, compelling the World Health Organization (WHO) to declare it as a global pandemic on March 11, 2020. Since being declared a global pandemic, COVID-19 has ravaged many countries worldwide and has overwhelmed many healthcare systems (Cascella et al., 2022). COVID-19 in Iraq was firstly identified on the 24th of February 2020 in the south of Baghdad at Al-Najaf city. Two weeks later, the Iraqi Ministry of Health (MOH) broadcasted that 101 cases have been tested positive of COVID-19 with 9 deaths cases in 14 provinces; Baghdad city had around 40% of those cases. This is suggestive of the fast-paced spread of COVID-19 across the country. Iraqis who visited Iran during the spring break mostly exposed to the infection of COVID-19 (Alsayed et al., 2022).

Cytokine storm is an umbrella term encompassing several disorders of immune dysregulation characterized by constitutional symptoms, systemic inflammation, and multiorgan dysfunction that can lead to multiorgan failure if inadequately treated (Fajgenbaum & June .,2020). Cellular entry of SARS-CoV-2 depends on the binding of S proteins covering the surface of the virion to the cellular ACE2 receptor and on S protein priming a host membrane serine protease. After entering respiratory epithelial cells, SARS-CoV-2 provokes an immune response with inflammatory cytokine production accompanied by a weak interferon (IFN) response.

plasma level of IL-6, considered as a significant cytokine contributing to Macrophage activation syndrome(MAS), increases both in mild and severe patient groups of COVID-19: severe patients have a significantly higher level of IL-6 than mild or nonsevere patients. the total count of lymphocytes and the subset of T cells are reduced in patients with SARS-CoV infection. Data from recent studies have suggested that SARS-CoV-2 infection can lead to immune dysregulation through affecting the subsets of T cells. The significant alleviation of T cells is observed in COVID-19 and more pronounced in severe cases. In patients with COVID-19, the level of helper T cells (CD3+, CD4+) and cytotoxic suppressor T cells (CD3+, CD8+), and regulatory T cells are below normal level while helper T cells and regulatory T cells in severe patients are remarkably lower than nonsevere patients. Regulatory T cells are responsible for the maintenance of the immune homeostasis with suppressing the activation, proliferation, and proinflammatory function of most lymphocytes including CD+4 T cells, CD+8 T cells, NK cells, and B cells. Furthermore, the percentage of naпve helper T cells amplifies while the percentage of memory helper T cells and CD28+ cytotoxic suppressor T cells decreases in severe COVID-19 (Tufan et al., 2020).

IL-8 mediates its biological effects through the binding to its cognate G-protein-coupled CXC chemokine receptors, CXCR1 and CXCR2, which activates a phosphorylation cascade to trigger chemotaxis and neutrophil activation as part of the inflammatory response. dysregulated signaling at the IL-8/CXCR1/2 axis has been identified as a possible cause to drive this immunopathology leading to an activated, prothrombotic, neutrophil phenotype characterized by degranulation and NET formation. By targeting IL-8/CXCR1/2, interference can occur within the cycle and attenuate neutrophil activation, degranulation, NETosis, and IL-8 release (Kaiser et al., 2021).

Role of dexamethasone in the treatment

Emerging randomized trial data in COVID-19 has shown improvements in mortality and ventilator-free days (VFDs) with corticosteroids. The National Institutes of Health (NIH) and World Health Organization (WHO) clinical guidelines were updated in September 2020 to provide recommendations on the use of corticosteroids in COVID-19. The cytokine mediated activation of neutrophils in the lungs leads to production of toxic mediators, such as reactive oxygen species, and injury to capillary endothelium and alveolar epithelium. (Johns et al., 2022).

Role of enoxaparin Patients with COVID-19 infection who develop severe pneumonia or ARDS show acute inflammation of the lower respiratory tract, including the lungs. Recent studies have demonstrated that tissues of COVID-19 lungs accumulate inflammatory cells, especially neutrophils, and inflammatory cytokines (e.g., IL-8). Although neutrophils are an important mechanism for the elimination of pathogens, including SARS-CoV2, the formation of these web-like structures also induces tissue inflammation and vascular thrombosis, leading to serious lung damage in patients with COVID-19 infection (Saithong et al., 2022). Abnormal coagulation is another contributing factor to the pathogenesis of lung injury in COVID-19 patients with severe pneumonia. It was found that increased D-dimer and fibrinogen levels and prolonged prothrombin time were observed in severe cases of COVID-19 infection, leading to thromboembolic vascular complications in

multiple organs. Therefore, one treatment option in cases with severe pneumonia is the administration of anticoagulant .

Patients and methods

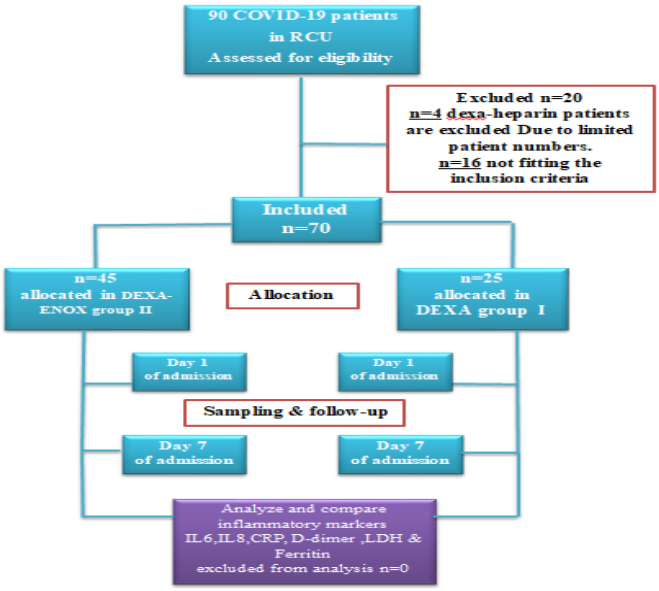

Figure 2.1 patient flowchart

Method and study design

prospective single center study, Total 70 iraqi patients with confirmed , severe COVID-19 infection admitted to RCU was done into two groups , 25 patients on dexamethasone only (group I) and 45 patients on dexamethasone and enoxaparin (group II). blood sample from each group collected in the first day and seventh day of admission .

Both group I and group II receive same standard therapy :

1. Oxygen therapy.
2. antiviral drugs : Remdesivir (first day : 200 mg intravenous infusion in 1 hour then maintenance dose in 100 mg intravenous infusion in 1 hour for 6 days)
3. Antibiotic drugs :ceftriaxone vial 1 g twice daily or Levofloxacin vial 0.5 g once daily intravenously .

Results

The comparison between the levels of all studied markers between Group I and II in the seventh day showed a slightly different pattern than that in the first day in that patients of group II showed significantly higher levels of D-dimer, CRP and LDH and a significantly lower levels of ferritin than that of Group I which is similar to that of the first day and the only difference where noticed in the levels of IL-8 which is become significantly higher in Group I patients than that of Group II as demonstrated in table 1

Table 1: comparison between Group I and II in the levels of all studied parameters in the seventh day of admission

	Group	N	Mean	Std. Deviation	Std. Error	P-value
D-Dimer	I	25	1049.5600	328.94453	65.78891	0.007
	II	45	2321.7333	2283.16047	340.35347	
CRP	I	25	2.7924	1.25480	.25096	<0.001
	II	45	11.6222	6.75232	1.00658	
Ferritin	I	25	862.1072	356.32827	71.26565	0.023
	II	45	659.6467	345.39547	51.48852	
LDH	I	25	292.2000	76.04933	15.20987	<0.001
	II	45	456.3556	174.87374	26.06864	
LYM	I	25	952.4000	146.00314	29.20063	0.974
	II	45	955.7778	497.79737	74.20725	
IL-6	I	25	14.8564	4.77649	0.95530	0.237
	II	43	13.5473	4.10092	0.62538	
IL-8	I	25	1109.0860	365.91236	73.18247	<0.001
	II	43	817.3121	248.65931	37.92019	

Correlations studies: Cross tabulating, Chi square and odd ratio results

Results illustrated in table 2 showed that the percentage of patients recovered after receiving the combination therapy were (73.3%) which is higher than that for patients receiving only dexamethasone. The Chi square results demonstrated that there was a significant correlation (p= 0.15) between the type of treatment and the recovery of patients which confirmed by the Odd ratio result which demonstrated that the risk of death in patients receiving mono therapy of dexamethasone (Group I) is higher than that of patients receiving combination therapy by about 3.5 times.

Table 2: Cross tabulating, Chi square and Odd ratio results of the studied group

			Group		Total
			I	II	
Prognosis	Get well	Count	11	33	44
		% Within Group	44.0%	73.3%	62.9%
	Dead	Count	14	12	26
		% Within Group	56.0%	26.7%	37.1%
Chi^2		Sig.	0.015		
		Phi.	0.291		
Odd Ratio		Value	3.5		
		P	0.0171		
		95 % Confidence interval (CI)	0.1020 to 0.8000		

Discussion

The comparison between the results of the first and seventh day

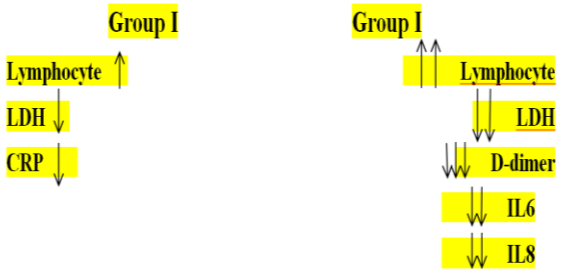

Figure 3 results of the first and seventh day between group I & group II

Figure 3 summerize the significant results between the two groups before and after receiving our studying drugs , Other parameters that not shows in previous figure also reduced in both groups after receiving either dexamethasone alone or combination (dexamethasone and enoxaparin) but because the mean of reduction is not statistically significant. The results of our study strongly support the studies of Debora et al (Debora et al., 2022), Mousavi et al (Mousavi et al., 2015) Significant clinical and basic science literature conducted by (Drago et al.,2020), also shows that heparin & enoxaparin possess anti-inflammatory effects as it can modulate the function and activity of mediators of the immune response, acute phase and complement proteins, and growth factors. The activity of several proteins acting as mediators of inflammation, including CD11b/CD18, eosinophil cationic protein, IL-8.

In the same line of Vitiello & ferrara , studies of Afsharirad & Entezari-Malek (Afsharirad & Entezari-Maleki ., 2023) , Cardillo et al (Cardillo et al ., 2021) interested percentage of patients recovered after receiving the combination therapy were (73.3%) which is higher than that for patients receiving only dexamethasone. The Chi square results demonstrated that there was a significant correlation (p= 0.15) between the type of treatment and the recovery of patients which confirmed by the Odd ratio result which demonstrated that the risk of death in patients receiving mono therapy of dexamethasone (Group I) is higher than that of patients receiving combination therapy by about 3.5 times.

In our study group II results according to prognosis of the first day in which ferritin and IL-6 of passed away patients were higher than who get well later also supporting by results of the seventh day with significant reduction in patients who still alive , indicating prognostic property of IL 6 this agree with the study line of Upadhyay et al (Upadhyay et al ., 2020) ,Ghanem et al (Ghanem et al ., 2022) , and disagree with Talwar et al (Talwar et al ., 2022) who was found IL6 not to be a potent marker for clinical outcomes in patients in terms of death vs survived. However, the IL-6 levels on admission can be correlated with the computed tomography (CT) severity scores.

A lived patients of group II showed interested significant reduction in LDH , D-dimer Ferritin & IL8 in addition to significant increase in rate of Lymphocyte , this highly reduction in inflammatory markers with use of combination therapy (dexamethasone & enoxaparin) providing biochemical and biological synergies by the action of enoxaparin as anti-inflammatory drug through

the transcription factor NF-κB .Blockade of this transcription factor can potentially reduce the activation of inflammatory molecules and regulate the expression and production of pro-inflammatory cytokines, chemokines, and adhesion molecules. Heparin may inhibit neutrophil chemotaxis and leukocyte migration during inflammation , also Vitiello & Ferrara Studies have shown that heparin and its analogs can inhibit cell penetration of SARS-CoV-2 by competing with heparanase. It has also been shown that heparanase can promote viral infection and spread. enoxaparin can inhibit the enzymatic activity of heparinase,so inhibiting viral spread. In comparison to alived patients of group I who received only dexamethasone showed reduction only in D-dimer , LDH & IL6 , increase rate of Lymphocyte .

Also in group I the level of IL8 become higher than group II in day 7 accepted synergistic activity of the combination in comparison with group II at same day but use dexamethasone only which analog of corticosteroids already used clinically as an anti-inflammatory and immunosuppressive agent, especially in the treatment of asthma, and it remains the most potent agent for treatment by decreases IL-8 gene expression in normal human embryonic lung fibroblasts by reducing the stability of its mRNA , this approved by Chang et al (chang et al ., 2001) and supported by our results , although in group I IL-8 not significantly change but it decreased by mean of IL8 group I decreased from 1212.0798 to 1109.0860 ,significantly change in group II the mean decreased from 1145.7424 to 817.3121 at day 7 of admission

Conclusion

1. Percentage of patients recovered after receiving the combination therapy were (73.3%) which is higher than that for patients receiving only dexamethasone. With interested correlation between treatment and the recovery of patients , the risk of death in patients receiving mono therapy of dexamethasone (Group I) is higher than that of patients receiving combination therapy dexamethasone and enoxaparin (group II) by about 3.5 times , supporting the great anti-inflammatory action of enoxaparin in addition to its anti-coagulant effect.
2. IL-6 and IL-8 to provide a diagnostic panel that may provide a good tool for prognosis from the first day of the admission.

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