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A Comparison of Efficacy of Two Brands of Enoxaparin in COVID-19 Patients: A Pilot Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Enoxaparin is a complex and biologically derived low-molecular-weight Heparin which is approved for a variety of clinical indications associated with thromboembolic events such as Deep Vein Thrombosis and Venous Thromboembolism. During COVID-19 it was frequently used as prophylaxis in the treatment of thromboembolic events. Nowadays, many brands have come up in the market for the same.
Objective: In Tricolour Hospital located in Vadodara, Gujarat, the ongoing brand of Enoxaparin 0.6 i.e., Clexane (Sanofi) falls short as well as in the pharmaceutical market. Hence, the management decided to procure another brand of Enoxaparin until Clexane is available to the vendors. Therefore, the present study was planned to study efficacy of two brands of Enoxaparin –one is Coguparine, (Venus Pharmaceuticals) and another LMWX- (Abbott) in COVID-19 patients in an isolation ward of hospital. The aim of present study was to compare the efficacy of two brands of Enoxaparin (Coguparine vs LMWX) for prophylactic treatment of thromboembolism observed in COVID-19 patients.
Methodology: Patients were randomly divided into 2 groups- A and B. Patients in group A received Coguparine while patients in group B received LMWX. Statistical analysis was carried out using paired t-test.

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Results: The laboratory reports of patients in Group-A presented few abnormal improvements in the Complete blood count but there was no concrete evidence about the same. On the other hand, patients in Group-B receiving LMWX showed improvement in CBC profile. Also, there was significant difference observed in C-Reactive Protein and D-Dimer profiles in both the brands.
Conclusion: This showed that for the cost-effective treatment and procurement of Enoxaparin there is no harm in using generic formulation of Enoxaparin as and when required. But LMWX was proved to be of standard quality in terms of efficacy.

Keywords: Enoxaparin; LMWX; coguparine; COVID-19; complete blood count; efficacy.

1. INTRODUCTION

"COVID-19 pandemic has given rise to many compelling indications associated with it. Prevalence for co-morbidities in patients with COVID-19 disease was 22.9% (95% CI: 15.8 to 29.9) for hypertension, 11.5% (9.7 to 13.4) for diabetes, and 9.7% (6.8 to 12.6) for cardiovascular disease (CVD). For chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), cerebrovascular disease and cancer, the pooled prevalence was all less than 4%" [1]. "The Incidence of thromboembolic disease is reported to be high in SARS-CoV2 disease and is seen in a multitude of organ systems ranging from cutaneous thrombosis to pulmonary embolism, stroke or coronary thrombosis sometimes with catastrophic outcomes" [2].

"COVID-19 is a systemic infection with a significant impact on the hematopoietic system and hemostasis" [3]. "On the same point, 82.1% of patients had lymphopenia, 36.2% had thrombocytopenia, and 33.7% had leukopenia" [4]. "Laboratory–confirmed severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2) infection is associated with alterations in the white blood cell (WBC) count. One in four COVID–19 positive patients experience some form of leukopenia, with the majority (63.0%) exhibiting lymphocytopenia. Furthermore, blood from severely ill patients featured more neutrophils and fewer lymphocytes than blood from patients with non–severe disease" [5]. A study said that "The trend of the eosinophil count has been known to correlate with viral infections, but we did not know the correlation was so significant in the case of COVID-19" [6]. "In the early stage of COVID-19 CRP levels were positively correlated with lung lesions and could reflect disease severity" [7]. "The d-dimer is an important prognostic tool, is often elevated in patients with severe coronavirus disease (COVID-19) infection and in those who suffered death" [8]. "An increase in d-dimer is the most significant change in coagulation parameters in severe COVID-19 patients, and progressively increasing values can be used as a prognostic parameter indicating a worse outcome. In addition, pulmonary microvascular thrombosis has been reported and may play a role in progressive lung failure. Prophylactic Low Molecular Weight Heparin (LMWH) has been recommended by the International Society on Thrombosis and Hemostasis (ISTH) and the American Society of Hematology (ASH)" [9].

Enoxaparin has played a crucial role as an anticoagulant agent in Thromboprophylaxis associated with COVID-19. Patients are apparently at high risk of venous thromboembolism (VTE). LMWH at higher doses than those recommended for thromboprophylaxis is used in some hospitals [10]. LMWH are a class of antithrombotic agents that are used in prophylaxis and treatment of deep vein thrombosis (DVT). Meta-analysis shows that LMWH shows superior efficacy to Unfractionated Heparin. Over the year's bioequivalent i.e., generic products have been introduced in the market, leading to cost reductions and increase access to this class of drugs [11]. "When compared with UFH, Enoxaparin was associated with superior efficacy as adjunctive antithrombin therapy among more than 49,000 patients across the ACS spectrum" [12].

The ongoing brand of Enoxaparin 0.6 i.e., Clexane (Sanofi) falls short in the Tricolour Hospital located in Vadodara, Gujarat, India as well as in the pharmaceutical market. The management decided to procure another brand of Enoxaparin until Clexane is available to the vendors. Therefore, various brands had been short listed in the hospital committee meeting and with the experts' discussed upon certain factors such as purchase rate and efficacy and then choose the procurement of the most suitable brand for the hospital. Hence, an open label study was conducted in the isolation ward of the hospital. A previous study showed that "branded formulation of enoxaparin produced a strong inhibition of both thrombin generation and

the progression of clot formation, whereas the generic formulation produced relatively weaker inhibitory effects and allowed for a faster progression of clot formation" [13]. Hence, the aim of present study was to compare the efficacy of two brands of Enoxaparin (Coguparine vs LMWX) for prophylactic treatment of thromboembolism observed in COVID-19 patients.

2. METHODOLOGY

An open labeled comparison study was initiated for 10 days in the isolation ward of tertiary care hospitals located in Vadodara, Gujarat. Total 10 patients suffering from COVID-19 infection were included in study as per the study criteria. In the study, the patients having moderate to severe COVID-19 and of age 25 years and above were included. Patients with co-morbid conditions including liver and renal dysfunction, patient's loss to follow-up, patient's use of anti-coagulant for some other indications were excluded from the study. Laboratory tests were performed twice at the time interval of 3 days. Lab parameters like Complete Blood Count (CBC), D-dimer and C - reactive protein were evaluated during the study.

3. RESULTS

Patients were equally divided in 2 groups named as Group A and Group B. Both the groups received different brands of enoxaparin. Group-A patients were given Coguparine (Venus pharmaceuticals) while the Group-B patients were given LMWX (Abbott pharmaceuticals). The patients were on the dose of Enoxaparin 60mg/0.6ml twice a day continuously for 7 days. Efficacy parameters were observed in both the groups. The laboratory investigations such as CBC, C - reactive protein test and D-dimer levels of all the patients were carried out and observed.

Statistical analysis was performed using paired t-test. The lab values for Hemoglobin, WBC and Neutrophils showed significant difference ($P<0.05$) among the efficacy of 2 brands. On the other hand, rest of the lab parameters showed no significant difference. Since the pilot study with small sample size could not showed major changes. However, large sample may show the apparent difference between two brands. All patients' age ranges from 29-84 years with mean age of 59 years as depicted in Table 1.

Table 1. Comparison of the lab results between generic and branded Enoxaparin

Parameters	Coguparine (Group-A) (N=5)		LMWX (Group-B) (N=5)		Reference Range
	Before	**After**	**Before**	**After**	
			Hematological		
Hemoglobin	11.42	11.82	12.92	13.4	13-17 g/dL
RBC	4.15	4.35	4.52	4.66	4.5-5.5x 10^6µL
PCV	32.68	34.96	37.2	38.84	40-50%
MCV	81.12	82.92	82.32	82.26	80-100 fL
MCH	27.86	27.9	28.62	28.34	27-31 pg
MCHC	34.96	33.66	34.76	34.5	32-36 g/dL
RDW_{CV}	**14.36**	**14.74**	13.8	13.58	11.5-14.5%
RDW_{SD}	42.36	43.7	41.58	41.42	39-46 fL
WBC	**10864**	**11286**	13790	12882	4-10x10^9
Neutrophils	**73.2**	**76.2**	**85.2**	**85.4**	40-70%
Lymphocytes	**23.6**	**17.6**	9.8	11	20-40%
Monocytes	2.4	5	4.8	2.6	2-8%
Eosinophils	0.8	1	0.2	1	1-4%
Basophils	0	0	0	0	0-1%
Platelet count	**356800**	**456000**	265200	296600	150000-450000/mcL
MPV	10.32	10.44	10.24	10.7	8-13 fL
PDW	11.96	11.48	11.92	12.82	9-17 fL
D-dimer					
	364.5	**2170.5**	1362	295.5	≤ 500 ug/L
C-Reactive Protein					
	16.74	**110.45**	121.63	14.70	0-10 mg/L

** The values in bold indicate abnormal progress in the lab data*

Table 2. Comparison of paired t-test between generic and branded Enoxaparin

Parameters	Coguparine (Tc) % Difference	LMWX (Tc) % Difference	Paired T test p-value
Hemoglobin	3.44	3.65	0.038*
RBC	4.70	3.05	0.108
PCV	6.74	4.31	0.095
MCV	2.19	0.07	0.792
MCH	0.14	0.98	0.051*
MCHC	3.79	0.75	0.676
RDW_{CV}	2.61	1.60	0.059*
RDW_{SD}	3.11	0.38	0.151
WBC	3.81	6.80	0.045*
Neutrophils	4.02	0.23	0.019*
Lymphocytes	29.12	11.54	0.079
Monocytes	70.27	59.46	1
Eosinophils	22.22	133.33	0.542
Platelet's count	24.40	11.18	0.137
MPV	1.16	4.40	0.741
PDW	4.09	7.27	0.330
D-dimer	142.48	128.68	0.716
C-Reactive Protein	147.35	156.87	0.954

** P less than 0.05 considered significance*

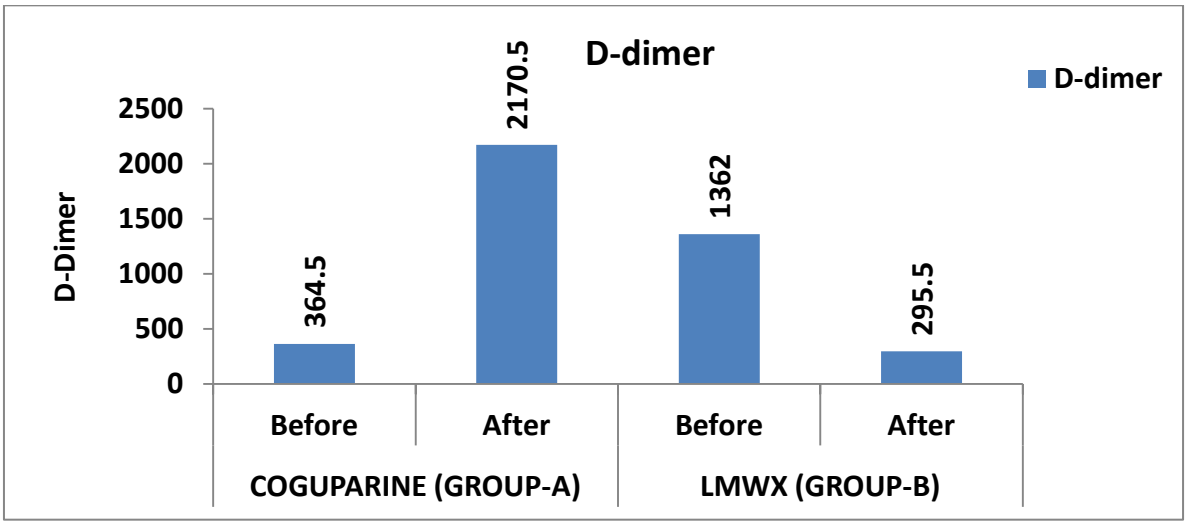

Fig. 1. Comparison of D-dimer values of both the brands

When two different brands were employed, there was no significant difference in the statistical ana -lysis performed in the treatment.

From the Table 1 and Table 2 can be derived that maximum hematological parameters did not show abnormal improvement, in patients of Group-A, who received Coguparine. From Fig. 1 and Fig. 2 it can be observed that patients receiving Coguparine did not show improvement in levels of D-dimer and C - reactive protein. On the other hand, patients of Group-B receiving LMWX showed improvement in D-dimer and C-Reactive Protein values compared to Group-A. Although, statistical analysis showed that only Hemoglobin, WBC and Neutrophils exhibited abnormal improvement, while rest all hematological parameters exhibited normal improvement in patients of Group-A. Since statistical analysis or the graphs are not considered the only deciding parameter and the sample size being small, we cannot confirm that which brand of Enoxaparin is better in terms of efficacy.

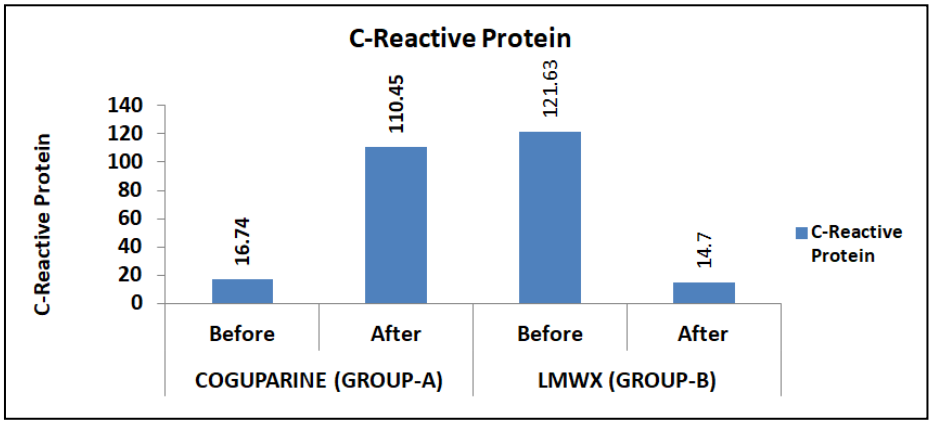

Fig. 2. Comparison of C-Reactive Protein values of both the brands

4. DISCUSSION

A study shows that “analysis of blood samples collected from primates treated subcutaneously with 1 mg/kg of either branded or generic enoxaparin showed that the branded enoxaparin was associated with a significantly stronger and more sustained anticoagulant effect in terms of inhibition of thrombin generation” [13]. Lage et al. compared “branded and generic LMWH for prophylaxis and treatment in intensive care unit patients, with clinical efficacy and safety being main outcomes. The efficacy and safety profiles of both preparations in that study were similar” [11].

The aim of current study was to compare the efficacy of 2 brands of Enoxaparin on the basis of the hematological profile of the COVID-19 positive patients. Since, the above-mentioned studies did not conduct their analysis on the ongoing pandemic conditions, this pilot study would be helpful while choosing between 2 brands of Enoxaparin. It shows that there are differences observed in the efficacy of both the brands with respect to lab data readings. This study does not completely justify which brand of Enoxaparin shows better efficacy on the patient as patients with different co-morbidities such as Diabetes Mellitus, Cardiovascular disease, etc. respond differently to Enoxaparin provided. Also, the statistical analysis does not prove the same. Apart from that, the statistical analysis does not prove the same. The abnormal improvement in the CBC profile might be minor significant to reflect in the statistical analysis conducted. Along with that, the sample size is also very small to predict any results therefore no concrete statement can be made regarding the efficacy of various brands of Enoxaparin. The sample size was considerably smaller compared to other studies, since there was very little time for data collection. Often generic or bioequivalent brands are chosen over standard brands to make the procurement process easy for the hospital and treatment cost-effective for the patient. It might be possible that although different brands show different levels of efficacy compared to the standard brand, they provide desired outcome with slower progress.

5. CONCLUSION

From the above pilot study, it was concluded that use of LMWX is better compared to Coguparine. Since the former showed major improvement in D-dimer and CRP levels while the latter show degradation the D-dimer and CRP profiles. There is no major difference in the CBC profile while using both the brands. But for the cost-effective treatment and procurement purpose the use of Coguparine can be considered efficacious for the patients as well as the hospitals.

CONSENT

As per international standard or university standard, patients’ written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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