CORRELATION OF PROPHYLACTIC AND THERAPEUTIC DOSE OF LMW HEPARIN WITH RESPECT TO OUTCOME IN CRITICALLY ILL PATIENTS OF COVID-19.

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ABSTRACT
Introduction- Recently, a novel coronavirus (2019-nCoV), officially known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused a severe pandemic infection worldwide with considerable morbidity and mortality. A relatively high mortality of severe coronavirus disease 2019 (COVID-19) is worrying, and the application of heparin in COVID-19 has been recommended by some expert consensus because of the risk of disseminated intravascular coagulation and venous thromboembolism. However, its efficacy remains to be validated.We aim to Correlate the association between prophylactic and therapeutic dosages of low molecular weight heparin (LMWH) on mortality and other morbidity outcomes in critically ill patients of COVID-19 .**Methods-** Consecutive patients admitted to Dr. S. C.GMC Medical college and hospital Nanded with laboratory-confirmed COVID-19 were included in this retrospective observational study. The diagnosis of COVID-19 was established according to World Health Organization interim guidance and confirmed by RNA detection of the SARS-CoV-2 in the microbiology laboratory of the hospital. Outcomes between COVID-19 patients treated with standard prophylactic LMWH enoxaparin dosage (subcutaneous enoxaparin 40–60 mg daily) or Therapeutic LMWH enoxaparin dosage (subcutaneous enoxaparin 40–60 mg twice daily) for 7 days were correlated. **Results** -Out of 100 patients 50 reccived P-LMWH & 50 reccived T-LMWH among that 12 %   patients expired in prophylactic group & 22% in therapeutic group. It was observed that the levels of D-dimer before & after of P-LMWH group were (D-dimer: 2.63 ± 1.77, 0.63 ± 1.19) and those of T-LMWH group were(D-dimer: 3.14 ± 2.15, 1.07 ± 1.56). the length of hospital stay was   (11 ± 2.21) days in the P-LMWH group and (11 ± 3.99) Days in the T-LMWH group. Simillarly the saturation level of oxygen ware (SPO2 98%) in P-LMWH group & (SPO2 97%) in T-LMWH group. 26% patients shows adverse effects to P-LMWH group & 32% patients to T-LMWH group. **Conclusion-** Study demonstrates that if you start earlier prophylactic LMW heparin to critically ill patients of covid 19 with raised D-dimer level the level of d-dimer will not further increased and comes down to normal value. Simillarly patients recover earlier and reduces hospital stay of patients with improvement in oxygen saturation.

KEYWORDS : COVID- 19, LMWH (low molecular weight heparin), Hospital mortality, D-dimer, Hospital stay

INTRODUCTION

In December-2019, Wuhan city in China, became the centre of an outbreak of pneumonia of unknown cause. By 7 Jan 2020, Chinese scientists had isolated a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously known as 2019-nCoV), from these patients with virus-infected pneumonia later designated coronavirus disease 2019 (COVID-19) in February, 2020, by WHO

The main clinical symptoms are fever, breathlessness, dry cough, fatigue, ageusia and anosmia , dirrhoea. The clinical spectrum appears to be wide, including asymptomatic infection, mild upper respiratory tract illness and severe viral pneumonia with occurrence of respiratory failure. This is associated with an increase of systemic inflammation, cytokine storm and diffuse endothelial injury, resulting in the most severe cases in multi-organ failure with consequently poor outcomes.

So far, there is no specific therapy for COVID-19. Hydroxychloroquine & Remdisivir has been suggested as having antiviral activity, As the cytokine storm appears to be a crucial pathogenetic process in COVID-19 patients, immunosuppression and immune modulation approaches have been tried by glucocorticoids & tocilizumab. Abnormal coagulation function has been demonstrated to be involved in the disease progression of COVID-19. Low molecular weight heparin (LMWH) administration in COVID-19 patients has been recommended by some expert consensus due to the risk of primary pulmonary thrombosis, venous thromboembolism and disseminated intravascular coagulation.

However, evidence about administration dosage and duration is limited and its efficacy on clinically relevant endpoints being yet to be demonstrated.

Methodology

Consecutive patients admitted to Dr. S. C.GMC Medical college and hospital Nanded from 1st june to 30th November 2020 with laboratory-confirmed COVID-19 were included in this retrospective observational study.

The diagnosis of COVID-19 was established according to World Health Organization interim guidance and confirmed by RNA detection (RT-PCR) of the SARS-CoV-2 in the microbiology laboratory of the hospital.

The data were collected through the electronic medical record system of our hospital.

The study was approved by institutional ethics committee.

Inclusion criteria
1) Critically ill Patients of age group greater than 18 yrs ,dignosed as rt-pcr positive for covid 19 with increased D-dimer level.

Exclusion criteria
1) Patients with age less than 18 yrs.
2) Patients having bleeding disorders
3) Patients who have been treated with LMW Heparin in previous 3 momths.
4) Patients with severe systemic diseases and congenital heart diseases.
5) Patients with liver and kidney insuffiency.
6) Patients allergic to LMW Heaprin.

Outcomes between COVID-19 patients treated with standard prophylactic LMW heparin dosage (subcutaneous 40–60 mg daily) or Therapeutic LMW heparin dosage (subcutaneous 40–60 mg twice daily) for 7 days were correlated.

The decision to adopt standard prophylactic or therapeutic LMWH dosage was based on the clinical judgment of the attending physician.

Statistical Analysis
we collected the Epidemiological, demographic, clinical, laboratory, treatment, and outcome data from electronic medical records.

Which was analysed using statistical analysis with MS excel and SPSS software version 21.

We will present categorical variables as numbers and percentages and continuous variables as mean and standerd deviation.

OBSERVATIONS & RESULTS
Out of 100 patients 50 reccived P-LMWH & 50 reccived T-LMWH Among that 6 (12%) patients expired in prophylactic group & 11 (22%) in therapeutic group.

Out of 50 patients in prophylactic 33 (66%) are with comorbidity & in therapeutic group 32 (64%) are comorbid.

It was observed that the levels of D-dimer before & after of P-LMWH group were (D-dimer(mcg/ml): 2.63±1.77, 0.63±1.19 . And those of T-LMWH group were (D-dimer (mcg/ml) : 3.14 ± 2.15, 1.07 ±1.56).

The length of hospital stay was (11 ± 2.21) days in the P-LMWH group and (11 ± 3.99) Days in the T-LMWH group.

Similarly the saturation level of oxygen ware (SPO2 98%) in P-LMWH group & (SPO2 97%) in T-LMWH group.

13 (26%) patients shows adverse effects to P-LMWH group & 16 (32%) patients to T-LMWH group.

Table1: Demographic characteristics & Comorbidities of patients with covid-19

Sr.No	parameters	P-LMW Heparin(n=50)	T-LMW heparin(n=50)
1	Age-(mean±SD)	48 ±12.70	51 ±13.39
2	Gender		
	Male- n(%)	35 (70%)	33 (64%)
	Female- n(%)	15 (30%)	17 (34%)
3	Comorbidity-n (%)		
	HTN	13 (26%)	11 (22%)
	IHD	3 (6%)	1 (2%)
	DM	10 (20%)	10 (20%)
	COPD	3 (6%)	2 (4%)
	AKI	1 (2%)	2 (4%)
	CKD	1 (2%)	1 (2%)
	PTB	1 (2%)	1 (2%)
	EPTB		1 (2%)
	MYD Syndrome		1 (2%)
	Tuberculous meningitis		1 (2%)
	Hypothyroidism		1 (2%)
	Sickle cell anemai	1 (2%)	

Table 2: Other mortality & morbidity outcomes

Sr.No	parameters	P-LMW Heparin(n=50)	T-LMW heparin(n=50)
4	Hosp.Mortality-n(%)		
	Expired	6 (12%)	11 (22%)
	Recovered	44 (88%)	39 (78%)
5	Spo2-(mean±SD)	98 ± 1.16	97 ± 1.13
6	Hospital stay-(mean±SD)	11 ± 2.21	11 ± 3.99
7	Adverse event-n (%)		
	HIT	4 (8%)	5 (10%)
	Bleeding	3 (6%)	3 (6%)
	Nausea, vomiting	4 (8%)	3 (6%)
	Pain at injection site	2 (4%)	4 (8%)
	Alopecia		1 (2%)

Table 3: Laboratory parameters in both groups

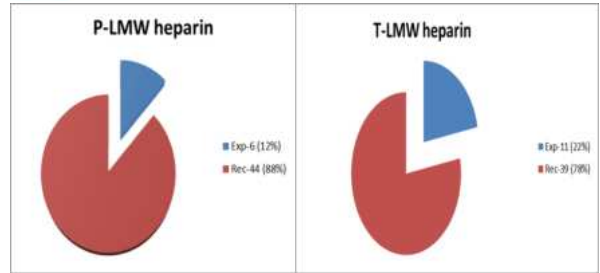| Sr.No	Lab parameter	P-LMW Heparin (n=50)		T-LMW heparin (n=50)	
		before	after	before	after
8	D-dimer-(mean±SD)	2.63±1.77	0.63±1.19	3.14 ± 2.15	1.07 ±1.56
9	Platlet count-lakh(mean±SD)	3.19 ±0.80	2.94 ±0.88	3.12±0.76	2.62±0.76

Figure1. Hospital mortality in patients treated with P-LMW heparin & T-LMW heparin
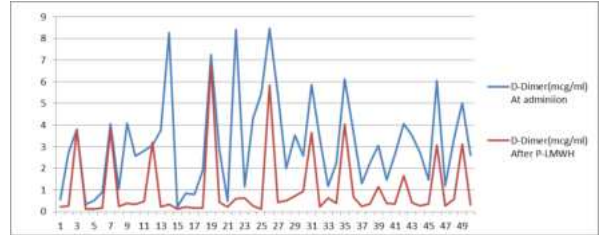

Figure2. D-dimer level in patients treated with P-LMW heparin at admission & after P-LMW heparin treatment.
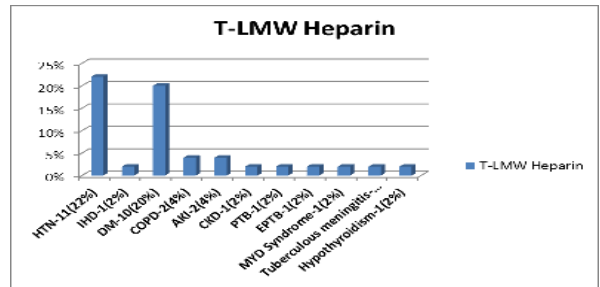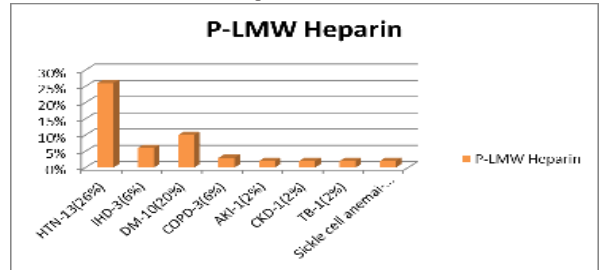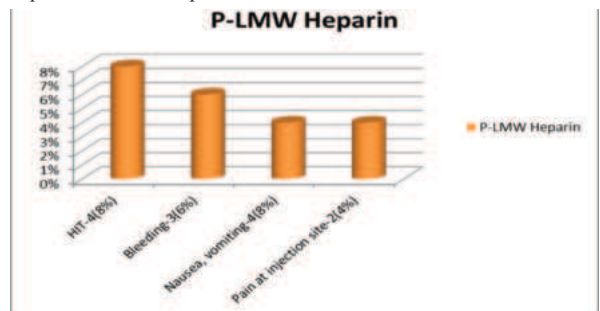

Figure3. Comorbidity observed in patients treated with P-LMW heparin & T-LMW heparin.
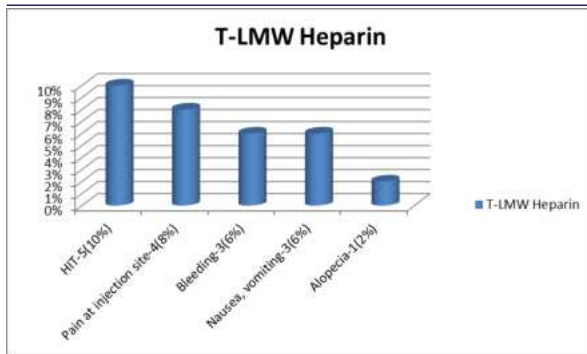
Figure 4. Adverse event observed in patients treated with P-LMW heparin & T-LMW heparin

DISCUSSION

Our study suggest that standerd prophylactic LMW heparin dosage ware effective in controlling incidence of hospital mortality among covid-19 patients. Previous report suggest that the therapeutic LMW heparin dosage seems to be associated with lower incidence of mortality compared to standerd prophylactic dosage of LMW heparin among critically ill patients of covid-19.

A retrospective cohort study conducted in Castel San Giovanni Hospital, ASL PC, Italy shows that Hospital mortality was signicantly lower in patients treated with therapeutic LMWH (17/126, 13.5%) than in those treated with prophylactic LMWH (32/131, 24.4%). Our study shows that hospital mortality was lower in patients treated with prophylactic LMWH(6/50 ,12%) than in those treated with therapeutic LMWH (11/50, 22%).

Previously, older age has been reported as an important independent predictor of mortality in SARS and MERS. The current study confirmed that increased age was associated with death in patients with COVID-19.

In our retrospective study, the level of D-dimer was markedly increased in patients with severe COVID-19, and the analysis further confirmed that odds of severe COVID-19 was associated with D-dimer greater than 0.5 μg/ml.

- Our study has some limitations. Small sample size is the major limitation of our study.
- Second, due to the retrospective study design. not all laboratory tests were done in all patients, including lactate dehydrogenase, IL-6, and serum ferritin. Therefore, their role might be underestimated in predicting in-hospital death.
- And Third, inadequate adherence to standard supportive therapy, and high-dose corticosteroid use might have also contributed to the poor clinical outcomes in some patients.
- Fourth, the influence of other therapies on these patients has not been evaluated;

CONCLUSION

Study concludes that if you start earlier prophylactic LMW heparin to critically ill patients of covid 19 with raised D-dimer level the level of d-dimer will not further increased and comes down to normal value. Simillarly patients recover earlier and reduces hospital stay of patients with improvement in oxygen saturation.

Anticoagulant therapy mainly with low molecular weight heparin appears to be associated with better prognosis in severe COVID-19 patients. Further prospective studies are needed to confirm this result.

Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional ethics committee.

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