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"TITLE" - HEPARIN AS AN INHALTION AGENT AMONG MODERATE AND SEVERE COVID-19 PATIENTS

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ABSTRACT

Introduction

COVID-19 is a pandemic prevailing for the past 16 months, which led to many innovations in the treatment in order to achieve good recovery rate. Lung involvement appears to be the single most determining factor in the outcome of patients. Various treatment protocols ranging from Pharmacotherapeutics to Physiotherapy have been tried. Multiple mutations, different presentations in different countries, different ethnics have posed additional problems. Along with the accepted protocols, Heparin nebulization was used in some countries particularly China with promising results. This method is innocuous and needs to be tested in our country. Aim of this study is to use Heparin nebulization to improve lung function and reduce the mortality in COVID-19 patient'sunfractionated heparin which is cheap and easily available and its ease of use can give promising good results in Covid management in developing and thickly populated country like INDIA.

Materials and Methods

Study design: Hospital based randomized comparative study
Study type: Interventional
Intervention mode: Parallel Assessment
Primary purpose: Therapeutic
Place of study: ICUs of CSR block, a dedicated COVID center, King George Hospital, Visakhapatnam. Andhra Pradesh., INDIA. Study population: 200 cases of COVID-19 positive patients with lung involvement admitted in Intensive care unit (ICU). Permission from IEC, AMC/KGH, Visakhapatnam. Selection of patients as per inclusion criterion. Written informed consent from patient and attendant along with high risk consent as they are treated in ICUs are taken prior to the study.The patients are divided into two groups one would be the study group and other group will act as controls. Outcome from both groups will be compared and analyzed for outcomes. Data is spread over excel sheet and data is analyzed using SPSS version 22.**Results** -Heparin nebulization is 6 times more effective in treating lung inflammation in covid than the standard routine treatment and regarding the outcome the deaths are two times more among the standard treatment (control) than the heparin nebulization (study) group. $P<0.05$ there is a significant association between hospital stay in days and Outcome of study. **Conclusion** - Heparin nebulization used in treating covid -19 lung pathology has given promising results. The mortality rate is reduced when compared to standard ICU protocols. UFHeparin used is cheap, easily available, low systemic side effects when compared to LMWH. India being developing country, with large population and limited resources,manpower, heparin nebulization can give good results in managing the covid-19 Pandemic for those who required treatment in ICUs.

"Keywords"–Intensive care Units (ICUs), Low molecular weight heparin (LMWH),Mortality rate, unfractionated heparin (UFH)

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Introduction

COVID-19 is a pandemic which affected the human life for the past two years leading to many innovations in the treatment in order to achieve good outcome. As per the WHO corona virus (COVID- 19) dashboard, dated May 1st, 2021, there have been more than 150 million globally confirmed cases of covid 19, including over 3 million deaths. The current pandemic has unfolded with increasing illness, unpredictable outcomes and devastating socioeconomic disruption of routine life has thrown life out of gear not only for the general public but also for health care workers, forcing them to not only deal with the strained health care system but also manage a disease that was unknown to the world before. There has been tremendous progress in terms of authorization and deployment of drug trials, vaccines and antibody therapies. There being no clear universal guidelines for the management of covid -19 for obvious reasons, a significant emphasis has been made on the fact that there has to be continuous search for therapies that would be of patient benefit. Lung involvement appears to be the single most determining factor in the outcome of patients. Various treatment protocols ranging from Pharmacotherapeutics to Physiotherapy have been tried. Multiple mutations, different presentations in different countries, different ethnics have posed additional problems. Along with the accepted protocols, Heparin nebulization[1] was used in some countries particularly China[4] and UK with promising results. This method is innocuous and needs to be tested in India. Unfractionated heparin which is cheap and easily available and its ease of use can give promising results in covid management in developing and thickly populated country like India.

Pathophysiology - Droplet inhalation, direct contact and fomites cause the entry of the virus into the respiratory tract. The spike(s) protein binds to host receptors and by endocytosis or membrane fusion enters host cell. ACE-2 has been identified as functional receptor for SARS- CoV and is highly expressed on the pulmonary epithelial cells[7]. Post membrane fusion[2], the viral particles inside cells replicate by pre existing single strand RNA through RNA polymerase activity (transcription). On entry into host it produces various pathological processes depending upon the host defence mechanism and the external supportive medical management.

Lung involvement - on entry into alveoli of lungs it causes hyper inflammation[5], micro angiopathy, DNA neutrophyll[24] extra cellular trapping. This increases the accumulation of inflammatory exudates creating dead space, hyaline membrane formation which hinders ventilation perfusion and the resulting hypoxia causes multi organ failure and death. Apart from the inflammation of lung any organ in the body can be involved and the generalized hyper coaguability[5,-8] cause various thrombo embolic manifestations[4] and their consequences.

Role of heparin in covid -19:- heparin has various properties and can be used in combating the thromboembolic manifestations systemically and also locally in the lung by inhalation.[11]

Properties of heparin - 1. Anti coaguation

2. Anti inflammatory

3. Mucolytic

4. Neo-angiogenic

5. Antiviral

Type of heparin-1. Low molecular weight heparin

2. Un fractionated heparin (UFH).

We use UFH in the form of inhalation that reduces the lung inflammation, improves saturation and there by corrects hypoxia and MODS.

Mode of action of UFH as nebulising agent:-

1.Antiviral activity- heparin sulphate which is one of the component of UFH competitively binds ACE receptors and there by prevents the adhesion of spike s protein of SARS CoV virus to alveolar epithelium[16,17,18,19] and prevents the entry of virus into host cells.

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2. Anti inflammatory - inhibition ofpro- inflammatory cytokines and prevent the recruitment of interleukins via blocking of key adhesion molecules expressed on vascular endothelium and there by release of nitric oxide which causes capillary dilatation and correction of hypoxia.

3.Anti coagulation effects- heparin inhibits coagulation activation through a range of mechanisms, including catalyzing the action of thrombin, release of tissue fibrinogen activator by the endothelium, causing fibrinolysis[2] and thrombolysis of microvasculature which further increase pulmonary capillary patency and correction of hypoxia. UFH in the form of inhalation as additional advantage over LMWH reduces the complication of heparin induced thrombocytopenia. (HIT)

4. Mucolytic effect[4]- UFH nebulization causes thick mucoid pulmonary exudates lysis,reduces sputum elasticity andexudates get expelled out there by decreasing dead space and improves ventilation perfusion ratio.

Aims & Objectives

To use unfractional Heparin as inhalational agent through nebulizer for improving the lung functions and reduce the mortality in COVID-19 patients.

Objectives

1. To improve the clinical outcome in moderate and severe disease patients who are conscious and coherent using unfractional heparin as inhalation.
2. To decrease the incidence of mechanical ventilation among the moderate and severe COVID-19 disease patients
3. Toreduce theICU and hospital stay.
4. To reduce the oxygen requirements, conserve oxygen, prevent oxygen toxicity and dependency.

Material and Methods

Study design: Hospital based randomized comparative study

Study type: Interventional

Intervention mode: Parallel Assessment

Primary purpose: Therapeutic

Place of study: ICUs of CSR block, a dedicated COVID center, King George Hospital, Visakhapatnam. Andhra Pradesh., India.

Study population: 200 cases of COVID-19 positive patients with lung involvement required ICU admission

Permission was taken from Institutional Ethics Committee, AMC/KGH, Visakhapatnam A.P. (Reg No. : ECR/197/Inst/KGH/2013/RR-20) Selection of patients is based on inclusion criteria. Informed and written consent from patient and patient attendants are taken. Detailed Case history is completed by using semi-structured questionnaire from all the study patients.

Inclusion Criteria

Age >=18 Years

Positive COVID test

Medical co morbidities

Spo2 80-94%

Exclusion criteria

Platelet count<15000cells/mm^3

Liver disorders

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Pregnant and post natal

Two groups of patients are taken into the study. Group I (**C**) 100 control patients in ICU who received the standard ICU management of COVID-19, Group II (Nebulization patients) - **N** 100 who received heparin nebulization along with standard ICU management of COVID-19.All routine investigations as per protocol and imaging of lung, Chest X ray are routinely done. Coagulation profile is done for Group II patients.

Heparin Nebulization:Prior consent is taken from the patient and the procedure of nebulization explained. Group II patients (**N**) receive heparin nebulization along with standard ICU management. 25000IU of unfractionated heparin is given in the form of inhalation 8th hourly with the average speed of nebulizer to the entire selected group in the inclusion criteria. The Saturation level of O2, Spo2 is recorded after10-15 min of every nebulisation episode with a separate chart for each patient apart from the routine case sheet.Patients those who are within the spo2 range of 80-94% on oxygen with Hudson mask/nrbm/hfno or NIV are considered. Nebulisation procedure is done in sitting position most of the times. For those who are on NIV, a T-piece connector is connected to NIV mask for nebulisation at the inhalation port and procedure is done withoutremoving NIV, as for the risk on removal there is a sudden fall of spo2.

The observed data is spread over excel sheet, the results observed from both the groups will be analyzed using SPSS Version 22.,Results obtained were tested for probability or association using Odds ratio, fisher's exact test, t-test or chi-square whichever is applicable.

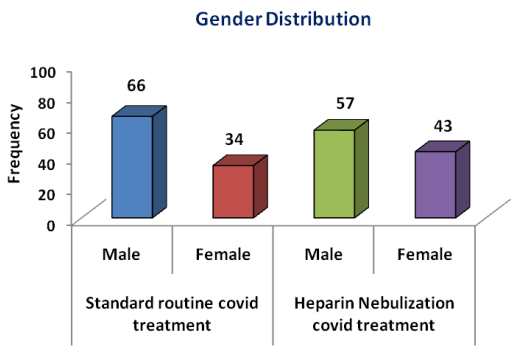
Results

Table 1: Showing relationship between age and hospital stay (ICU /Ward) among the study and control groups

Study Group	Variables	N	Min	Max	Mean	SD
Standard covid treatment	AGE	100	22	80	51.15	13.009
	ICU STAY (Days)	100	1	36	5.04	5.486
	WARD STAY (Days)	100	0	26	3.52	5.181
	TOTAL HOSPITAL STAY (Days)	100	1	54	8.56	8.762
Heparin Nebulization covid treatment	AGE	100	18	80	50.43	13.723
	ICU STAY (Days)	100	2	27	6.53	3.794
	WARD STAY (Days)	100	0	24	8.43	6.343
	TOTAL HOSPITAL STAY (Days)	100	2	36	14.96	7.856

The mean age of the study group is 50.43 and among the controls is 51.15.The ICU stay in days the mean is 6.53 in the study group and 5.04 among the controls. The ward stay in the study group is 8.43 and among the controls is 3.52respectively. Total hospital stay in days mean is 14.96 in study group and among the controls is 8.56.It is observed among the study group versus control group participants are near similar in all the characters but there is significant difference observed among the two groups in the hospital length of stay, where the control group there is increased hospital stay when compared with study group because the study group length of hospital stay decreased as the patients became clinically stable and recovered soon

Figure 1: Showing gender distribution among the study and control groups in the study



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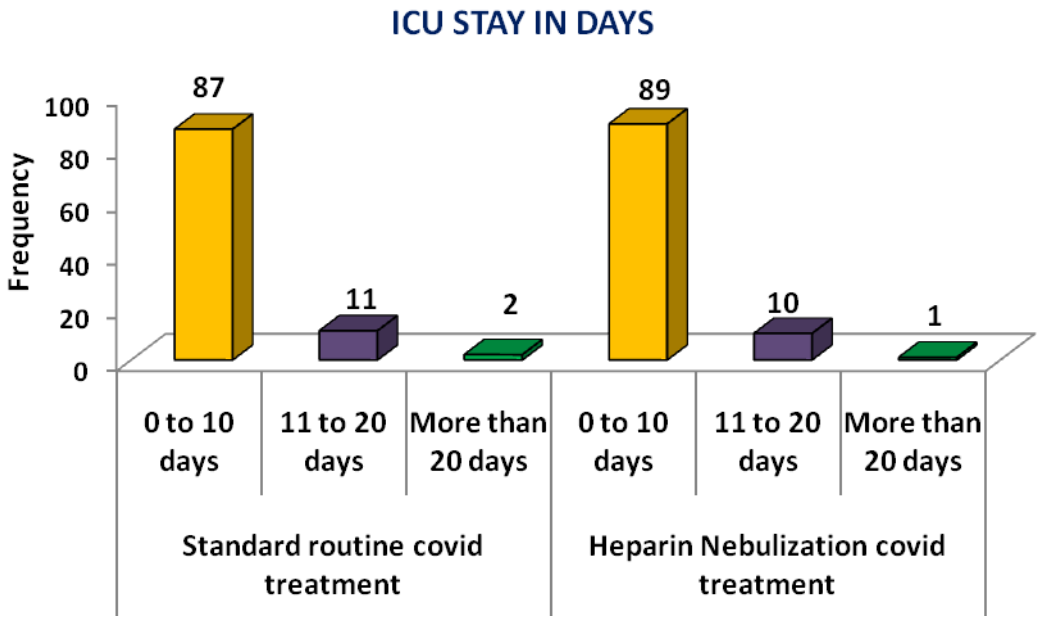
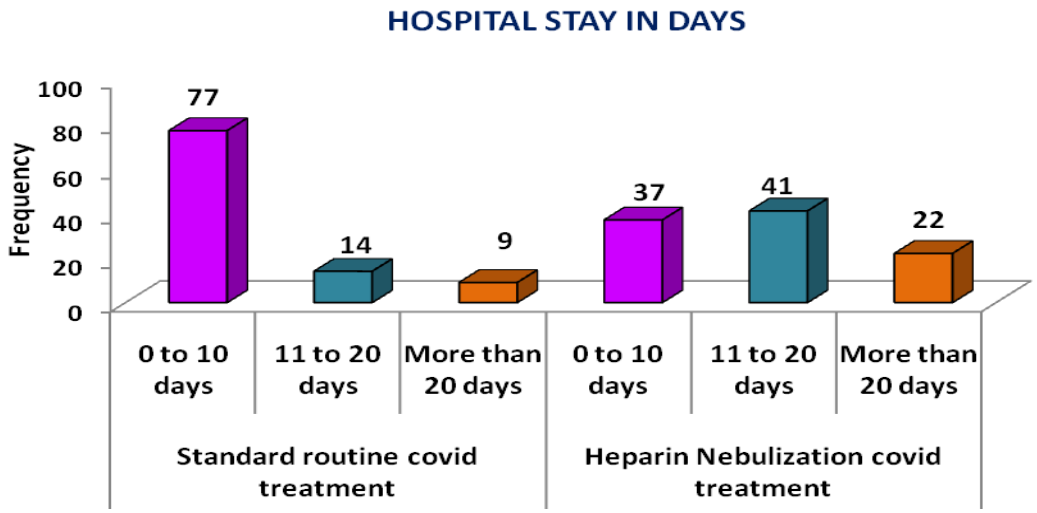
Male preponderance is observed among the study (66%) and control groups (57%) than the females in the study.

Figure 2: Showing length of ICU stay (days) - Standard routine Covid treatment (control) group versus Heparin nebulization+ Covid treatment (Study)group



It is observed that the standard treatment ICU stay was 87% in 0-10 day's category versus Heparin nebulization treatment by 89% in 0-10 day's category, the higher the frequency the lesser the ICU stay which was observed with Heparin Nebulization + standard Covid treatment.

Figure 3: Length of stay in Hospital wards (Days) - Standard Covid treatment group versus Heparin nebulization+ Standard Covid treatment group



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The standard treatment in ward stay was 77 % in 0-10 days category versus Heparin nebulization treatment by 37 % in 0-10 days category, in category of 11-20 days the maximum is observed in heparin nebulization (study) group than 14% in the standard routine treatment (control) group

Table 2: Showing treatment outcome – Standard Covid treatment group versus Heparinnebulization + Covid treatment group

Study Group	Outcome variable		(χ2 ,P<0.05) *
	Deaths	Discharges	
Standard Covid treatment(100)	81(81%)	19(19%)	(33.628,p<0.05)
Heparin Nebulization covid treatment(100)	41(41%)	59(59%)	
Total(200)	122(61%)	78(39%)	

*- P<0.05 there is a significant association between Study group and Outcome of study by using chi-square test

There is significant impact of heparin nebulisation in the study group as 59 (59%)discharged while compared with the control group which is only 19 (19%) got discharged and remaining 81% were deceased.

Table 3: Risk Estimation- Standard Covid treatment group versus Heparin nebulization + standard Covid treatment group

Risk Estimate	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Study Group (Standard routine covid treatment / Heparin Nebulization covid treatment)	6.135	3.238	11.624
For cohort Outcome = Deaths	1.976	1.533	2.546
For cohort Outcome = Discharges	0.322	0.208	0.498

Heparin nebulisation is 6 times more effective than the standard routine treatment and regarding the outcome the deaths are 2 times more among the standard treatment (control) group than the heparin nebulisation (study) group

Table 4: Gender versus outcome (Deaths and Discharges)

Gender	Outcome variable		(χ2 ,P<0.05) *
	Deaths	Discharges	
Male(123)	80(65%)	43(35%)	(2.193,0.139)
Female(77)	42(41%)	35(59%)	
Total(200)	122(61%)	78(39%)	

*- P<0.05 there is no significant association between Gender and Outcome of study by using chi-square test

Table 5: Risk estimation versus outcome (Deaths and Discharges)

Risk Estimate	Value	95% Confidence Interval	
		Lower	Upper

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Odds Ratio for Gender (Male / Female)	1.55	0.866	2.774
For cohort Outcome = Deaths	1.192	0.937	1.518
For cohort Outcome = Discharges	0.769	0.546	1.084

No significance is noted in the risk versus outcome by gender.

Table 6: Length of ICU days – Standard Covid treatment group versus Heparin nebulization+ standard Covid treatment group

ICU STAY IN DAYS	Outcome variable		(χ2 ,P<0.05) *
	Died	Discharge	
0 to 10 days(176)	104(59.10%)	72(40.90%)	(2.393,0.271)
11 to 20 days(21)	16(76.20%)	5(23.80%)	
More than 20 days(3)	2(66.70%)	1(33.30%)	
Total(200)	122(61%)	78(39%)	

*- P>0.05 there is no significant association between Study group and Outcome of study by using Fisher's Exact Test.

Table 7: Hospital stay (Days) - Standard Covid treatment group versus Heparin nebulization + standard Covid treatment group

HOSPITAL STAY IN DAYS	Outcome variable		(χ2 ,P<0.05) *
	Died	Discharge	
0 to 10 days(114)	90(59.10%)	24(40.90%)	(37.258,<0.05)
11 to 20 days(55)	23(41.80%)	32(58.20%)	
More than 20 days(31)	9(29%)	22(71%)	
Total(200)	122(61%)	78(39%)	

*- P<0.05 there is a significant association between hospital stay in days and Outcome of study by using Chi-Square Test.

Heparin nebulisation is 6 times more effective in treating lung inflammation in covid than the standard routine treatment and regarding the outcome the deaths are two times more among the standard Covid treatment (control) than the heparin nebulization + Covid treatment (study) group.

Discussion

Covid -19 infection in humans is posing a challenge in treatment and management issues globally. Mortality is primarily due to involvement of lung and various treatment modalities have evolved .Thisstudy is conducted in COVID tertiary care center established inKing George Hospital Visakhapatnam. In ICUs heparin nebulization is used in treating lung inflammation versus the standard ICU protocols. A promising result is obtained from the study. Unfractinated heparin which is used in nebulisation is safe when compared to LMWH which is administered via parental route. UFH has short half life of 4-5 hours and gets easily metabolized by the liver and also when given in aerosol form very little gets absorbed systemically.HIT–heparin induced thrombocytopenia is very dangerous complication seen with LMWH and such a complication never occurs in UFHeparin when used in aerosol form. Heparin nebulisation reduces the inflammation of lung[1, 2,][4, 5,][11, 14] by stabilizing the mast cells in respiratory mucosa, reduces the dead space and increases the nitric oxide levels at the capillary levels, lyses the micro thrombi in the pulmonary capillaries. This improves the lung microcirculation and helps to maintain the ventilation perfusion index. Also the 8th hrly interval between each nebulisation helps to avoid the risk of local mucosal bleeding in the airways. The thick mucus plugs in the bronchi gets thinned out and get expelled on cough. Heparinnebulization is easy to administer for those patients who requires admission in ICUs and is easily acceptable by the patients, it also doesn't need any expertise to exercise the procedure.

Conclusion -Heparin nebulization used in treating covid -19 lung pathology has given promising results. The mortality rate is reduced when compared to Standard ICU protocols. UFHeparin used is cheap, easily available, low systemic side effects when compared to LMWH. INDIA being developing country, with large population

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and limited resources,manpower, heparin nebulisation can give promising results in Covid ICUs considering the threat of 3rd wave in future.

Conflict of Interest - None to be declared

Funding - Nil

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