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KEY WORDS: Steroid, Hyperglycaemia, Diabetes, COVID-19, Insulin.

RETROSPECTIVE STUDY ON GLYCAEMIC CONTROL OF THE MIDDLE-AGED PATIENTS RECEIVING STEROID THERAPY IN COVID ICU.

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ABSTRACT

Background and Aim: Novel Coronavirus (SARS-CoV2) was first reported in end of December 2019 in Wuhan, China and subsequently had become a global pandemic causing high mortality and morbidity rate. Pre-existing chronic diseases like Diabetes mellitus, obesity are further associated with worse outcome in presence of COVID-19 infection. Steroid therapy, in particular glucocorticoids (GC), has great role in treatment of acute and chronic inflammatory conditions. But GCs precipitate hyperglycaemic state by different mechanisms. This study was aimed for assessment of glycemic control and its impacton outcome of patients having received steroid therapy in COVID ICU(Intensive Care Unit). Hence our objectives were to estimate the mean blood sugar level and mean insulin requirement of the middle aged (45-60 years) patients at different time intervals daily during their stay and to estimate the mortality rate of these patients. **Settings And Design:** it was a retrospective cohort study where total eneumeration of patients were counted during study period by serial sampling technique. **Materials And Method:** Patients admitted in ICU were divided into 4 groups either diabetic (on insulin or oral hypoglycaemic agents[OHA]) or non diabetic (either requiring insulin or not). Then data collected based on study parameters were compiled to obtain our aim of the study by using standard statistical analysis method. Result: Total steroid dose, mean Capillary Blood Glucose (CBG) values and mean insulin requirement were higher in diabetic groups. But early initiation of insulin therapy potentially improved mortality rate and decreased ICU stay in both non-diabetics and diabetics. **Conclusion:** It had been concluded that aggressive insulin therapy from very early stage of hyperglycaemic state of any group of patients led to significantly decreasing mortality rate and thus reducing ICU stay in a positive manner.

INTRODUCTION:

Novel Coronavirus (SARS-CoV2) was first reported in end of December 2019 in Wuhan, china[1] and subsequently has become a global pandemic causing high mortality and morbidity rate.[2] Pre-existing chronic diseases like Diabetes mellitus, Obesity are further associated with worse outcome in presence of COVID-19 infection and virus induced respiratory dysfunction.[3]

Increased viral replication in vivo, suppression of antiviral immune response, increased permeability of vasculature and subsequent collapse of alveolar epithelium significantly affect pulmonary function.[4,5] Acute inflammatory state in COVID-19 patients has been associated with pathogenesis of hyperglycaemia.[6]

Steroid therapy, in particular glucocorticoids(GC), has great role in treatment of acute and chronic inflammatory conditions.[7] But GCs decrease peripheral insulin sensitivity, increase hepatic gluconeogenesis, trigger insulin resistance on the level of lipid metabolism and adipose tissue as well as inhibit pancreatic insulin production and secretion, thus precipitating hyperglycaemic state.[8,9,10]

Our study was aimed for assessment of glycaemic control and determination of outcome of patients having received steroid therapy in COVID ICU. Hence our objectives were to estimate the mean blood sugar level and mean insulin requirement of the middle aged (45-60 years) patients admitted in ICU at different time intervals daily during their stay and to estimate the mortality rate of these patients receiving steroid therapy in COVID ICU.

Gianchandani R, Esfandiari NH, Ang L, Iyenger J, Knotts S, Choksi P et al published an article on 2020 regarding managing hyperglycaemia in the COVID-19 inflammatory storm and concluded that prompt glycaemic control was critical measure to decrease ICU mortality and morbidity rate.[6]

Aberer F, Hochfellnar DA, Sourij H, Mader JK also showed urgency for prompt glycaemic control for steroid induced hyperglycaemia (SIHG).[11] In concordance with these studies we had decided to focus how glycaemic control could be improvised for SIHG in COVID ICU.

MATERIALS AND METHOD:

After receiving institutional ethics committee clearance and keeping confidentiality of patient's identity, a retrospective cohort study had been undergone in our institute. We had taken total enumeration of patients with COVID RTPCR(Reverse Transcriptase polymerase chain reaction) positive report admitted in COVID ICU from May 2021 to June 2021 aged between 45-60 years and having received steroid therapy by serial sampling technique. Then they were divided into 4 groups. In group A the diabetic patients already in insulin therapy were included(n=8).

In group B diabetic patients on oral hypoglycemic agents (OHA) were taken (n=24). In group C non diabetic patients having received insulin were enrolled (n=18) and in group D non diabetic patients not requiring insulin were included (n=10). We had excluded all those patients receiving chronic steroid therapy for any other illness. Then data collection had been done from individual patient records in medical record section of institute according to our study parameters. Our study parameters were age, sex, body weight, duration of steroid therapy, total steroid dose received per day, mean capillary blood glucose (CBG)value of each day, mean regular insulin requirement of each day, total regular insulin requirement in stay, additional insulin required, average duration of insulin therapy and outcome of the patients. The raw data were tabulated in master chart as per study protocol and data compilation had been done. Reduction of redundant data were considered and the parameters relevant with our objective were further enlisted in the study tabulation sheet. The compiled data were statistically analyzed using SPSS Version 22.0 software and following methodology. The results obtained from statistical analysis were further tabulated and

displayed in the final report. Continuous variables were expressed as Mean, Median and Standard Deviation and compared across the groups using Mann-Whitney U test/Kruskal Wallis Test as appropriate. Categorical variables were expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate. An alpha level of 5% had been taken, i.e. if any p value is less than 0.05 it had been considered as significant.

Blood glucose (mg/dL)	Insulin (units)
61-150	0
151-200	3
201-250	5
251-300	8
301-350	10
351-400	12
>400	15[a]

[a]Physician should be contacted.

Any episodes of hypoglycaemia had been treated with 25% dextrose and following subsequent judicious fluid therapy with proper CBG monitoring. Ryle's tube feeding was continued to those patients who were able to take feed properly without any complications.

RESULTS:

Demographic variable like age, sex were statistically insignificant (Figure 1 and Figure 2). Body weight in group A and group B were greater than group C and group D which was statistically significant (Table 1). Total steroid per day for group A and group B were higher than group C and group D which was statistically significant (Figure 3). Duration of steroid therapy in all 4 groups were statistically insignificant (Figure 4).Pre-steroid baseline mean CBG values of each groups were calculated which clearly showing higher baseline CBG values in diabetic groups. (Table 5)Mean CBG value per day in group A was higher than that of group B from day 1 to day 10 and it was statistically significant from day 1 to day 8. Mean CBG value per day in group C was greater than group D and it remained statistically significant from day 3 to day 7. Overall comparison of mean CBG value per day in 4 groups was statistically significant from day 1 to day 8 (Table 2). Mean total regular insulin requirement per day in group A was higher than that of group B from day 1 to day 10 and it remained statistically significant from day 1 and day 8. Similarly comparison of mean total regular insulin requirement per day in non diabetic groups (Group D required no insulin at all) were statistically significant from day 4 to day 6. Overall comparison of mean total regular insulin requirement per day in all 4 groups were statistically significant from day 1 to day 8 (Table 3). Mean total regular insulin per day in Group A and Group B were higher than that of Group C which were statistically significant (Figure 5). Total regular insulin requirement in stay were higher in group A and group B than that of group C which was statistically significant (Figure 6). Additional insulin requirement in all groups were comparable and statistically insignificant (Figure 7). Outcome of the patient were comparable in each group which remained statistically insignificant (Figure 8). Average duration of insulin therapy were less in group C compared to group B and group A (Table 4).

DISCUSSION:

Glucocorticoids (GC) are often prescribed as they have been confirmed to improve outcomes in various autoimmune and inflammatory diseases including COVID-19. Recommended doses of GC therapy lead to hyperglycaemia in patients leading to higher risk of acute and chronic complications.

This study was aimed to assess the glycemic control of these COVID positive patients receiving steroid therapy in ICU and also to observe the subsequent outcome of these patients.

Our study included middle aged (45-60 years) group of patients who were COVID RTPCR positive admitted in ICU. Body weight in patients having previously diabetes were more than non-diabetic groups because of which they required higher amount of insulin. Insulin requirement reduced dramatically as patient's clinical condition improved which corroborated with a study done by Gianchandani R and team.[6]

Significant hyperglycaemia (>180mg dl^{-1}) was observed more common among COVID 19 patients associated with obesity and diabetes. The pro-inflammatory process initiated due to hyperglycemia among diabetics[12] and insulin resistance among obese patients got further stimulated due to sudden viral infection like COVID-19.[13,14] This had led to increased steroid requirement among diabetic patients with COVID-19 to control the inflammatory state which was supported by other studies.[15]

On the other hand, recommendation of OHA usage in mild cases receiving steroid therapy was already available.[16] However recommendations regarding initiation of insulin therapy among ICU patients who were either on OHA or not is lacking.

The group C patients developed hyperglycemia from day 3 in general and were put on insulin therapy as per recommendations of the guideline.[16] The mortality outcome among this group was 11.11% compared to 25% among diabetic on OHA and 37.5% among diabetic on insulin.

Further these patients showed faster improvement of their glycaemic status and clinical parameters within a short period of ICU stay (3-4 days). Although statistically it was not significant, yet this trend prompted us to infer that even non-diabetic patients could have significant positive outcome if put on judicious insulin regimen from the very initial stage of hyperglycaemia.[17] Scheduled regular insulin in sliding scale and basal insulin significantly led successfully lowering hyperglycaemic state and thus decreasing ICU stay. In our study average duration of insulin therapy in non-diabetics was lesser than diabetics (either on insulin or on OHA). Although average duration of insulin therapy in diabetics on insulin was lesser than diabetics on OHA, it could be due to increased mortality rate in diabetics on insulin. Still we observed prompt insulin therapy overall decreased the duration of therapy in diabetics as well as non-diabetics. Our study was in concordance with other studies.[17,18]

Regarding the treatment targets there was no clear evidence available.[19] According to the American Diabetes Asssociation (ADA) Treatment plan should be individualized for each patients depending on factors like comorbidities, life expectancy, patient compliance and risk for developing hypoglycaemia.[20] Generally for ICU patients, target glucose range was considered at 140-180 mg dl^{-1}. If there was no risk of relevant hypoglycaemia then strict glucose control should be done at a range of 110-140 mg dl^{-1}.[21] But because of the chronic inflammatory storm and complex drug therapies in COVID-19 infection, there was larger glucose fluctuations which subsequently led to develop higher chances of hypoglycaemia.[22] Hence strict glucose control was not followed here in our COVID ICU. Moreover in the course of treatment, dose modification of steroids had been done which resulted in altered glucose lowering therapies like

requirement of additional insulin therapy or dose reduction in regular insulin therapy. So to avoid any analytical discrepancies mean regular insulin requirement was taken for statistical analysis. Ultimately major aim was to avoid both hypoglycaemic and hyperglycaemic episodes for these patients.

Our study had several limitations. Firstly, the data generated could be further structured by modifying the data collection procedure. Secondly, the observations done in different groups were done for feasibility of carrying out statistical comparisons. Thirdly, in this pandemic with rapid rise of severe cases, there were many confounding factors (anxiety, other drugs causing hyperglycaemia) that we were unable to consider at that time. Fourthly, meals taken in ICU was not exactly at the same time for all patients. So Mean CBG value for that duration was taken into consideration. At last, COVID ICU in our set up had opened in second wave with a lot of hurry to determine a strict glycaemic control protocol to manage SIHG. Hence we had really a small study period. Hence the analytical result of our study needs to be implemented on larger scale and for a longer duration to obtain desired outcome.

There was no conflict of interest.

CONCLUSION:

Steroid induced hyperglycaemia (SIHG) is a recognized potential complication among severe COVID-19 patients in ICU. Comorbidity like diabetes mellitus (either on OHA or insulin) further aggravates this hyperglycaemic status. Our study estimated the burden of hyperglycaemia among various groups of ICU patients. The outcome of this study substantiates that aggressive insulin therapy from early hyperglycaemic state of any group of patient can be significant contributor in determining their outcome in a positive manner.

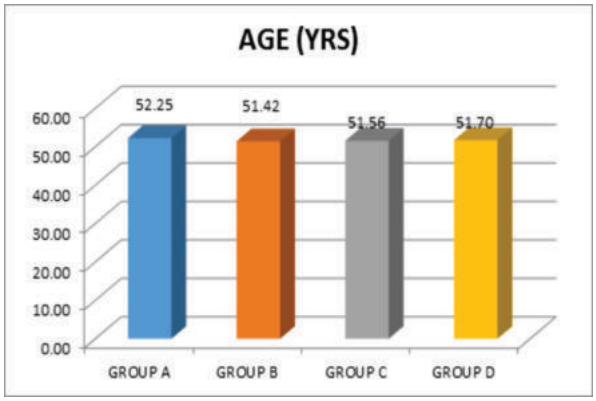

Figure 1: Age in all 4 groups remained statistically insignificant.

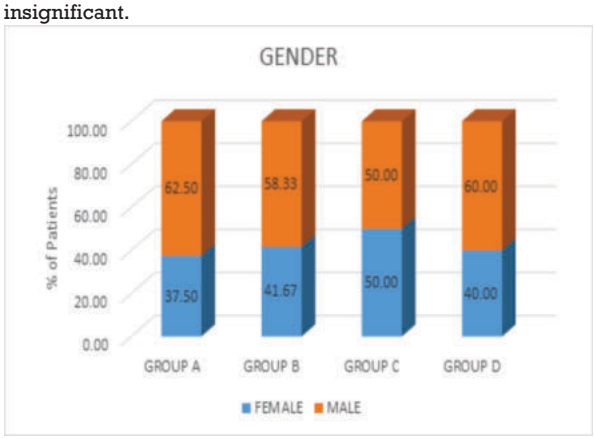

Figure 2: Gender In All 4 Groups Remained Statistically Insignificant.

Table 1: Body Weight In Group A And Group B Were Greater Than That In Group C And Group D Which Remained Statistically Significant.

	GROUP														
	GROUP A			GROUP B			GROUP C			GROUP D			p Value Between		
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	A vs. B	C vs. D	Overall
BODY WT (KG)	64.63	66.50	4.57	67.17	67.00	4.53	61.61	60.00	4.45	65.40	68.00	5.42	0.219	0.062	0.008

Table 2: Mean Capillary Blood Glucose (CBG) Value Per Day In Group A And Group B Were Higher Than That Of Group C And Group D Which Remained Statistically Significant From Day 1 To Day 8.

	GROUP														
	GROUP A			**GROUP B**			**GROUP C**			**GROUP D**			**p Value Between**		
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	A vs. B	C vs. D	Overall
MEAN CBG (mg/dl) - D1	400.38	397.50	20.13	249.25	248.00	20.72	107.44	107.00	5.36	110.40	112.00	5.72	<0.001	0.135	<0.001
MEAN CBG (mg/dl) - D2	386.25	380.00	18.72	244.33	238.00	23.62	113.56	111.50	7.16	109.80	109.00	5.43	<0.001	0.211	<0.001
MEAN CBG (mg/dl) - D3	372.88	370.00	15.60	238.67	232.50	24.38	129.50	130.00	16.76	109.20	108.00	5.29	<0.001	0.001	<0.001
MEAN CBG (mg/dl) - D4	349.13	345.00	26.44	229.33	222.50	28.50	141.61	138.00	15.48	108.30	109.00	3.27	<0.001	<0.001	<0.001
MEAN CBG (mg/dl) - D5	318.25	303.00	40.04	219.21	204.00	38.89	153.83	156.00	20.65	108.10	108.50	4.93	<0.001	<0.001	<0.001

MEAN CBG (mg/dl) - D6	297.13	294.00	40.41	211.83	196.00	47.86	145.89	142.50	28.41	108.60	108.50	5.46	0.001	<0.001	<0.001
MEAN CBG (mg/dl) - D7	284.25	270.00	49.56	201.33	180.50	57.02	132.50	122.00	34.35	107.60	108.00	2.88	0.004	0.008	<0.001
MEAN CBG (mg/dl) - D8	273.43	230.00	73.48	206.33	170.00	64.77	119.06	108.00	31.10	104.40	103.50	4.58	0.021	0.051	<0.001
MEAN CBG (mg/dl) - D9	345.00	345.00	35.36	276.00	299.00	81.14	220.00	220.00	45.25				0.165	NA	0.177
MEAN CBG (mg/dl) - D10	365.50	365.50	28.99	323.33	328.00	33.25	235.00	235.00	21.21				0.248	NA	0.107

Table 3: Mean Total Regular Insulin Per Day In Group A And Group B Were Higher Than That Of Group C Which Were Statistically Significant From Day 1 To Day 8.

	GROUP														
	GROUP A			GROUP B			GROUP C			GROUP D			p Value Between		
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	A vs. B	C vs. D	Overall
TOTAL INSULIN/DAY - D1	27.00	27.00	3.21	12.75	10.00	3.05	0.00	0.00	0.00	0.00	0.00	0.00	<0.001	1.000	<0.001
TOTAL INSULIN/DAY - D2	25.50	24.00	2.78	11.92	10.00	3.15	0.00	0.00	0.00	0.00	0.00	0.00	<0.001	1.000	<0.001
TOTAL INSULIN/DAY - D3	24.75	24.00	2.12	11.17	10.00	2.76	1.00	0.00	2.06	0.00	0.00	0.00	<0.001	0.115	<0.001
TOTAL INSULIN/DAY - D4	21.50	20.00	2.07	10.67	10.00	2.68	2.33	0.00	3.01	0.00	0.00	0.00	<0.001	0.025	<0.001
TOTAL INSULIN/DAY - D5	19.00	18.00	3.55	9.50	10.00	3.97	3.83	6.00	2.87	0.00	0.00	0.00	<0.001	0.001	<0.001
TOTAL INSULIN/DAY - D6	17.25	18.00	3.54	8.75	6.00	4.86	2.67	0.00	3.07	0.00	0.00	0.00	<0.001	0.014	<0.001
TOTAL INSULIN/DAY - D7	16.00	16.00	4.66	8.33	6.00	5.65	1.22	0.00	2.92	0.00	0.00	0.00	0.002	0.180	<0.001
TOTAL INSULIN/DAY - D8	15.43	10.00	6.90	8.89	6.00	6.03	1.06	0.00	2.71	0.00	0.00	0.00	0.015	0.181	<0.001
TOTAL INSULIN/DAY - D9	22.00	22.00	2.83	15.50	18.00	6.61	11.00	11.00	7.07				0.140	NA	0.155
TOTAL INSULIN/DAY - D10	22.00	22.00	2.83	20.00	20.00	4.00	10.00	10.00	0.00				0.543	NA	0.125

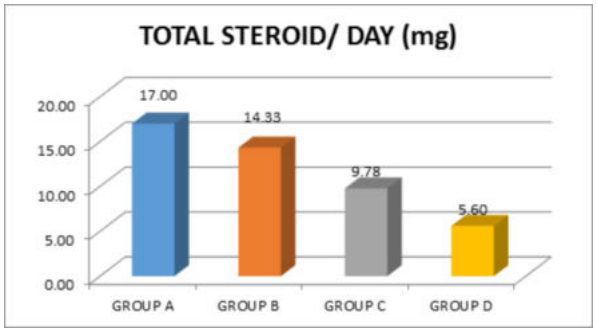

Figure 3: Total Steroid Per Day In Group A And Group B Were Greater Than That Of Group C And Group D Which Were Statistically Significant.

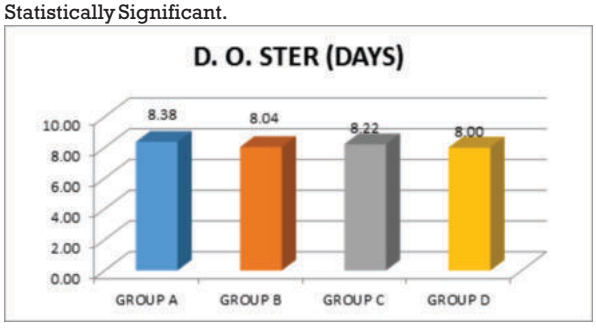

Figure 4: Duration Of Steroid Therapy In All 4 Groups Remained Statistically Insignificant.

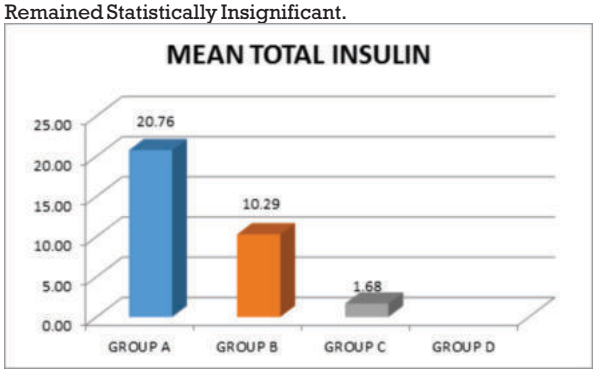

Figure 5: Mean Total Regular Insulin Per Day In Group A And Group B Were Higher Than Group C Which Were Statistically Significant.

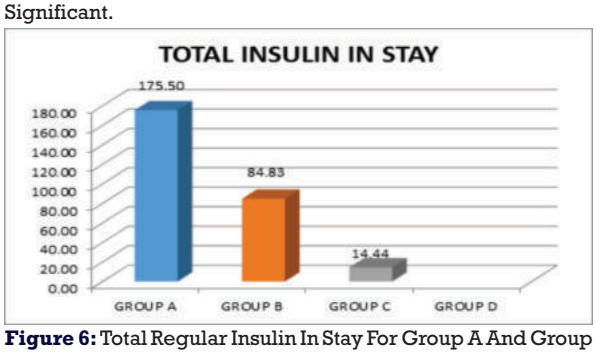

Figure 6: Total Regular Insulin In Stay For Group A And Group B Were Higher Than That Of Group C Which Remained Statistically Significant.

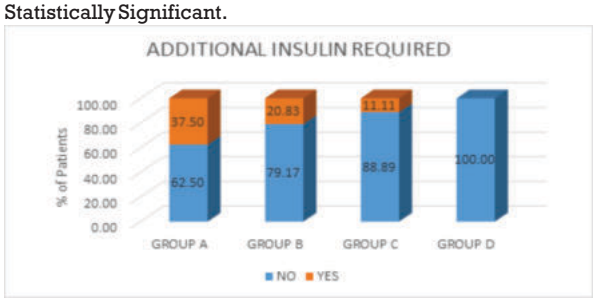

Figure 7: Additional Insulin Required In All 4 Groups Remained Statistically Insignificant.

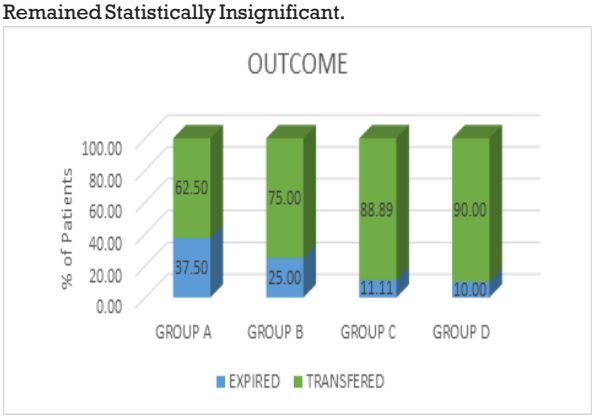

Figure 8: Outcome In All 4 Groups Remained Statistically Insignificant.

Table 4: Average Duration Of Insulin Therapy Were Less In Group C Compared To Group B.

GROUPS	AVERAGE DURATION OF INSULIN THERAPY
A	6.7
B	7.87
C	2.27
D	0

Table 5: Pre-steroid Mean CBG Value In Each Group.

GROUPS	PRE-STEROID MEAN CBG
A	325.375
B	202.375
C	88.166
D	81.700

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