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RESEARCH ARTICLE

Comparative Study between the Uses of High Dose Corticosteroid Therapy for Short Duration *Versus* Low Dose Corticosteroid for Long Duration in Severe Lung Contusion with ARDS

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Abstract:

Introduction:

Corticosteroids are used in ARDS to prevent lung fibrosis. The best dose, duration and regimen are still the points of debate among physicians.

Aim of the Work:

The aim of this study is to make a comparison between two corticosteroid regimens, *i.e.* short-duration high dose versus long- duration low dose corticosteroid use in ARDS due to lung contusion with VAP for lowering both morbidity and mortality rates and early weaning from ventilator.

Patients and Methods:

Patients who had >3 on Murray score and ≥6 on CPIS were allocated randomly in two groups of 120 patients each. Group A received 30 mg/kg methyl-prednisolone slowly intravenously in 250 ml normal saline every 8 hours for only 48 hours, while group B received 1 mg/kg/day methyl-prednisolone divided into three doses given every 8 hours for two weeks. The study lasted for 16 days; morbidity was considered if no improvement was observed in any or all clinical parameters of both Murray and CPIS scores and if there was failure in removing patients from the ventilator within the studied period.

Results:

Significant improvement was observed in patients of group B compared to group A with regard to APACH II ≤10 score, arterial oxygen saturation≥95, hypoxic index ≥300, lung infiltrate in chest X-ray, lung compliance, response of the lung to recruitment maneuver, the return of core temperature to normal, normal tracheal secretion, the return of leucocytic count to normal, negative qualitative sputum culture and a significantly higher number of patients were removed from the ventilator of group B compared to group A. However, mortality rate was not significant between the two groups.

Conclusion:

Low dose corticosteroid if used for a long duration significantly lowers morbidity and accelerates recovery, and in turn, accelerates weaning from ventilator compared to high dose corticosteroid used for a short duration. While the difference between the two regimens was not significant with regard to the mortality rate, still further studies are needed to emphasize a fixed corticosteroid dose and regimen in ARDS due to lung contusion.

Keywords: Low dose *versus* high dose, Corticosteroids, Ventilator, Leucocytic, Severe lung contusion, Ventilator-associated pneumonia.

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1. INTRODUCTION

Severe lung contusion after chest trauma can cause Acute Respiratory Distress Syndrome (ARDS). The inflammatory process of the ARDS following chest trauma is divided into three phases. The first one is the exudative phase; in this stage, progressive leakage of fluid in the alveolar space occurs with concomitant progressive hypoxemia. The second phase is the proliferative stage and during this stage, the migration of the inflammatory cells with proteinaceous exudate occurs into the alveolar space with a concomitant progressive reduction in lung compliance. The last stage is the fibrotic phase which is considered the last step in this traumatic inflammatory process developed in the lung after ARDS due to trauma. The marked reduction in lung immunity during this process may lead to

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secondary bacterial infection, especially in those patients who develop respiratory failure and are ventilated for a longer time and lead to ventilator-associated pneumonia (VAP) [1 - 4].

The incidence of chest trauma in the United States is 12 per million population per day. It is responsible for 20-25% of all deaths in the USA. The most common cause of death from lung contusion is hypoxic respiratory failure, followed by secondary bacterial infection and the development of VAP [5 - 7]. The standard management of these patients includes controlled mechanical ventilation with protective lung strategy (mentioned in detail in patient and methods), pain control, pulmonary toilet and oxygen therapy [8 - 10]. Corticosteroids are used as potent immune-suppressive and anti-inflammatory agents. These improve and modulate capillary permeability in severe inflammation and prevent the development of fibrosis at the inflammatory site. These are used by many clinicians and intensivists in ARDS either due to severe sepsis, trauma and VAP. Many trials have been done on the role of corticosteroids as immune-modulators to prevent the development of ARDS [11 - 14]. But still no consensus has been reached regarding the standardized dose, duration and/or regimen among intensivists for its use in ARDS due to sepsis, lung trauma, and /or VAP.

1.1. Aim of Work

The aim of this study is to compare the uses of high dose corticosteroid therapy for short duration with low dose corticosteroid therapy for long duration in ARDS due to severe lung contusion with superadded VAP to lower both morbidity and mortality rate and lead to early weaning from the ventilator.

2. MATERIALS AND METHODS

Patients who had severe chest trauma with massive lung contusion and admitted to King Abdel Aziz specialist hospital between January 2018 and February 2020 in the intensive care unit were selected. Those who presented the clinical parameters of ARDS, respiratory failure complicated by VAP were enrolled in our study.

2.1. Inclusion Criteria

Adult patients aged >18 and <65 years, hypercapnia with PH <7.25, hypoxic index less than 200 (PaO2/FIO2), bilateral parenchymatous lung infiltration in the chest Xray, were included. All selected patients received conventional ventilation with protective lung strategy for 3 days with controlled mechanical ventilation mode (CMV), fraction inspired oxygen (FIO2) of 100%, Positive end expiratory pressure (PEEP) adjusted to achieve target arterial oxygen saturation (SPO2) of ≥90%. Sedation and pain control were done by both midazolam and fentanyl infusion to achieve Richmond Agitation-Sedation Scale (RASS) -2. Protective lung strategy applied included head elevation more than 45-degree, daily assessment for both analgesic and sedative dose, early nasogastric feeding to prevent bacterial translocation and flooding of the blood with gram-negative septicemia, usage of the minimal PEEP to maintain SPO_2≥90%. Qualitative sputum culture was taken after 3 days from ventilation. After 3 days of conventional ventilation, only 240 patients were enrolled in our study. Those who had a Murray score (for diagnosis of ARDS) of ≥3 and CPIS (clinical pulmonary infection score) (for diagnosis of VAP) ≥ 6 were involved. All patients were randomly allocated in 2 groups with 120 patients in each. Randomization sequence was created using Excel 2007 (Microsoft, Redmond, WA, USA) with a 1:1 allocation using random block sizes of 2 and 4 by an independent doctor [17]. All patients received intravenous antibiotics meropenem 1 gm slowly intravenous every 8 hours for the first 8 days and then antibiotics were given according to sputum culture and antibiotics sensitivity. Group A received a high dose (30 mg/kg) of methylprednisolone slowly intravenous in 250 ml normal saline every 8 hours for only 4 days while group B received 1 mg/kg/day of methylprednisolone divided into three doses given every 8 hours for two weeks. This study was conducted for 16 days.

VAP was diagnosed in our study by CPIS 6 or more while the severity of lung contusion was assessed by Murray score of 3 or more (Tables **1** and **2**).

Table 1. Clinical parameters of Murray score [15].

Clinical Parameter of Murray Score	0	1	2	3	4
Hypoxic index PaO2/FIO2 On FIO2 100%	≥ 300	299-225	224-175	174-100	<100
Chest X-ray	Non	1 quadrant infiltrated	2 quadrant infiltrated	3 quadrant infiltrated	4 quadrant infiltrated
PEEP	≤5	6-8	9-11	12 - 14	≥ 15
Compliance ml /cm H2O	≥ 80	79-60	59- 40	39-20	≤ 19

Table 2. Modified clinical-pulmonary infection score (CPIS) [16].

CPIS	0	1	2
Tracheal secretion	Rare	abundant	Abundant & purulent
Chest X-ray infiltrate	No infiltrate	diffuse	localized
Temperature ºC	>36.5and <38.4	>38.5 and <38.9	≥39 or ≤36
Leucocytic count per mm^3	>4000and<11000	<4000 or>11000	>11000 and/or toxic band form > 500
Hypoxic index PaO_2/FIO_2 mmHg	>240 or evidence of ARDS	--	< 240 and no evidence of ARDS
Microbiology	Negative	--	Positive

Table 3. Shows the demographic data of the patients in the two groups.

	Group A (120)		Group B (120)		p value
	No.	%	No.	%	
Age by years					
18-30	55	45.8	59	49.2	**0.909**
31- 45	30	25.0	31	25.8	
46- 55	18	15.0	14	11.7	
56- 65	15	12.5	13	10.8	
>65	2	1.7	3	2.5	
Sex					
Female	32	26.7	34	28.3	**0.772**
Male	88	73.3	86	71.7	

6 patients from group A died from ARDS with multiple organ failure. After 5, 7, 9, 10,13 and 14 days consecutively from the start of the study, 5 patients died in group B from progressive hypoxemia and respiratory failure, 3 after 9 days and 2 after 13 days.

2.2. Any Patient Having a Score of 6 or more is Considered as Having VAP

King Abdelaziz research and ethical committee approved the project.

For all the patients, laboratory work was done on admission that included complete blood count, blood chemistry, cardiac enzyme to exclude cardiac contusion, coagulation profile, liver function tests, kidney function tests and evaluation of arterial blood gases to calculate the hypoxic index.

All the patients in both the groups were followed for 16 days with regard to parameters of Murray score and CPIS, which include APACHE II score, oxygen saturation recorded by pulse oximetry, hypoxic index, response to recruitment maneuver, chest X-ray, compliance (measured by ml/cmH2O) from the lung dynamics on the screen of the ventilator, core body temperature, nature and amount of tracheal secretion, total leucocytic count, qualitative sputum culture that was taken at the end of the 1st 8 days and another at the end of 16 days, and ventilated associated pneumonia (VAP) which was considered in our study if CPIS ≥6. Percutaneous tracheostomy was done to all patients in both groups at the end of the first week.

Only two major well-known complications of steroids were selected and followed in all patients in both groups of our study, *i.e*. myopathy and gastropathy. Diagnosis of myopathy was done after complete steroid regimen was followed (4 days in group A while 2 weeks in group B) and considered in our study if one of the two findings was observed, *i.e*. 1st- CPK (creatine phosphokinase) more than 750 U/L in female patients and more than 1000 U/L in male patients together; 2nd- electromyography (EMG) applied to Biceps femoris (Hamstrings group) and showed characteristic polyphasic, short duration, and low amplitude measurement of the motor unit action potential duration. While the diagnosis of steroid gastropathy, in our study, was made by a picture of erosive gastritis or peptic ulcer seen by upper endoscopy, which was done after the end of the steroid regimen.

3. STATISTICAL ANALYSIS OF THE DATA

Data were fed into the computer using IBM *SPSS software package version 21.0.*

Qualitative data were described using the number and percent. A comparison between different groups regarding categorical variables was made using the Chi-square test.

3.1. Sample Size Calculation

Depending on the research context, including the researcher's objectives and proposed analyses, the following formula was used to calculate the required sample size in this study;

Where n is the sample size, Z is the statistic corresponding to the level of confidence, P is expected prevalence, and d is precision (corresponding to effect size). The level of confidence was 95%. By using this equation, the sample size was 100 cases in each group (*i.e*., 200 cases in the two groups).

Table 4. Shows the APACH II score for all patients in both groups in the studied period.

	1st 4 days No. (120)		2nd 4 days No. (118)		3rd 4 days No. (116)		4th 4 days No. (114)	
Group A	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Above 25	109	90.8	96	81.4	60	51.7	40	35.1
15 - 25	9	7.5	11	9.3	34	29.3	33	29.0
11 - 14	2	1.7	8	6.8	14	12.1	29	25.4
≤ 10	0	0.0	3	2.5	8	6.9	12	10.5
	1st 4 days No. (120)		**2nd 4 days No. (120)**		**3rd 4 days No. (117)**		**4th 4 days No. (115)**	
Group B	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**

(Table 4) contd.....

Above 25	98	81.7	57	47.5	28	23.9	10	8.7
15 - 25	18	15.0	32	26.7	34	29.1	36	31.3
11 - 14	4	3.3	19	15.8	36	30.8	44	38.3
≤ 10	0	0.0	12	10.0	19	16.2	25	21.7
p value	0.119		0.0001*		0.0001*		0.0001*	

Table **3** represents the demographic data of patients in both groups showing no significant difference between the two groups with regard to age and sex.

Table **4** compares the APACH II score of patients in both groups all over the duration of the study and shows a significant improvement in the score of patients in group B in the second, third and fourth 4 days of the study as 12, 19 and 25 patients having score 10 or less at the end of 8,12,16 days consecutively while 3, 8 and 12 patients in group A achieved this score at the same duration of the study.

Table **5** compares the arterial oxygen saturation (SPO2) of patients in both groups all over the duration of the study and shows significant improvement in arterial oxygen of group B (7, 22, 49 and 55 patients) having SPO2 95% or more at the end of 4, 8, 12and 16 days consecutively while group A (0,8,12 and 22 patients) achieving this saturation at the same duration of the study.

Table **6** compares the hypoxic index of patients in both groups all over the duration of the study and shows significant improvement in patients of group B (17, 39, 48 and 54 patients) having hypoxic index of 300 or more at the end of 4, 8, 12and 16 days consecutively while group A (10, 19, 25 and 30 patients) achieving this index at the same duration of the study.

Table **7** compares parenchymatous lung infiltrate on the chest X-ray of patients in both groups all over the duration of the study and shows a significant improvement in chest X-ray in the first, third and fourth 4 days as patients of group B had less than 1 quadrant infiltration (22,36,48 and 62 patients) at the end of 4, 8, 12 and 16 days consecutively while group A (14,23,28 and 30 patients) achieved same chest X-ray findings at same duration of the study.

Table **8** compares lung compliance of patients in both groups all over the duration of the study and shows significant improvement in lung compliance of group B (22,40,54 and 66 patients) having 80 cm or more at the end of 4,8,12 and 16 days consecutively while group A (12,25,28 and 31 patients) achieving the same compliance at the same period consecutively.

Table 5. Shows Oxygen saturation recorded by the pulse oximeter for all patients in both groups in the studied period.

O_2 saturation	**1st 4 days No. (120)**		**2nd 4 days No. (118)**		**3rd 4 days No. (116)**		**4th 4 days No. (114)**	
Group A	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
≤ 80%	54	45.0	37	31.4	16	13.8	4	3.5
81% – 85%	30	25.0	22	18.6	13	11.2	4	3.5
86% – 90%	23	19.2	26	22.0	37	31.9	40	35.1
91% – 94%	13	10.8	25	21.2	38	32.8	44	38.6
≥95%	0	0.0	8	6.8	12	10.3	22	19.3
O_2 saturation	**1st 4 days No. (120)**		**2nd 4 days No. (120)**		**3rd 4 days No. (117)**		**4th 4 days No. (115)**	
Group B	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
≤ 80%	29	24.2	17	14.2	1	0.9	0	0.0
81% – 85%	25	20.8	18	15.0	7	6.0	0	0.0
86% – 90%	38	31.7	30	25.0	13	11.1	14	12.2
91% – 94%	21	17.5	33	27.5	47	40.2	46	40.0
≥95%	7	5.8	22	18.3	49	41.9	55	47.8
p value	0.003*		0.003*		0.0001*		0.0001*	

Table 6. Shows the Hypoxic index for all patients in both groups in the studied period.

PaO2/FIO2	**1st 4 days No. (120)**		**2nd 4 days No. (118)**		**3rd 4 days No. (116)**		**4th 4 days No. (114)**	
Group A	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
< 100	22	18.3	12	10.2	8	6.9	6	5.3
100 – 174	24	20.0	14	11.9	11	9.5	10	8.8
175 – 224	46	38.3	40	33.9	32	27.6	24	21.1
225 – 299	18	15.0	33	28.0	40	34.5	44	38.6

(Table 6) contd.....

≥ 300	10	8.3	19	16.1	25	21.6	30	26.3
PaO2/FIO2	**1st 4 days No. (120)**		**2nd 4 days No. (120)**		**3rd 4 days No. (117)**		**4th 4 days No. (115)**	
Group B	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
< 100	15	12.5	5	4.2	0	0.0	0	0.0
100 – 174	22	18.3	14	11.7	10	8.6	3	2.6
175 – 224	32	26.7	22	18.3	15	12.8	12	10.4
225 – 299	34	28.3	40	33.3	44	37.6	46	40.0
≥ 300	17	14.2	39	32.5	48	41.0	54	47.0
p value	0.03*		0.003*		0.0007*		0.001*	

Table 7. Shows the Chest X-ray taken for all patients in both groups in the studied period.

	1st 4 days No. (120)		**2nd 4 days No. (118)**		**3rd 4 days No. (116)**		**4th 4 days No. (114)**	
Group A	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Bilateral lung infiltrate (all quadrant)	30	25.0	13	11.0	10	8.6	7	6.1
≥ 4 quadrant infiltrates	36	30.0	28	23.7	24	20.7	20	17.5
3-1 quadrant infiltrate	40	33.3	54	45.8	54	46.6	57	50.0
Less than 1 quadrant infiltrate	14	11.7	23	19.5	28	24.1	30	26.3
	1st 4 days No. (120)		**2nd 4 days No. (120)**		**3rd 4 days No. (117)**		**4th 4 days No. (115)**	
Group B	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Bilateral lung infiltrate (all quadrant)	22	18.3	12	10.0	0	0.0	0	0.0
≥ 4 quadrant infiltrates	14	11.7	22	18.3	47	40.2	25	21.7
3-1 quadrant infiltrate	62	51.7	50	41.7	22	18.8	28	24.4
Less than 1 quadrant infiltrate	22	18.3	36	30.0	48	41.0	62	53.9
p value	0.0005*		0.288		0.0001*		0.0001*	

Table 8. Shows compliance (ml/cmH_2O) for all patients in both groups in the studied period.

ml/1cmH_2O		**1st 4 days No. (120)**		**2nd 4 days No. (118)**		**3rd 4 days No. (116)**		**4th 4 days No. (114)**
Group A	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
≤ 19	22	18.3	12	10.2	10	8.6	9	7.9
20 – 39	15	12.5	14	11.9	12	10.3	9	7.9
40 – 59	26	21.7	22	18.6	16	13.8	10	8.8
60 – 79	45	37.5	45	38.1	50	43.1	55	48.3
≥ 80	12	10	25	21.1	28	24.1	31	27.1
ml/1cmH_2O		**1st 4 days No. (120)**		**2nd 4 days No. (120)**		**3rd 4 days No. (117)**		**4th 4 days No. (115)**
Group B	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
≤ 19	10	8.3	2	1.7	0	0.0	0	0.0
20 – 39	11	9.2	8	6.7	3	2.6	0	0.0
40 – 59	19	15.8	16	13.3	20	17.1	16	13.9
60 – 79	58	48.3	54	45.0	40	34.2	33	28.7
≥ 80	22	18.3	40	33.3	54	46.1	66	57.3
p value		0.029*		0.007*		0.0001*		0.0001*

Table **9** compares the number of patients responding to recruitment maneuver in both groups all over the duration of the study and shows a significant improvement in the response of the lung to recruitment maneuver of group B (45,67,85 and 107 patients) showing a positive response at the end of 4, 8, 12 and 16 days consecutively while group A (30, 48, 60 and 80 patients) achieving the same results at the same period of time consecutively.

Table 9. Shows the numbers of patients who responded to recruitment maneuver for all patients in both groups in the studied period.

days	Group A		Group B		p value
	No.	%	No.	%	
1st 4 days	30 /120	25.0	45/120	37.5	0.036*
2nd4 days	48 / 118	40.7	67/120	55.8	
3rd4 days	60 / 116	51.7	85/117	72.6	
4th 4days	80/ 114	70.2	107/115	93.0	

Recruitment maneuver is considered the clinical test of lung compliance and starts by increasing the peak inspiratory pressure to 40 cm/H_2O for 40 seconds and observing the saturation (SpO_2); if it improved to more than 95%, the responder was considered in our study.

Table **10** compares the core temperature recorded in both groups all over the duration of the study and shows a significant improvement in return of the core temperature to normal in group B compared to group A(13,15,35 and 60 patients) which showed normal core temperature at the end of 4,8,12 and 16 days consecutively while 22, 58, 81, 105 patients in group B achieved the same temperature in the same periods.

Table **11** compares the nature and amount of tracheal secretion in both groups all over the duration of the study and shows the significant return of tracheal secretion to normal in group B compared to group A in which 11, 19, 26 and 60 patients had normal scanty tracheal secretion at the end of 4, 8, 12 and 16 days consecutively while 30, 60, 90 and 106 patients in group B achieved the same result in the same period.

Table **12** compares the total leucocytic count in both groups all over the duration of the study and shows the significant return of leucocytic count to normal in group B compared to group A in which 17, 20, 35 and 61 patients had normal scanty tracheal secretion at the end of 4,8,12 and16 days consecutively while 68,77,90 and 100 patients in group B achieved the same result in the same time periods.

Table 10. Shows the core temperature according to CPIS for all patients in both groups in the studied period.

	1st 4 days No. (120)		2nd 4 days No. (118)		3rd 4days No. (116)		4th 4 days No. (114)	
Group A	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
0 in CPIS	13	10.8	15	12.7	35	30.2	60	52.6
1 in CPIS	12	10.0	15	12.7	36	31.0	26	22.8
2 in CPIS	95	79.2	88	74.6	45	38.8	28	24.6
	1st 4 days No. (120)		**2nd 4 days No. (120)**		**3rd 4days No. (117)**		**4th 4 days No. (115)**	
Group B	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
0 in CPIS	22	18.3	58	48.3	81	69.2	105	91.3
1 in CPIS	38	31.7	31	25.8	22	18.8	10	8.7
2 in CPIS	60	50.0	31	25.8	14	12.0	0	0.0
p value	0.0001*		0.0004*		0.0001*		0.0001*	

Table 11. Shows the amount and nature of tracheal secretion according to CPIS for all patients in both groups in the studied period.

	1st 4 days No. (120)		2nd 4 days No. (118)		3rd 4days No. (116)		4th 4 days No. (114)	
Group A	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
0 in CPIS	11	9.2	19	16.1	26	22.4	60	52.6
1 in CPIS	16	13.3	18	15.3	40	34.5	30	26.3
2 in CPIS	93	77.5	81	68.6	50	43.1	24	21.1
	1st 4 days No. (120)		**2nd 4 days No. (120)**		**3rd 4days No. (117)**		**4th 4 days No. (115)**	
Group B	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
0 in CPIS	30	25.0	60	50.0	90	76.9	106	92.2
1 in CPIS	50	41.7	33	27.5	23	19.7	9	7.8
2 in CPIS	40	33.3	27	22.5	4	3.4	0	0.0
p value	0.0001*		0.0002*		0.0001*		0.0003*	

Table 12. Shows total leucocytic count according to CPIS for all patients in both groups in the studied period.

CPIS	1st 4 days No. (120)		2nd 4 days No. (118)		3rd 4days No. (116)		4th 4 days No. (114)	
Group A	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
0 in CPIS	17	14.2	20	16.9	35	30.2	61	53.5
1 in CPIS	15	12.5	19	16.1	40	34.5	33	28.9
2 in CPIS	88	73.3	79	66.9	41	35.3	20	17.5
	1st 4 days No. (120)		**2nd 4 days No. (120)**		**3rd 4 days No. (117)**		**4th 4 days No. (115)**	
Group B	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
0 in CPIS	68	56.7	77	64.2	90	76.9	100	87.0
1 in CPIS	22	18.3	22	18.3	15	12.8	15	13.0
2 in CPIS	30	25.0	21	17.5	12	10.3	0	0.0
p value	0.0001*		0.0001*		0.0001*		0.0001*	

Table **13** compares the level of LDH recorded in all patients of both groups in the studied period and shows a significant decrease in the number of patients having a high LDH in group B compared to group A.

Table **14** compares the level of C-reactive protein recorded in all patients of both groups in the studied period and shows a significant decrease in the numbers of patients having high C - reactive protein in group B compared to group A.

Table 13. Shows the LDH level for all patients in both groups in the studied period.

LDH	1st 4 days No. (120)		2nd 4 days No. (118)		3rd 4days No. (116)		4th 4 days No. (114)	
Group A	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
100-200 U/L	0	0.0	0	0.0	5	4.3	17	14.9
201-400 U/L	0	0.0	15	12.7	23	19.8	37	32.5
401-600 U/L	36	30.0	40	33.9	40	34.5	22	19.3
>600 U/L	84	70.0	63	53.4	48	41.4	38	33.3
	(n=120)		**(n=120)**		**(n=117)**		**(n=115)**	
Group B	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
100-200 U/L	15	12.5	42	35.0	66	56.4	82	71.3
201-400 U/L	70	58.3	54	45.0	40	34.2	33	28.7
401-600 U/L	15	12.5	24	20.0	11	9.4	0	0.0
>600 U/L	20	16.7	0	0.0	0	0.0	0	0.0
P value	0.0001*		0.0001*		0.0001*		0.0001*	

Table 14. Shows the CRP level for all patients in both groups in the studied period.

CRP	1st 4 days		2nd 4 days		3rd 4 days		4th 4 days	
	(n=120)		**(n=118)**		**(n=116)**		**(n=114)**	
Group A	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
0-100 mg/L	2	1.7	2	1.7	7	6.0	19	16.7
101-200 mg/L	2	1.7	17	14.4	25	21.6	39	34.2
201-300 mg/L	34	28.3	38	32.2	38	32.8	20	17.5
>300 mg/L	82	68.3	61	51.7	46	39.7	36	31.6
	(n=120)		**(n=120)**		**(n=117)**		**(n=115)**	
Group B	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
0-100 mg/L	58	48.3	40	33.3	64	54.7	80	69.6
101-200 mg/L	13	10.8	52	43.3	38	32.5	30	26.1
201-300 mg/L	43	35.8	24	20.0	13	11.1	3	2.6
>300 mg/L	6	5.0	4	3.3	2	1.7	2	1.7
P value	0.0001*		0.0001*		0.0001*		0.0001*	

Table **15** compares the qualitative sputum culture of patients in both groups and shows a significant reduction in the number of patients having positive sputum culture in group B (40 and 50 patients at 8 and 16 days consecutively) while patients having positive culture in group A (65 and 88 patients at 8 and 16 days consecutively).

Table 15. Shows the number of qualitative positive sputum cultures after 8 and 16 days consecutively from the first day of our study.

Number of Patients with Positive Sputum Culture		Group A		Group B	P value
	No.	%	No.	%	
after 1st 8 days & at the end of 16 days	65/118 88/114	55.1 77.2	40/120 50/115	33.3 43.5	0.007* 0.001*

Table 16. Shows the number of patients weaned from the ventilator at the end of the study.

	Group A		Group B	
	No.	%	No.	%
Weaned patients	88/114	77.2	105/115	91.3
P value	0.003*			

Table 17. Shows morbidity recorded at the end of the period of the study in both groups.

Morbidity	Number of patients in Group A (114)		Number of patients in Group B (115)		P value
	No.	%	No.	%	
APACH II score > 25	40	35.1	10	8.7	0.001*
Desaturation SPO2 ≤ 80%	4	3.5	0	0.0	0.21
Hypoxic index <100	6	5.3	0	0.0	0.08
X-ray chest (all quadrant lung infiltrates)	7	6.1	0	0.0	0.076
Lung compliance ≤19 ml/cmH_2O	9	7.9	0	0.0	0.042*
NO response to recruitment	34	29.8	8	6.9	0.003*
Core temp.2 on CPIS	28	24.6	0	0.0	0.001*
Tracheal secretion 2 on CPIS	24	21.1	0	0.0	0.001*
Leucocytic count 2 on CPIS	20	17.5	0	0.0	0.002*
High LDH >600 U/L	38	33.3	0	0.0	0.001*
C-reactive protein > 300 mg/L	36	31.6	2	1.7	0.001*
Positivesputum culture **After 8th day** **After 16th day**	65 88	57.0 77.2	40 50	34.8 43.5	0.009* 0.001*
Myopathy	65	57.0	40	34.8	0.009*
Gastropathy	40	35.1	10	8.7	0.001*
Failure of weaning from the ventilator at the end of the study period	26	22.8	10	8.7	0.001*
Mortality rate	6	5.3	5	5.2	0.925

Table **16** compares the number of patients weaned from the ventilator in both groups at the end of the study and shows a significantly higher number of weaned patients in group B (105 from 115 patients) compared to group A (88 from 114 patients).

Table **17** compares the rate of morbidity in both groups at the end of the study and shows a significant reduction in the number of patients having APACHII >25, saturation ≤ 80%, hypoxic index <100, all quadrant parenchymatous lung infiltrate, lung compliance ≤ 19 ml/cmH_2O, no response to recruitment maneuver, no improvement in one or all measured clinical parameters CPIS score, LDH >600 U/L, C-reactive protein >300 mg/L, positive sputum culture at 8th and 16th days of the study and failure of weaning from the ventilator.

Table **17** compares the mortality rate of group A of 5.3% (6 patients died) with the mortality rate of group B being 5.2% (5 patients died).

The difference in the mortality rate was not significant between the two groups.

4. DISCUSSION

4.1. As Regard with Improvement in the General Condition of the Patients

The improvement in APACHII score, total leucocytic

count, and core temperature in patients of group B compared to group A could be due to better control of systemic manifestation of both VAP and ARDS by the prolonged use of corticosteroid even with low dose than the higher dose of corticosteroid for a short duration and thus better tissue oxygenation and better systemic immunity which rapidly control the general manifestation of the systemic inflammatory response of both VAP and ARDS. This indicates that there is no significant advantage of using high dose methyl prednisolone compared to low dose and the improvement in the systemic manifestation of both VAP and ARDS in patients was duration-dependent and not dose-dependent.

4.2. As Regard with Improvement of the Lungs Condition

This could be classified into clinical improvement, in terms of both *tissue oxygenation* recorded by oxygen saturation, hypoxic index and *pulmonary function improvement* recorded by compliance improvement and improvement in the response of lung to recruitment maneuver all over the duration of the study.

Also radiologically, patients of group B showed significant improvement of parenchymatous lungs infiltrate on chest X-ray all over the duration of the study compared to patients of group A. This could be due to better improvement of the local immunity of the lungs due to pulmonary vasodilatation from better oxygenation (as an increase in lung tissue oxygenation caused pulmonary vasodilatation and increased blood supply of the lungs and thus improved local immunity of the lungs); moreover, the local immunity of the lungs seemed to be significantly better in the group that used longer duration of corticosteroids even with a lower dose, indicating that the improvement in the local manifestation of both VAP and ARDS in the lungs was also duration-dependent and not dose-dependent.

4.3. With Regard to Bacteriological Improvement

Measured by the results of qualitative sputum cultures conducted on all patients at 8^{th} and 16^{th} days respectively, significant higher numbers of positive results were shown among patients of group A compared to patients of group B. This could be due to better oxygenation in both local lung tissue and systemic global tissue perfusion which improved both local and systemic immunity and thus led to better control of both lung infection and bacteremia in the group that used corticosteroids for long duration, again proving that improvement of both local and systemic immunity with corticosteroids is duration dependent and not dose dependent.

4.4. With Regard to Controlling Laboratory Markers of Tissue Destruction

There was a significant decrease in the markers of tissue destruction (LDH and C reactive protein) in patients of group B compared to group A. This could be due to better control of parameters of both VAP and ARDS by low dose corticosteroid than high dose corticosteroid, which might be better in stopping the cascade of sepsis and thus stopping tissue destruction.

4.5. With Regard to Steroid Complication

With regard to steroid complication Regarding steroid myopathy and gastropathy, patients of group A showed significantly higher myopathy and gastropathy compared to patients of group B. This could be explained by dependency of both complications on the dose of the steroid and not on its duration.

Steroid myopathy can be explained by decreased protein synthesis and accelerated protein degradation, mitochondrial dysfunction, electrolytes disturbance and /or decreased sarcolemmal excitability. Steroid gastropathy developed in 50 patients from the 229 patients completed the finding of our study (21.8%). The low number of that complication can be explained by the presence of antistress given to all patients in both groups in the form of omeprazole 40 mg slowly intravenous once daily; still however many authors believe that steroid gastropathy is only an experimental complication [20]. The postulated physiological explanation of that is the inhibition of the cytoprotective gastric prostaglandins, gastric mucous and /or gastric bicarbonate synthesis with marked impairment of both angiogenesis and epithelial repair of the gastric mucous membrane [21].

4.6. With Regard to Morbidity and Mortality

APACH II score above 25, Desaturation SPO2 $\leq$ 80%, Hypoxic index less than 100, X-ray chest (all quadrant lung infiltrate), Lung compliance >19 ml/cmH2O, NO response to recruitment, Positive sputum culture after 8th day and after 16th day, and Failure of weaning from the ventilator at the end of the studied duration were significantly higher in patients of group A compared to patients of group B. While the mortality rate was not significant between the two groups.

The results of the first four days showed an interesting point as significant improvement was observed in the patients of the group with the low dose corticosteroid (group B) compared to the group that received high dose corticosteroids (group A) even at the same duration. This may be due to two reasons; either the high dose corticosteroids reduce the immunity of those patients more than the low dose corticosteroids so patients of group A did not recover from VAP soon compared to group B, or due to the rapid development of respiratory muscle myopathy with high corticosteroids resulting in the fact that lung mechanics on the ventilator becomes better with the intake of low dose. Thus, patients having low dose corticosteroids get early weaning from the ventilator.

Our results support the findings of many studies done on the usage of corticosteroids in ARDS. Schein *et al*., in 1987 [18], conducted an interesting study on fifty-nine patients suffering from septic shock complicated by Adult Respiratory Distress Syndrome (ARDS), who were allocated in three groups. One group of patients received 30 mg/kg methylprednisolone sodium succinate, the patients of the other group received 6 mg/kg dexamethasone sodium phosphate while the third group received no steroid. They found a marked improvement in both steroid groups with respect to both lung function and hemodynamics of the septic shock but they did not compare the methylprednisolone group versus the

dexamethasone group. Meduri *et al*. carried out two important studies; first one in 1998 [19] on sixteen patients having both ARDS and Multiple Organ Dysfunction Syndrome (MODS) and concluded that prolonged administration of methylprednisolone in patients with unresolving ARDS was associated with improvement in lung injury and MODS scores, and reduced mortality. The second study done in 2007 [20] on ninety-one patients with severe early ARDS patients was randomized (2:1 fashion) to methylprednisolone infusion (1 mg/kg/d) *versus* placebo. They concluded that methylprednisolone-induced down-regulation of systemic inflammation was associated with significant improvement in pulmonary and extrapulmonary organ dysfunction and reduction in duration of mechanical ventilation and ICU length of stay. Tang *et al*., in 2009 [21], did a metanalysis review on 648 patients enrolled in 9 studies with moderate to severe ARDS and concluded that prolonged usage of methylprednisolone with 0.5 mg/kg/day for 10 days improved all clinical parameters of ARDS and accelerated weaning from ventilators without reported myopathy or neuropathy or major infection.

Another study was done by Prabhu Varsha *et al*. in 2017 [22] on the Efficacy of Corticosteroids in Acute Respiratory Distress Syndrome: An Observational Study, in which they concluded that the use of glucocorticoids in ARDS showed benefits, especially when started early in the course of treatment with reduced mortality and decreased ventilator days. Again Meduri *et al*. [23] did another study in 2018 and published an updated meta-analysis incorporating nine randomized trials on 816 patients with ARDS titled Prolonged low-dose methylprednisolone treatment is highly effective in reducing the duration of mechanical ventilation and mortality in patients with ARDS in Journal of Intensive Care and proved that there is moderate-to-high quality evidence that prolonged glucocorticoid therapy is safe and reduces (1) time to endotracheal extubation, (2) duration of hospitalization, and (3) mortality rate, and increases the number of days free from mechanical ventilation, (4) intensive care unit stay, and (5) hospitalization in comparison to placebo.

4. RESULTS

Our study was one of the unique trials that compared the low dose corticosteroid for a long term therapy *versus* the high dose of corticosteroid in short term therapy; yet more research work is needed employing various steroid preparations other than methylprednisolone and more research work is needed for making a final decision regarding the best preparation, best dose and best regimen of steroid usage in ARDS. Two major limitations could be observed in our study; first one was the involvement of only two famous complications of steroid administration (myopathy and gastropathy) and ignoring the rest. So, more research work is needed in this point to involve all/or most of the well-known steroid complications to evaluate the risk-benefit ratio for steroid use in this field. Another limitation of our study was the use of methylprednisolone in ARDS due to both lung trauma and VAP and ignoring the rest of other causes of ARDS. So, still further study is needed at this point to evaluate the use of steroids in ARDS due to pancreatitis, spinal injury and other factors.

CONCLUSION

Low dose corticosteroid used for a long duration significantly lowers morbidity and accelerates weaning from ventilator compared to high dose corticosteroid used for a short duration. Although the difference between the two regimens was not significant with regard to the mortality rate, still further study is required to emphasize a fixed corticosteroid dose and regimen in ARDS due to lung contusion.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This project was approved by King Abdelaziz research and ethical committee, Saudi Arabia.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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None.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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