# ROLE OF HYDROCORTISONE THERAPY IN PREVENTION OF HOSPITAL ACQUIRED PNEMONIA IN MULTIPLE TRAUMA PATIENTS

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## ABSTRACT

**Introduction:** The role of stress dose of hydrocortisone in management of trauma patients is currently unknown.
**Objectives:** In this study, we evaluated the efficacy of hydrocortisone therapy in prevention of hospital acquired pneumonia in multiple trauma patients.
**Methods:** The study was conducted on 30 patients admitted to Critical Care Medicine Department, at Alexandria Main University Hospital with multiple trauma. All patients were subjected on admission to complete history taking, complete physical examination and Laboratory investigations and measurement of vital signs . patients were randomly assigned to a continuous intravenous infusion of either hydrocortisone (200 mg/d for 5 days, followed by 100 mg on day 6 and 50 mg on day 7) or placebo. The treatment was stopped if patients had an appropriate adrenal response then measurement of hospital acquired pneumonia ,duration of mechanical ventilation and mortality through 21 days.
**Results: :** In group A 12 of 30 patients (40%) developed pneumonia (P 0.046*) with 9 patients (30%) developed VAP once and 3 patients(10%) developed VAP twice while in group B 20 of 30 patients (66.6%) developed pneumonia with 15 patients (50%) developed VAP once while twice in 5 patients (16.6%).Days of mechanical ventilation in hydrocortisone group were 3-15 with mean 7.9±2.31 and in placebo group were 3-21 with a mean 10.98±3 . In our study 10% (3 out of 30 patients) died in hydrocortisone group and 13.4%(4 out of 30 patients ) in placebo group.
**Conclusion:** In intubated trauma patients, the use of an intravenous stress-dose of hydrocortisone, compared with placebo, resulted in a decreased risk of hospital acquired pneumonia

**Keywords:** pneumonia, hydrocortisone, multiple trauma

{**Citation:** Mohammed Moustafa Megahed, Tamer Nabil Habib, Mostafa hefnawy. Role of hydrocortisone therapy in prevention of hospital acquired pneumonia in multiple trauma patients. American Journal of Research Communication, 2016, 4(6): 29-45} www.usa-journals.com, ISSN: 2325-4076.

## INTRODUCTION

Severe trauma is one of the leading causes of death and illness in the world. The overall rate of posttraumatic pneumonia reaches an incidence of 40 percent to 60 percent, mainly in patients with traumatic brain injury (TBI).[1-4] Early posttraumatic pneumonia increases the duration of mechanical ventilation, hospitalization, and risk of death.[5] Thus, prevention posttraumatic pneumonia is a major clinical and economical issue.

Both experimental and clinical data suggest that corticosteroid use may decrease the occurrence and severity of nosocomial [hospital-acquired] pneumonia in patients treated in intensive care units (ICUs). [6-9]

Multiple trauma is defined as having 2 or more traumatic injuries and an injury severity score higher than 15. Severe TBI is defined as a GlasgowComa Scale score of less than or equal to 8 after initial care.[10]

The term Critical Illness Corticosteroid Insufficiency (CIRCI) has replaced the older terms relative adrenal insufficiency and functional hypoadrenalism.[11]Adrenal insufficiency in critical illness is best diagnosed by random total cortisol less than 10 microgram/dL(A baseline cortisol level in the single digits in the setting of refractory shock is diagnostic) or by A positive ACTH stimulation test (the change in cortisol level after the administration of 250 micrograms of ACTH is less than 9 micrograms per deciliter).[12-14]

Trauma-related corticosteroid insufficiency was also correlated with systemic inflammatory response syndrome.It has been suggested that hydrocortisone attenuates the overwhelming inflammatory response without immunosuppression, restoring an adequate immune response to infection. We postulated that treatment with stress-dose levels of hydrocortisone would diminish the prevalence of hospital acquired pneumonia.[15]

Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs 48 hours after admission that had not been incubating at the time of admission. The risk of VAP is highest early in the course of hospital stay, and estimated to be 3% per day during the first 5 days of ventilation, 2% per day during 5-10 days of ventilation, 1% per day during days afterwards. [16,17] Pneumonia is considered when at least 2 signs :body temperature more than 38,leukocytosis more than 12000/mL, or leukopenia less than 4000/mL; purulent pulmonary secretions associated with the appearance of a new infiltrate are present or when change occurred in an existing infiltrate on chest x-ray.The diagnosis of VAP is needed to be confirmed by a lower respiratory tract sample using a quantitative culture with a predefined positive threshold of $10^4$ colony-forming units per milliliter (CFU/mL) for a bronchoalveolar lavage or non bronochoscopic sample and $10^3$CFU/mL for a protected specimen brush . [16,17]

## AIM OF THE WORK

The aim of this study is to assess the efficacy of hydrocortisone therapy in prevention of hospital acquired pneumonia in multiple trauma patients.

## METHODS

### Participants

This prospective study was conducted on 60 patients admitted to Critical Care Medicine Department , at the Alexandria Main University Hospital with multiple trauma. The study was approved by the medical ethics committee of Alexandria faculty of Medicine. An informed consent from patients was taken before enrollment to the study.

**Inclusion criteria**

1. Adult patients of both sexes.
2. Intubated multiple trauma Patients expected to be mechanically ventilated more than 48 hours.
3. Multiple trauma patients who are defined as having two or more traumatic injuries and injury severity score more than 15 or severe TBI which is defined as Glasgow coma scale equal or less than 8.

**Exclusion criteria**

1. Patients with previous adrenal insufficiency.
2. Patients with history of previous immunosuppression.
3. Pregnant female.
4. Patients with history of corticosteroids therapy during last 6 months.

All patients were subjected on admission to complete history taking, complete physical examination and Laboratory investigations. During admission the following parameters were monitored: Vital signs, Glasgow coma score (GCS),injury severity score, arterial blood gases (ABG) and withdrawal of a blood sample for mea surement of basal cortisol level for all patients to diagnose corticosteroid insufficiency which is defined as random total cortisol less than 10 microgram/dl or A positive ACTH stimulation test (the change in cortisol level after the administration of 250 micrograms of ACTH is less than 9 micrograms per deciliter).[12-14]

- Patients will be randomly classified into two groups :

  **Group A**: who will receive hydrocortisone therapy within 36 hours of the trauma onset. Hydrocortisone will be continuously administered as follow: 200 mg/d for 5 days, 100 mg on day 6, 50mg on day 7 for patients with corticosteroid insufficiency. After receiving the results of basal cortisol level, treatment will be stopped if patients has adapted corticosteroid function. After completion of treatment on day7.

  **Group B:** will receive placebo by use in a syringe containing 48 mL of saline isotonic solution
- After randomization, the following parameters will be done in the ICU for all patients included in the study as follow:

  1. Vital signs every 4hours.

2. ABG daily.
3. GCS assessment daily.
4. Assessment of pulmonary secretions: amount, colour daily.
5. lab investigation: complete blood count (CBC), serum sodium ($Na^+$), serum potassium ($K^+$), Blood Urea Nitrogen (BUN), serum creatinine daily and C - reactive protein (CRP) .
6. CXR will be done if at least 2 signs for diagnosis of pneumonia appeared: body temperature more than 38, leukocytosis more than 12000/mL, or leukopenia less than 4000/mL; purulent pulmonary secretions.
7. The diagnosis of VAP will be confirmed by a lower respiratory tract sample using a quantitative culture with a predefined positive threshold of $10^4$ colony-forming units per milliliter (CFU/mL) for non bronochoscopic broncho alveolar lavage.[16,17]
8. The following secondary outcomes will be measured:
    1. Duration of mechanical ventilation.
    2. Duration of ICU stay.
    3. Hyponatremia, ,organ failures and duration of vasopressor support

    .
    4. Mortality rate.

***Statistical Analysis***

Data were analyzed using SPSS software package version 18.0 (SPSS, Chicago, IL, USA). Quantitative data were expressed using range, mean, standard deviation and median while Qualitative data were expressed in frequency and percent. Qualitative data were analyzed using Chi-square test also exact tests such as Fisher exact was applied to compare the two groups. Normally distributed quantitative data were analyzed using student t-test while quantitative data that were not normally distributed was analyzed using Mann Whitney test for comparing the two groups. In addition, ROC was used to determine sensitivity of different variables in predicting mechanical ventilation requirement. p value equal or less than 0.05 was considered significant.

**RESULTS**

– **Comparison between the two groups according to demographic data:** There were 11 females (36.7%) and 19 males (63.3%) in group A, while in group B, there were 14 female

s (46.7%) and 16 males (53.3%). There was no significant difference between the two grou ps as regards sex and regarding the age of studied patients, it ranged from 18-64 years with a mean of 38.23 ± 12.44 years in group A, and 19-68 years with a mean of 40.80 ± 12.38 yea rs in group B, showing no significant difference between the two groups.

– **Comparison between the two groups according to Glascow coma scale (GCS) on admis sion table(1), figure (1)** :

As regard GCS on admission, it ranged from 4-15 with a mean of 8.77 ± 3.38 in group A, and 4-14 with a mean of 8.20± 2.73 in group B, showing no significant difference between the t wo groups.

**Table(1): Comparison between the two groups according to Glascow coma scale (G CS) on admission**

| | Group A | Group B | P |
|---|---|---|---|
| **GCS on admission** | | | |
| Range | 4-15 | 4-14 | |
| Mean | 8.77 | 8.20 | 0.239 |
| S.D. | 3.38 | 2.73 | |

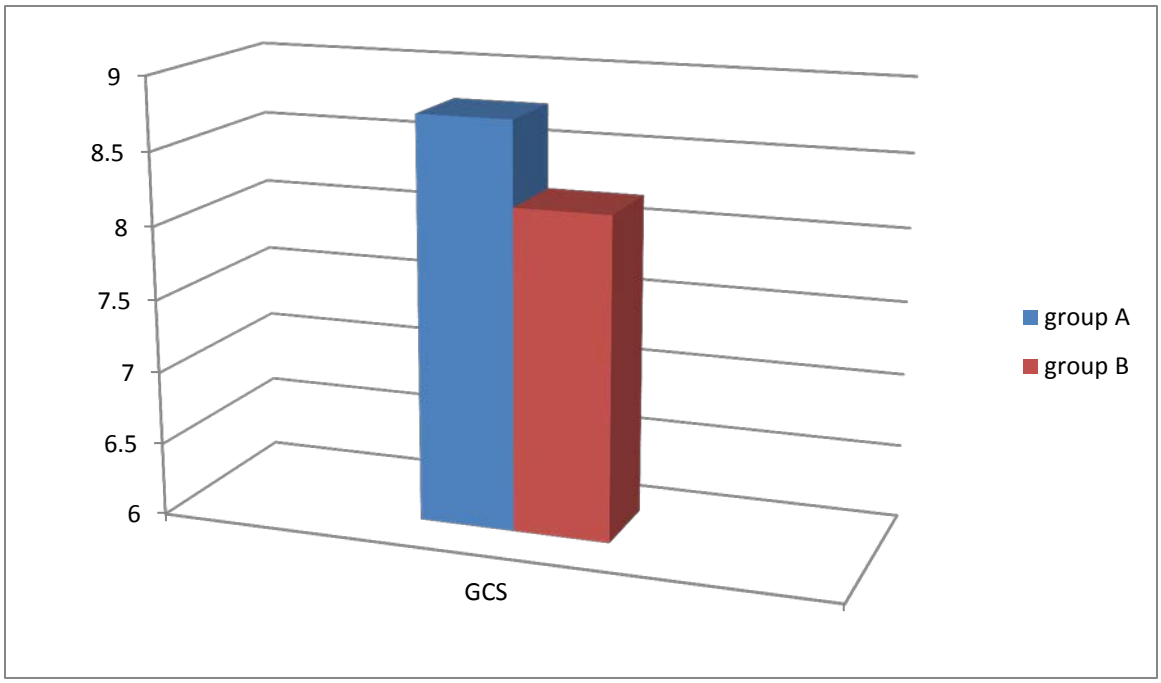


**Figure (1): Comparison between the two groups according to Glasgow coma scale (GCS) o n admission.**

**Comparison between the two studied groups regarding injury severity score (ISS):**

**AS regard ISS,** it ranged from 14-34 with a mean of 25.10 ± 4.52 in group A, and 16-34 with a mean of 25.63 ± 5.19 years in group B, showing no significant difference between the two groups.**table(2), figure (2).**

**Table (2): Comparison between the two studied groups regarding injury severity score**

| | Group A | Group B | P |
|---|---|---|---|
| **Injury severity score** | | | |
| Range | 14-34 | 16-34 | |
| Mean | 25.10 | 25.63 | 0.336 |
| S.D. | 4.52 | 5.19 | |

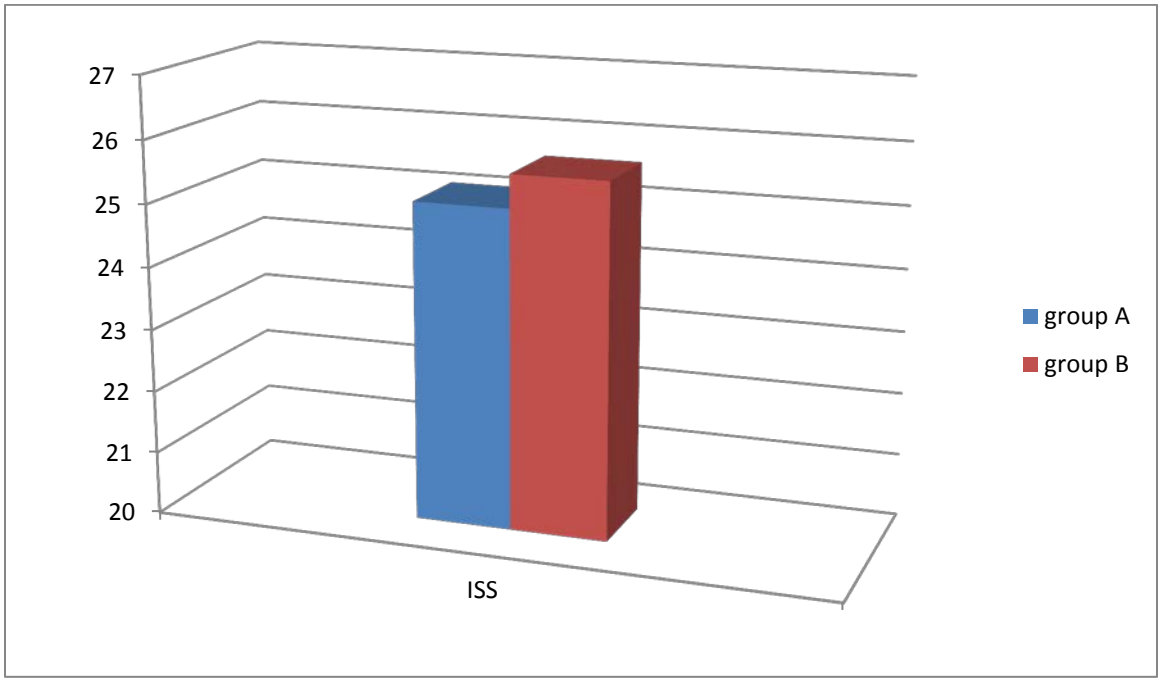


**Figure (2): Comparison between the two studied groups regarding injury severity score.**

**Comparison between the two studied groups regarding hospital acquired pneumonia in all patients Table(3), Figure(3):**

As regard hospital acquired pneumonia , the number of patients who had no attacks of pneumonia in group A was 18 patients (60%) and in group B was 10 patients(33.3%) and the number of patients who had one attack of pneumonia in group A was 9 patients (30%) and in group B was 15 patients(50%) and the number of patients who had two attacks of pneumonia in group A was 3 patients (10%) and in group B was 5 patients(16.7%), showing significant difference between the two groups.

**Figure (3): Comparison between the two studied groups regarding hospital acquired pneumonia in all patients**

| | Group A | | Group B | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Free | 18 | 60.0 | 10 | 33.3 |
| Once | 9 | 30.0 | 15 | 50.0 |
| Twice | 3 | 10.0 | 5 | 16.7 |
| P | 0.045* | | | |

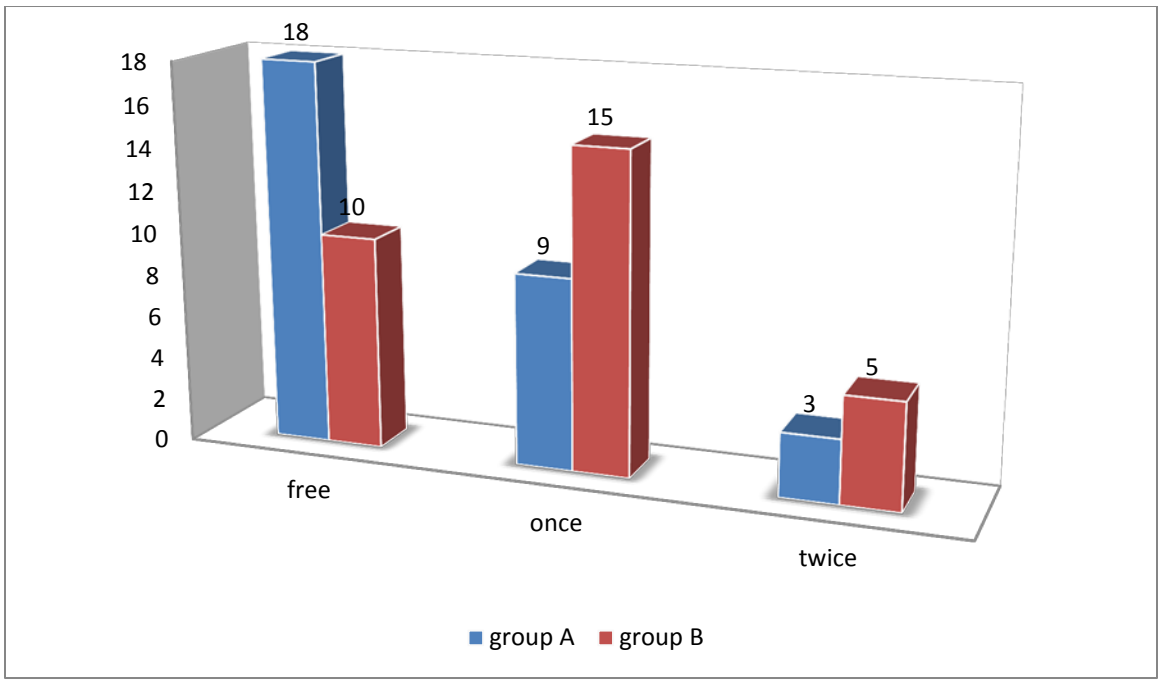


**Figure (3): Comparison between the two studied groups regarding hospital acquired pneumonia in all patients.**

Comparison between the two studied groups regarding culture findings table (4).

As regard results of non bronchoscopic bronchoalveolar lavage (minibal), the number of patients who had pseudomonas aerguinosa in minibal in group A was 5 patients (16.7%) and in group B was 4 patients(13.3%) and the number of patients who had klebsiella in minibal in grou p A was 4 patients (13.3%) and in group B was 5 patients(16,7%) and the number of patients w ho had Acinetobacter in minibal in group A was 4 patients(13.3%) and in group B was 4 patient s(13.3%) and the number of patients who hadMRSA in minibal in group A was 2 patients(6.7 %) and in group B was 2 patients(6.7%) and the number of patients who had proteus in minib al in group A was 1 patient(3.3%) and in group B was 1 patient(3.3%) and the number of patie nts who had E.coli in minibal in group A was 0 patient (13.3%) and in group B was 2 patients(6, 7%). the difference between two groups was not stastically significant.

**Table (4): Comparison between the two studied groups regarding culture findings**

| Culture findings | **Group A** | | **Group B** | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Pseudomonaaer. | 5 | 16.7 | 4 | 13.3 |
| Klebsiella | 4 | 13.3 | 5 | 16.7 |
| Acinetobacter | 4 | 13.3 | 4 | 13.3 |
| MRSA | 2 | 6.7 | 2 | 6.7 |
| Proteus | 1 | 3.3 | 1 | 3.3 |
| E.coli | 0 | 0.0 | 2 | 6.7 |
| P | 0.236 | | | |

Comparison between the two studied groups regarding days of mechanical ventilation, days of I CU stay, days of hsoptial stay and days of vasopressor support table(5), figure (5).

- **As regard days of mechanical ventilation,** it ranged from 3-15 with a mean of 7.9 ± 2.31 in group A, and 3-21 with a mean of 10.98 ± 3.98 in group B, showing significant differ ence between the two groups.
- **As regard days of ICU stay,** it ranged from 4-21 days with a mean of 9.89± 3.21 in grou p A, and 5-21 with a mean of 13.6 ± 4.02 in group B, showing significant difference bet ween the two groups.
- **As regard days of hospital stay,** it ranged from 7-28 days with a mean of 13.9± 5.22 days in group A, and 8-32 days with a mean of 16,9 ± 6.01days in group B, showing signifi cant difference between the two groups.

– **AS regard days of vasopressor support** ,it ranged from 2-4 days with a mean of 2.62± 0.1 6 days in group A, and 2-5 days with a mean of 3.36 ± 0.89 days in group B, showing si gnificant difference between the two groups.

**Table (5): Comparison between the two studied groups regarding days of mechanical venti lation, days of ICU stay, days of hsoptial stay and days of vasopressor support**

| | **Group A** | **Group B** | P |
|---|---|---|---|
| **Days of Mechanical Ventilation** | | | |
| Range | 3-15 | 3-21 | |
| Mean | 7.98 | 10.98 | 0.0031* |
| S.D. | 2.31 | 3.98 | |
| **Days of ICU stay** | | | |
| Range | 4-21 | 5-21 | |
| Mean | 9.89 | 13.6 | 0.0027* |
| S.D. | 3.21 | 4.02 | |
| **Days of hospital stay** | | | |
| Range | 7-28 | 8-32 | |
| Mean | 13.9 | 16.9 | |
| S.D. | 5.22 | 6.01 | 0.017* |
| **Days of vasopressor support** | | | |
| Range | 2-4 | 2-5 | |
| Mean | 2.62 | 3.36 | 0.021* |
| S.D. | 0.16 | 0.89 | |

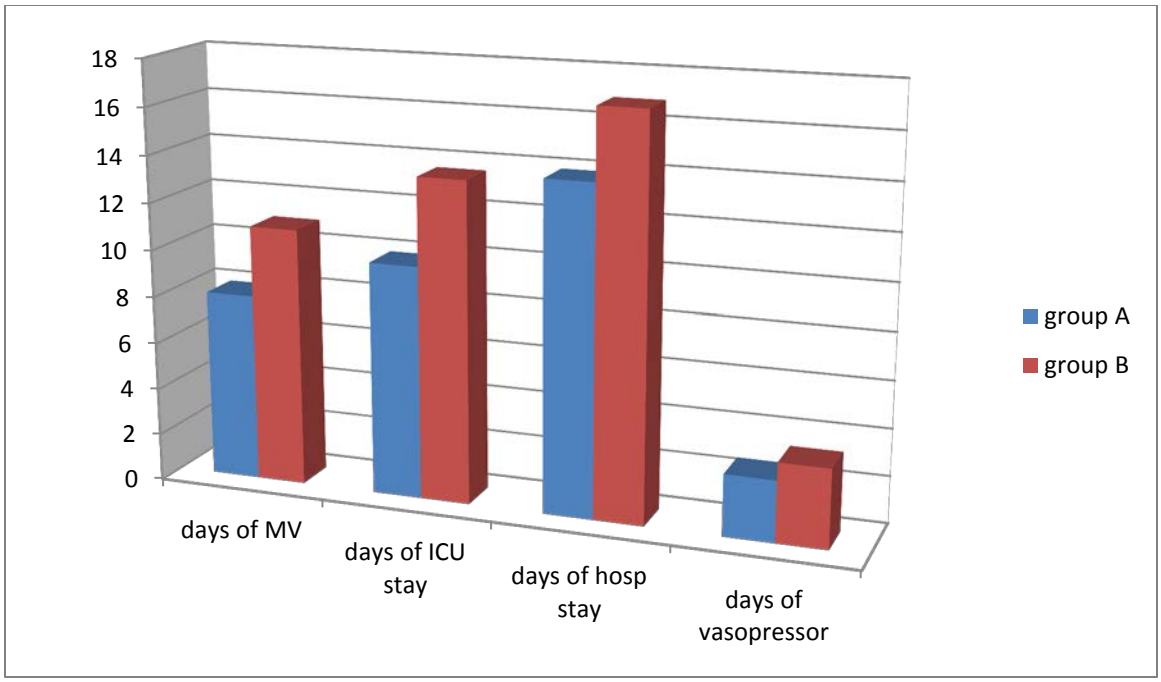


**Figure (5): Comparison between the two studied groups regarding days of mechanical venti lation ,days of ICU stay, days of hsoptial stay and days of vasopressor support**

**Comparison between the two studied groups according to Mortality**

As regard mortality , the number of deaths in group A was 3 patients with mortality rate 10% and the number of deaths in group B was 4 patients with mortality rate 13.4% and the diffe rence between two groups was not stastically significant**.**

**Table (6):** Comparison between the two studied groups according to mortality.

| | **Group A** | | **Group B** | | P |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| Mortality<br><br>Yes<br>NO | <br><br>3<br>27 | <br><br>10.0<br>90.0 | <br><br>4<br>26 | <br><br>13.4<br>86.6 | 0.699 |

## DISCUSSION

The aim from the present study was to evaluate the role of intravenous hydrocortisone infusion in stress dose in prevention of hospital acquired pnemonia in multiple trauma patients.

The study was carried out on adult patients of both sexes: All patients were admitted to the Alexandria Main University Hospital and diagnosed as polytrauma patients on mechanical ventilation for at least 48 hours based on Trauma and Injury Severity Score (TRISS).

The results of our study as regards the follow up for white blood cells for the 30 patients of both groups by assessing mean white blood cells reported that mean WBC in group B higher than group A and the difference was stastically significant .

These results were similar to the results of Roquilly A et al.(161) 31% of patients in hydrocortisone group had elevated mean white blood cells compared to 54% of patients in placebo group had elevated mean white blood cells.

The results of our study as regards the follow up for body temperature for the 30 patients of both groups by assessing mean body temperature reported that mean body temperature in group B higher than group A and the difference was stastically significant

These results were similar to the results of Roquilly A et al.(161) 34% of patients in hydrocortisone group had elevated mean body temperature compared to 59% of patients in placebo group had elevated body temperature.Also in Osime OC. et al (190) 29% of patients in hydrocortisone group had elevated mean body temperature compared to 53% of patients in placebo group had elevated body temperature .

The results of our study as regards the follow up for abnormal X-ray chest for the 30 patients of both groups which is either appearance of new consolidation or infiltrate or further worsening of the old one were higher in group B all over the period of ICU stay which denote lesser incidence of pneumonia in group A.

These results were similar to the results of Roquilly A et al.(161) 28 from 74 patients in hydrocortisone group had abnormal X-ray chest compared to 41 from 76 patients in placebo group had abnormal X-ray chest.

By summation of the above mention data and gathering the criteria for diagnosis of VAP in both groups in each day of their ICU stay it was found that incidence and frequency of VAP in group A 12 of 30 patients (40%) developed pneumonia (P 0.046*) with 9 patients (30%) developed VAP once and 3 patients(10%) developed VAP twice while in group B 20 of 30 patients (66.6%) developed pneumonia with 15 patients (50%) developed VAP once while twice in 5 patients (16.6%), Similarly the results reported by Roquilly A et al.(219) and Bulger EM et al(220) study which was conducted on 149 patients, hydrocortisone group 26 patients (35.6%)

developed pneumonia with 24 patients (32.9%) developed VAP once and 2 patients (2.7%) developed VAP twice ,while in placebo group 39 patients (51.3%) developed pneumonia with 31 patients (40.8%) developed VAP once and 8 patients (10.5%) developed VAP twice .

So group A had less incidence and frequency of VAP in comparison with group B (p0.044) (group A 18 of 30 patients (60%) and in group B 10 of 30 patients(33.3%) were free of pneumonia and no minibal culture was withdrawn to them, similarly in Roquilly A. et al(219) and in Bulger EM. et al(220) the 47 patients (64.4%) in hydrocortisone group and 37 patients (48.7%) in placebo group free of pneumonia episode).thus stress dose of hydrocortisone in poly trauma patients was effective in decreasing the incidence of both early and late ventilator associated pneumonia.

The results of our study as regards the type of organism found in the result of Minibal cultures was found that pseudomonas (in group A was found in the result of 5 cultures 16.6% and in group B was found in the result of 4 cultures 13.3% ) and klebsilla (in group A was found in the result of 4 cultures 13.3% and in group B was found in the result of 5 cultures 16.6% ) followed by acinetobacter (in group A was found in the result of 4 cultures 13.3% and in group B was found in the result of 4 cultures 13.3% ) were the most gram –ve organisms and MRSA was the main gram +ve organism (in group A was found in the result of 2 cultures 6.6% and in group B was found in the result of 2 cultures 6.6% ) .

Similar results were in Popovic N. et al(206) which conducted over 108 traumatic patient the dominating gram–ve organism was pseudomonas and the dominating gram+ve organism was MRSA Similarly, Ibrahim EH. Et al(222) P aeruginosa was the most common Gram-negative bacterial pathogen isolated from the BAL cultures and Staphaureus was the most common Gram-positive bacterial pathogen isolated from the BAL cultures .

The results of our study as regards the days of mechanical ventilation were 3-15 with mea n 7.9±2.31 in group A and 3-21 days with a mean 10.98±3 in group B showing significant differe nce between the two groups.

In agreement of our study as regard days of mechanical ventilation , in Roquilly A et al(21 9) and in Bulger EM et al(220) days of MV in hydrocortisone group were 12 days with median 8 days and 16 days with median 8.5 days in placebo group with 4 days free of MV difference bet ween the two groups (p0.001).

These results were close to the result of in 24th International Symposium on Intensive Care and Emergency Medicine (221) which shows that patients with VAP has longer period of mechanical ventilation than patients without VAP (with mean 27.61 ± 20.19 verses 10.41 ± 13.21 days ) also in Zygun DA(223) patients who developed VAP had a longer duration of mechanical ventilation (15 versus 8 days, $p < 0.0001$).

Another study Popovic N et al (206)which was conducted on polytauma with or without chest trauma 108 patients group I days of MV ranged from 9-22 while group II ranged from 3-12 days.

That result denotes that patients developed pneumonia has increased duration of mechanical ventilation as VAP is a main cause of delayed weaning due to difficult weaning which may render the patient more liable to develop multiple attacks of VAP, multi organ failure, sepsis or sever sepsis due to systemic inflammatory response syndrome and suppressed immunity which leads to increase morbidity and hospital mortality rates with range between 30% and 50%.(226,227)

The results of our study as regards the days of ICU stay**,** it ranged from 4-21 days with a mean of 9.89± 3.21 in group A, and 5-21 with a mean of 13.6 ± 4.02 in group B, showing signif icant difference between the two groups.

These results were similar to the results of Roquilly A et al(219) and in Bulger EM et al(2 20) days of ICU stay was 18 days with median 15 days in hydrocortisone group and days of ICU stay was 24 with median 16 days in placebo group .Also in Ibrahim EH, et al(224) the ICU lengt h of stay was significantly longer for patients with early-onset nosocomial pneumonia (10.3 ± 8.3 days; $p < 0.001$) and late-onset NP (21.0 ± 13.7 days; $p < 0.001$) than patients without nosocomia l pneumonia.

Another study , Zygun DA et al.(223) patients who developed VAP had a longer intensive care unit (17 versus 9 days, $p < 0.0001$) and hospital (60 versus 28 days, $p = 0.003$) lengths of stay.Also in 24th International Symposium on Intensive Care and Emergency Medicine .(221) which shows that patients with VAP had longer period of ICU stay than patients without VAP (with mean 30.79 ± 18.06 verses 12.25 ± 14.97 days).

The result of our study as regard serum sodium level, mean serum sodium level was higher in group A than group B and the difference was stastically significant .

Similar results in Roquilly A et al(212) , in hydrocortisone group 7 of 76 patients (9.2%) in the placebo group and none of the 73 in the hydrocortisone group developed hyponatremia (p 0.01).

Mortality of VAP in trauma patients is low. (224) The result of our study as regard mortality rate, 10% (3 out of 30 patients) died in group A (2 from sepsis and one from severe bleeding from liver laceration) while in group B 13.4%(4 out of 30 patients ) died (2 from sepsis and one from pulmonary embolism and one from brain edema and herniation ) with no significant difference between both groups.

The result of our study was similar to the results in Roquilly A, et al.(219) and in Bulger EM. et al(220). Four of 76 patients (5.3%) in the placebo group and 6 of 73 (8.2%) in the hydrocortisone group died (p=0.44)

Another study was Ciesla DJ etal. (224)A 12-Year Prospective Study of Post injury Multiple Organ Failure 112 of 1244 patients died (mortality rate 8%) and in Osime OC. et al (190) A total of 5,537 cases presented to the AEU of the University of Benin Teaching Hospital 5,446 were due to trauma (98.4%). A total of 127 patients died (case fatality rate: 2.3%). Also in Zygun DA etal.(223) VAP was not associated with increased hospital mortality.

At the end it was obvious that hydrocortisone group had less incidence and frequency of both early and late onset VAP due to its immune modulatory effect whether in the ebb phase or in the flow phase and that in turns decrease their period of mechanical ventilation and the early weaning decrease their period of ICU stay which in turns decrease rate of complications of prolonged mechanical ventilation and ICU stay, morbidity, antimicrobial therapy and economic costs as pneumonia is the most common cause of prolonged period of mechanical ventilation .

## CONCLUSION

In intubated trauma patients, the use of an intravenous stress-dose of hydrocortisone, compared with placebo, resulted in a decreased risk of hospital acquired pneumonia

## STATEMENT OF INTEREST

No conflict of interest.

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