Effect of acute kidney injury on weaning from mechanical ventilation in critically ill patients

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Abstract: Acute Kidney Injury (AKI) is a frequently encountered condition in hospitalized patients specially critically ill patients in ICUs. This condition is not a single organ failure but it is a multi-organ syndrome as AKI negatively affects many other organs. In our study we chose to investigate the effect of AKI on respiratory system. Specifically on the mechanically ventilated patients and how AKI would affect the weaning of these patients. Our study sample was 150 mechanically ventilated patients. They were divided into 2 groups according to their renal function: **Group A:** 50 patients with normal kidney function; **Group B:** 100 patients suffered from AKI at any point during their admission. Serum Creatinin (SCr) and urine output was routinely recorded at admission and every 24 hours. Duration of MV, duration of weaning, rate of weaning failure and mortality rates were recorded among other data such as demographic data, SAPS score at admission, cause of admission and co-morbidities. These data were statistically analyzed between the 2 groups. As regard demographic data, SAPS score, cause of admission and co-morbidities, they all showed no statistical significant difference between the 2 groups. As regard duration of MV and duration of weaning (length of time elapsed from the moment the patient reached weaning criterion to the time the patient was extubated), there were significant statistical difference between the two groups. As the group of patients suffered from AKI lasted longer on MV and had longer duration of weaning. As regardrate of weaning failure, it was significantly higher in AKI patients (Group A). While successful first time weaning was higher in non AKI patients (Group B). Mortality rate was also significantly higher in patients was AKI (Group A) than non AKI patients (Group B). In conclusion, AKI has significant deleterious effect on respiratory system. Which is clearly seen in our resulted. As AKI significantly worsened the outcome of mechanically ventilated patients regarding days of MV, weaning failure and up to mortality rates.

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1. Introduction

Acute kidney injury (AKI) is the most common cause of organ dysfunction in critically ill adults, with a single episode of AKI, despite of stage, carrying a significant morbidity and mortality risk **(Doyle and Forni, 2016)**. Both clinical and translational laboratory studies have demonstrated very complex mechanisms of inter-actions between the injured kidney and distant organs such as the lung, heart, liver, gut, brain, and hematologic system **(White et al., 2011)**.

AKI imparts a dim outcome on different settings of critically ill patients **(Lassnigg et al., 2004).** Decreased renal function is accompanied by immune depression and disturbances in homeostasis of acid–base and volume status that can adversely affect respiratory function **(Hoste and De Waele, 2005)**.

Besides that, the prescence of AKI in critically ill patients frequently contributes to depression of mental status and accumulation of several drugs' metabolites, which can further compromise the level of consciousness which can further delay weaning from mechanical ventilation **(Rabb et al., 2003).**

Lung and kidney function are intimately related in both health and disease. Respiratory changes help to mitigate the systemic effects of renal acid-base disturbances, and the reverse is also true (**Pierson, 2006).**

Aim of Work

This study will evaluate the effect of AKI on weaning of mechanically ventilated patients.

2. Patients and Methods

Study settings:

This study was conducted on mechanically ventilated patients for more than 48 hours in intensive care units of Ain Shams University hospitals after obtaining an approval from the Research Ethical Committee.

Inclusion criteria:

1. Age between 18 and 70 years old
2. Sex: male or female
3. Invasive mechanical ventilation > 48 hours

Exclusion criteria

1. End stage renal failure on renal replacement therapy on admission.
2. Patients on mechanical ventilation after pulmonary resection or brain surgery.
3. Previous partial or radical nephrectomy.
4. Morbid obesity with BMI > 30Kg/ M2.
5. ICU readmissions.

All patients received the standard of care according to the protocols of intensive care units in Ain shams University Hospitals as regards mechanical ventilation strategy and trial of weaning criteria when the following criteria were fulfilled:

- low FiO2 (< 0.5) with PaO2 > 80 mmHg
- PEEP < 8 CmH2O
- hemodynamic stability (little to no inopressors)
- able to initiate spontaneous breaths (good neuromuscular function)
- adequate conscious level, GSC ≥ 8 (table 1)

When these criteria were fulfilled, spontaneous breathing trial (PEEP of 5 cm H2O and pressure support of 6 cm H2O) for 30 minutes was undertaken. If the respiratory rate/tidal volume ratio stayed < 100 and there was no clinical evidence of respiratory distress, extubation or disconnection from ventilator (for tracheotomized patients) was performed. The spontaneous breathing trial was repeated only once a day for those patients who failed.

Duration of weaning is defined as the length of time elapsed from the moment the patient reached weaning criterion to the time the patient was extubated or disconnected from the ventilator (for tracheotomized patients). Weaning failure is defined as the need to re-intubate or to reconnect tracheotomized patients to the ventilator within 48 hrs after weaning.

Serum Creatinin (SCr) and urine output were routinely recorded at admission and every 24 hours. Patients were divided into 2 groups:

Group "A": patients on mechanical ventilation with normal kidney function throughout the entire duration of mechanical ventilation.

Group "B": patients on mechanical ventilation suffered from AKI at any point during the duration of mechanical ventilation.

AKI is defined as any of the following:

Increase in SCr by ≥ 0.3 mg/dl (≥ 26.5 mmol/l) within 48 hours; or Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.

Oliguria is defined as urine excretion less than 400 mL/day.

The following data was recorded:

1. Age, Sex and weight of the patient
2. Cause of ICU admission
3. Co-morbidities (Hypertension, Diabetes, etc.)
4. Simplified acute physiology score (SAPS) II (table 2) at admission
5. S. creatinine on admission and every 24 hours
6. Urine output every 24 hours and duration of oliguria if occurred
7. duration of mechanical ventilation, duration of weaning, and rate of weaning failure
8. Mortality rate

This study ended by completion of the estimated sample size 150 patients. 50 patients in group A and 100 patients in group B.

Statistical analysis

The data were tested for normality using the Anderson-Darling test and for homogeneity variances prior to further statistical analysis. Categorical variables were described by **number and percent** (N, %), where continuous variables described by mean and standard deviation **(Mean, SD)**. **Chi-square test** used to compare between categorical variables where compare between continuous variables by **Independent-Samples T test**. **A two-tailed p < 0.05** was considered statistically significant. All analyses were performed with the **IBM SPSS 20.0** software.

3. Results

1) Demographic data

As regard age, sex, and weight, there were no statistically significant differences between the two groups (p-value> 0.05) as shown in table (R-1).

Table R-1: Comparison between the two different groups as regard sex, age (in years) and weight (in Kg).

Sex	Group A (AKI) (n=100)		Group B (Non AKI) (n=50)		P. value
	No.	%	No.	%	
Male	56	56.0	30	60.0	0.641
Female	44	44.0	20	40.0	
	Range	**Mean±SD**	**Range**	**Mean±SD**	**P. value**
Age	34 - 91	64.37±10.33	44 - 90	66.04±10.4	0.353
WT (Kg)	55 - 120	78.37±11.49	55 - 120	76.3±11.27	0.297

Data are presented as mean ±SD regarding the age and weight. While sex is presented as numbers and percentage. P>0.05 was considered statistically non-significant between the 2 groups.

2) Co-morbidities

As regard Co-morbidities there were no statistically significant differences between the two groups (p-value> 0.05) as shown in table (R-2).

3) Cause of admission

As regard different causes of admission there were no statistically significant differences between the two groups (p-value> 0.05) as shown in table (R-3)

4) SAPS Score:

As regard SAPS score on admission there were no statistically significant differences between the two groups (p-value> 0.05) as shown in table (R-4).

Table R-2: Comparison between the two different groups as regard the co-morbidities.

	Group A (AKI) (n=100)		Group B (Non AKI) (n=50)		P. value
	No.	%	No.	%	
Co-morbidities					
No	7	7.0	2	4.0	0.397
Asthmatic	10	10.0	3	6.0	
Asthmatic+DM	2	2.0	1	2.0	
Asthmatic+HTN	0	0.0	3	6.0	
DM	15	15.0	7	14.0	
DM+HTN	17	17.0	13	26.0	
DM+IHD	4	4.0	2	4.0	
HTN	23	23.0	7	14.0	
HTN+IHD	9	9.0	6	12.0	
IHD	1	1.0	1	2.0	
HTN+DM+IHD	12	12.0	5	10.0	

CO-morbidities data are represented as numbers and percentage.
P>0.05 was considered statistically non-significant between the 2 groups.

5) Duration of Mechanical Ventilation:

Patients were observed during their mechanical ventilation days which maximally lasted for 8 days. There were significant statistical difference between the two groups as shown in table (R-5) and figure (R-3), as the group of patients suffered from AKI lasted longer on MV (P value <0.05)

Table R-3: Comparison between the different two groups as regard cause of admission.

	Group A (AKI) (n=100)		Group B (Non AKI) (n=50)		P. value
	No.	%	No.	%	
Cause of admission					
Acute severe asthma	6	6.0	3	6.0	0.824
AHPE	11	11.0	7	14.0	
Cardiogenic shock	4	4.0	3	6.0	
CHF	10	10.0	3	6.0	
Corpulmonale	4	4.0	4	8.0	
CVS	34	34.0	13	26.0	
Pneumonia	5	5.0	6	12.0	
Post arrest	3	3.0	2	4.0	
Post op	10	10.0	3	6.0	
Pulmonary embolism	3	3.0	1	2.0	
Septic shock	10	10.0	5	10.0	

Cause of admission data are represented as number and percentage.
P>0.05 was considered statistically non-significant between the 3 groups.

Table R-4: Comparison between the two different groups as regard SAPS score on admission.

	Group A (AKI) (n=100)		Group B (Non AKI) (n=50)		P. value
	Range	Mean±SD	Range	Mean±SD	
SAPS score	18 - 70	39.83±10.9	18 - 69	40.5±9.45	0.712

SAPS score is represented as range & Mean±SD. P>0.05 was considered statistically non-significant between the 2 groups.

Table R-5: Comparison between the two different groups as regard duration of mechanical ventilation id days.

	Group A (AKI) (n=100)		Group B (Non AKI) (n=50)		P. value
	Range	Mean±SD	Range	Mean±SD	
Duration of MV IN DAYS	2 - 8	4.29±2.18	2 - 8	3.46±1.53	0.02*

Duration of MV is represented as range & Mean±SD.
*P<0.05 was considered statistically significant between the 2 groups.

6) Duration of weaning:

Duration of weaning lasted longer in patients with AKI (Group A) which resulted in significant statistical difference between the 2 groups as shown in table (R-6) and figure (R-4) (P value <0.05)

Table R-6: Comparison between the two different groups as regard duration of weaning in hours.

	Group A (AKI) (n=100)		Group B (Non AKI) (n=50)		P. value
	Range	Mean±SD	Range	Mean±SD	
Duration Of Weaning IN HOURS	0 - 3	1.54±0.72	0 - 2	1.16±0.68	0.002*

Duration of weaning is represented as range & Mean±SD.
* P<0.05 was considered statistically significant between the 2 groups.

7) Weaning failure

Rate of weaning failure was significantly higher in AKI patients (Group A) as shown in table (R-7) and figure (R-5). While successful first time weaning was higher in non AKI patients (Group B) (P value <0.05)

Table R-7: Comparison between the two different groups as regard rate of weaning failure.

	Group A (AKI) (n=100)		Group B (Non AKI) (n=50)		P. value
	No.	%	No.	%	
Rate of weaning failure					
0 (Successful 1st weaning trial)	52	52.0	38	76.0	0.018*
1 (failed weaning once)	34	34.0	9	18.0	
2 (failed weaning twice)	14	14.0	3	6.0	

Rate of weaning failure is represented as numbers and percentage.
* P<0.05 was considered statistically significant between the 2 groups.

8) Mortality Rate:

Mortality rate was significantly higher in patients was AKI (Group A) than non AKI patients (Group B) as shown in table (R-8) and figure (R-6) (P value <0.05)

Table R-8: Comparison between the different groups as regard mortality.

	Group A (AKI) (n=100)		Group B (Non AKI) (n=50)		P. value
	No.	%	No.	%	
Mortality					
Absent	42	42.0	37	74.0	<0.001*
Present	58	58.0	13	26.0	

Mortality rate is represented as numbers and percentage.
* P<0.05 was considered statistically significant between the 2 groups.

4. Discussion

Acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS) are 2 frequent contributing causes of admission to the intensive care unit (ICU), with significant implications for patient morbidity, mortality and health care resource consumption **(Dessap et al., 2016).**

Acute kidney injury (AKI) is the main common cause of organ dysfunction in critically ill patients, through a sole episode of AKI, despite of stage, carrying a considerable morbidity and mortality risk **(Doyle and Forni, 2016).**

Even though several drugs to avoid and treat AKI have revealed benefits in preclinical models, no definite agent has been shown to do good to AKI in humans. Furthermore, in spite of notable advances in dialysis techniques that facilitate management of AKI in hemo-dynamically unstable patients with shock, dialysis-requiring severe AKI is still connected to an unacceptable elevated mortality rate. So, focusing merely on renal damage and loss of kidney function has not been adequate to improve outcomes of patients with AKI. Recent statistics from basic and clinical research have begun to clarify complex organ interactions in AKI between kidney and remote organs, including heart, lung, spleen, brain, liver, and gut **(Doi and Rabb, 2016)**.

Acute kidney injury (AKI) happens in twenty percent of hospitalized patients and 30–50% of admissions to the intensive care unit (ICU). AKI is the most frequent in-patient consult to nephrologists, and is linked to significant morbidity and mortality. The in-hospital mortality of patients with severe AKI in need of dialysis is thirty three percent overall and >50% in patients inside the ICU. Moreover, patients who develop AKI stay in hospital longer and are twice as likely to be discharged to short term or long term care amenities as those who do not suffer from AKI. The development of acute respiratory failure in patients with AKI raises the probability of discharge to an extensive care facility **(Faubel and Edelstein, 2016).**

Dysfunction of other organs is a vital cause of dim outcomes from AKI. Plenty of clinical and epidemiologic information show that AKI is related with remote organ dysfunction in lung, heart, brain, and liver. Current advancements in basic and clinical research have demonstrated physiologic and molecular mechanisms of distant organ interactions in AKI, including leukocyte activation and infiltration, generation of soluble factors like inflammatory cytokines/chemokines, and endothelial injury. Oxidative stress and creation of reactive oxygen species, plus dys-regulation of cell death in remote organs, are also important mechanisms of AKI-induced remote organ dysfunction **(Lee et al., 2018).**

In this study patients were divided into two groups. 100 patients with AKI in group A and 50 patients without AKI in Group B to asses effect of AKI on weaning of mechanical ventilation. All patients were mechanically ventilated. Demographic data, cause of admission and co-morbidities were recorded. SAPS score and serum creatinin were measured at admission. Then daily serum creatinin and daily urine output was measured. Also duration of mechanical ventilation in days, duration of weaning, rate of weaning failure and mortality rate for each group were measured.

Demographic data, co-morbidities, cause of admission and SAPS score as well as S. Creat. at admission showed no significant difference between the 2 groups.

Regarding days of MV, we found that the days of MV in the group of patients with AKI were statistically significantly longer than the days of MV in patients without AKI (with a p-value< 0.05).

In 2007, Vieira and his colleagues conducted a Observational, retrospective study in a 23-bed medical/surgical intensive care unit (ICU) in a cancer hospital. They studied the effect of AKI on weaning of mechanical ventilation on a total of 140 patients: 93 with AKI and 47 without AKI (controls). The results showed that the duration of MV was significantly higher in AKI group than the control group (median duration of mechanical ventilation: 10 [6-17] vs. 7 [2-12] days, p =.017) which coincides with our study.

In 2011, Pan and his colleagues conducted a retrospective observational study in a respiratory ICU to asses risk factors for prolonged mechanical ventilation (PMV). Of 154 patients enrolled, 41 patients (26.6%) had PMV. Patients with PMV showed occurrence of AKI since day 1 of MV, which conclude that acute kidney injury on MV initiation day is an independent risk factor for PMV. This also coincides with our results.

Ralib and his coworkers in 2018 conducted a retrospective cohort study extracted data from the Malaysian Registry of Intensive Care in four Malaysian tertiary ICUs between January 2010 and December 2014. To investigate the incidence, risk factors, and outcome of AKI. AKI was defined as twice the baseline creatinine or urine output <0.5 ml/kg/h for 12 h. they found out that AKI patients had a longer duration of mechanical ventilation. This coincides with our results.

Regarding duration of weaning, we found out that patients with AKI (Group A) lasted longer than in patients without AKI (Group B) with statistically significant difference (p-value< 0.05).

Vieira and his colleagues in their study in 2007, concluded that the duration of weaning from mechanical ventilation in AKI patients was longer than in group of patients without AKI. Which coincides with our results.

Regarding weaning failure in our study, it was significantly higher in AKI patients (Group A) while successful first time weaning was higher in non AKI patients (Group B) (p-value< 0.05).

Also studied effect on weaning failure was **Vieira and his colleaguesin 2007,** they also found out statistically significant difference in weaning failure rate from MV between patients with AKI which had higher rate of weaning failure unlike patients without AKI. Which coincides with our results.

Regarding mortality, our study showed significant statistical difference between the 2 groups (p-value< 0.01). There was higher mortality rate among the group of patients with AKI than the patients that didn't suffer from AKI.

In 1998, Chertow in his colleagues conducted a study to determine whether there is an independent association of acute renal failure requiring dialysis with operative mortality after cardiac surgery.42,773 patients who underwent cardiac surgery were evaluated to determine the association between acute renal failure sufficient to require dialysis and operative mortality. They found out that Acute renal failure was independently associated with early mortality following cardiac surgery, even after adjustment for comorbidity and postoperative complications.

Vieira et al in 2007 in their study concluded that ICU mortality rate were significantly greater in the AKI patients than the group that didn't suffer from AKI. As shown in our results.

Also about that result, **In 2008 Barrantes and his colleagues** conducted a retrospective cohort study on population consisted of 471 patients with no recent history of renal replacement therapy who were admitted to the medical intensive care unit during 1 yr. medical records of all patients were reviewed using a data abstraction tool. Demographic information, diagnoses, risk factors for acute kidney disease, physiologic and laboratory data, and outcomes were recorded. They found out that the mortality rate of patients who met criteria for acute kidney injury was significantly higher than that of patients who did not have acute kidney injury.

Kingah and his colleagues in 2018 performed a study on patients with a solid malignancy admitted to an intensive care unit (ICU) at a tertiary academic medical center were enrolled. Clinical data upon admission and during ICU stay were collected. Hospital, ICU, and six months outcomes were documented. Using multivariate analysis, acute kidney injury was associated with hospital mortality.

Also in **2018, Mohammadi and his colleagues** performed a retrospective cohort study, on 900 patients admitted to the ICU during a one year period from 2014 to 2015 to evaluate the incidence rate, risk factors and clinical outcome of AKI using the RIFLE classification in ICU patients. They found out that the mortality rate was 58.3% for AKI patients, and 13.4% for non-AKI patients (P<0.001). This coincides with our result.

The limitations of this study other conditions like sepsis and other organ failures were not assessed whether they have effect on MV and mortality or not. Nor was renal replacement therapy (RRT).

Conclusion:

Our study shows that there is significant effect of renal dysfunction on the outcome of patients on MV regarding their weaning and mortality rate. AKI lengthens MV and weaning duration and increases ICU mortality in critically ill patients.

Recommendation:

It is recommended to further assess the effect of RRT on weaning and on mortality. Also to study the effect of AKI on other organs and how to avoid it as early as possible.

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