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Research Article

Furosemide in Hypovolemic shock

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A b s t r a c t

Background: Shock is a common clinical state, we face chocked patients in causality, surgical and gynecological specialties like stab wounds, road traffic accidents, placenta Previa, placenta accrete, placenta pericreta, ectopic pregnancy, perforated viscus, etc. All such patients undergo surgical exploration and the majority of them are shifted to ICU to complete monitoring and support. A high percentage of them develop acute kidney injury intra and postoperatively and carry a high mortality rate because of not-so-good nursing care in ICU in Iraq.
Aim of the Study: to clarify that Furosemide can protect kidney function during shock and reduce ICU admission and mortality rate.
Method: 100 shocked patients were enrolled in this study which was done in the medical city hospital, Al-Sadder General hospital, and Alkindi teaching hospital in Iraq/Baghdad from January 2019 to June 2020. Patients were divided into 2 groups: group SN this includes 50 patient who received 2 ml normal saline as placebo(control group)and second group SL which include 50 patient who received 2 ml (20 mg) furosemide (study group). This trial was a double-blind study, both the patient and the junior anesthesia doctor do not know about the study conducted. patients below the age of 14 years were excluded from the study.
98 patients of those 100 patients were involved in multiple stab wound injuries, multiple bullet injuries, and road traffic accidents, and only 2 patients were diagnosed with ectopic pregnancy.
Result: ICU admission and mortality rate was less in patients receiving furosemide compared to patients who received placebo (2% and 14% versus 1%and 7%respectively).
Conclusion: furosemide reduces ICU admission and mortality rate in shocked patients.

Introduction

Shock is defined as a clinical state of inadequate tissue perfusion, hypotension is defined as a clinical state when mean blood pressure is less than 60 mm. Hg or systolic blood pressure is less than 90 mm. Hg. Shock usually presented with tachycardia, low volume pulse, hypotension, sweating, decrease mental state, and oliguria. Shock is clinically classified in:

1- Hypovolemic shock: It is due to hemorrhage, burn, vomiting and diarrhea
2- Distributive shock: It is due to septicemia (septic shock), vasodilating drugs, anaphylactic shock, and spinal cord injury.
3- Cardiogenic shock: It is due to arrhythmia, myocardial infarction, heart failure, valvular heart diseases, and cardiomyopathy .
4- Obstructive shock: It is due to tension pneumothorax, large haemopneumo thorax, severe aortic or mitral valve diseases, hypoplastic left ventricle, and pulmonary embolism.

During shock, there is an imbalance between oxygen delivery and oxygen requirement, so there is a decreased oxygen supply, and this leads to tissue hypoxia. This hypoxia leads to cellular injury and release of inflammatory mediators and free oxygen radicals which further compromise tissue perfusion by changes in the function and structure of microvessels. The survival rate of shock depends on initial resuscitation and monitoring of the patient and protection of vital organs (kidney, heart, and brain) from organ dysfunction. Shock is usually classified into four stages as shown in the table [1].

Table (1): stages of shock

	stage 1*	stage 2	stage 3	stage 4
Blood loss	<750 ml	750-1500	1500-2000	>2000
% blood loss	<15%	(15-30)%	(30-40)%	>40%
Pulse rate	<100	>100	>120	>140
Blood pressure	120/80	normal	decrease	desrease
Respiratory rate	15-20	20-30	30-40	>40
Urine output ml/hr	<30	20-30	5-20	Negligible
Neurological signs	Slightly anxious	Slightly anxious	Confused	Lethardic

* compensatory stage

The mechanism of action of furosemide is by blocking Na/K/Cl channels which are located in proximal convoluted tubules and thick ascending loop of Henle, so the result will be:

1- Increase secretion of calcium and magnesium.

2- Inhibition of Na &K entrance to macula densa, so this will lead to :

-inhibition of tubuloglomerular feedback mechanism which leads to renal vasodilation which is essential in a shocked patient, it leads to maintain renal circulation

-increase in renin production which in turn leads to an increase in angiotensin 2 which leads to an increase in blood pressure and glomerular perfusion and an increase in aldosterone secretion which leads to sodium and water reabsorption, which impair diuresis.

As we know that sodium and water absorption in the proximal convoluted tubules and loop of Henle is an active process done through Na/k ATPase, so it requires energy and oxygen. Loop diuretics like furosemide which inhibit sodium and water reabsorption through inhibition of Na/K ATPase reduce the amount of energy expended by the nephrons thereby reducing oxygen consumption; this will at least protect the kidney from the harm of hypoxia in a situation of poor perfusion as in shock.

The first step of treating patients with shock after maintaining proper airway and breathing is to maintain circulation by giving crystalloids or colloids fluids in hypovolemic and hemorrhagic shock respectively [1]. Giving these fluids vigorously and quickly will lead to systemic venous congestion which can impair renal functions (this is called congestive nephropathy) through several mechanisms:

- The blood pressure across the kidney (renal perfusion pressure) which equal to mean arterial pressure minus central venous pressure(like any organ perfusion pressure), so reduction of mean arterial pressure in shock and elevation of central venous pressure during the fluids therapy can reduce the effective renal perfusion pressure and this will leads to further inadequate renal perfusion.
- Venous congestion after vigorous fluid administration can lead to intra-renal interstitial edema which can lead to renal compartment syndrome which further compromises renal perfusion [2].

So giving furosemide (20-40) mg in shocked patient management with fluid may relieve venous congestion and improve renal function.

Subject and Methods

This trial was conducted in the Medical city teaching hospital, Alkindi teaching hospital, and Alsadir hospital, Baghdad, Iraq from January 2019 to June 2020. One hundred patients were selected for this study. All these patients are admitted to the hospital in a shocked state, 50 patients were involved in a road traffic accident with pure abdominal trauma, 48 patients involved in bullet injury and two patients had ruptured ectopic pregnancy. All problems and complications of the surgical operation were explained to the relatives of the patients preoperatively. All those patients were clinically examined, the American society of anesthesiologist (ASA) state of patients, and the stage of shock assessed preoperatively. . All patients were shifted to the theater from the casualty department after signing their surgical consent and resuscitation and after preparation for surgical operation. In the theater, all these patients underwent explorative laparotomy under general anesthesia. Two peripheral lines were inserted preoperatively, resuscitation started with crystalloid solutions and blood, standard monitoring (ECG, PR, BP, SPO2, ETCO2, CVP, and UOP) was done. General anesthesia was conducted by ketamine 1-2 mg /kg body WT and propofol 0.5-1mg /kg body WT as inducing agents with esmeron 0.3-0.5 mg/kg body WT as a muscles relaxant, also tramal 0.5-1 mg/kg body weight was given as analgesic drug. Anesthesia maintained with oxygen 99% and isoflurane 1%. During anesthesia Foley's catheter was put in and the central venous line was inserted in the subclavian vein to monitor urine output and central venous pressure respectively. Patients were allocated randomly into two groups using sealed envelope methods as follow:

1. First Group (the control group) consists of shocked patients who received 2ml normal saline called SN.
2. Second group (the study group) consists of shocked patients who received 2 ml furosemide 20 mg called SL

Statistical analysis

After collecting all the data from patients regarding age, weight, ASA, shock grade, blood urea, serum creatinine, admission to RCU, and mortality rate, we use statistical packing of social sciences (SPSS version 2019) to find the results. All results were expressed as a mean+-standard deviation. We use an unpaired t-test from compare means menu from analysis to compare means of the two groups (SN & SL).

Ethical approval was obtained from the Medical city teaching hospital.

Results

Results were summarized in the following tables and graphs:

Table (2) :Demographic profile

	control group	study group	p value	significance
age	53.96+-15.07	55.92+-16.29	0.267	NS
gender	1.46+-0.503	1.48+-0.504	0.421	NS
weight	71.92+-10.75	74.5+-11.21	0.121	NS
ASA	1.8+-0.69	2.00+-0.728	0.082	NS
shock stage	3.04+-0.781	3.16+-0.738	0.216	NS

Table (3): Mean, standard deviation, p value and significance of mean BP, PR, CVP, blood urea, s. creatinine, ICU admission and mortality rate.

	control group	study group	p value	significance
Mean BP	76.64+-9.88	78.66+-5.44	0.103	NS*
pulse rate	137.09+-7.59	133.38+-3.80	0.001	HS
CVP	4.08+-0.80	4.21+-0.62	0.176	NS
blood urea	58.12+-15.69	49.62+-11.05	0.001	HS
S. creatinine	1.47+-0.418	0.98+-0.190	0.001	HS
ICU admission	0.28+-0.453	0.04+-0.1979	0.001	HS
mortality rate	0.14+-0.35	0.02+-0.141	0.013	S

* NS=non-significant, HS=high significant, s=significant

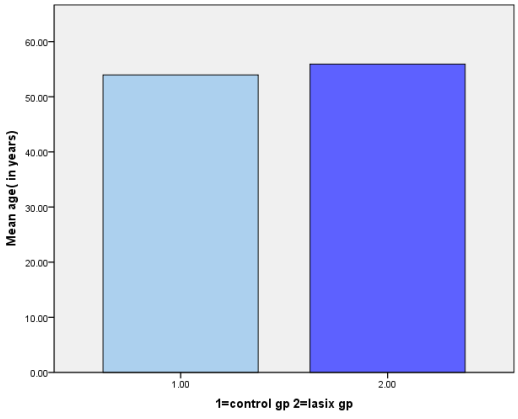


Figure (1): shocked patients received normal saline versus shocked patients received Furosemide in terms of age, there is no significant statistical difference (p=0.267).

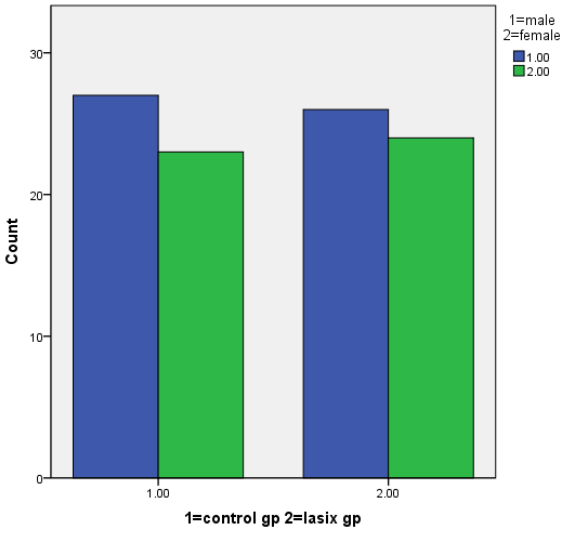


Figure (2): shocked patient received 2 ml normal saline group versus shocked patients received 2 ml Furosemide group in sense of gender, there is no significant statistical differences (p=0.421)

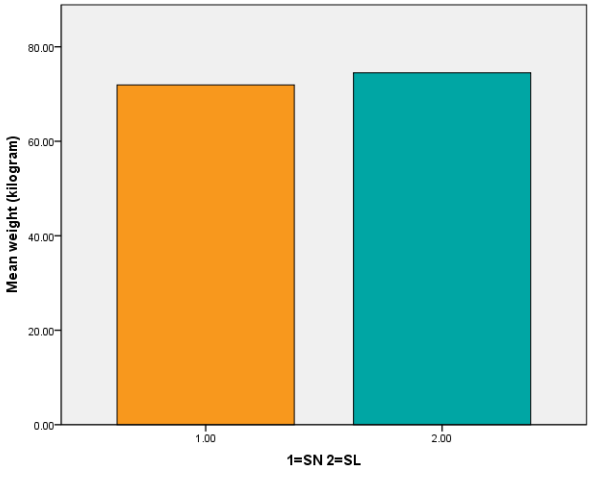


Figure (3): shocked patients received 2ml normal saline group versus shocked patients received 2 ml Furosemide group in sense of weight, there is no significant statistical difference (p=0.121).

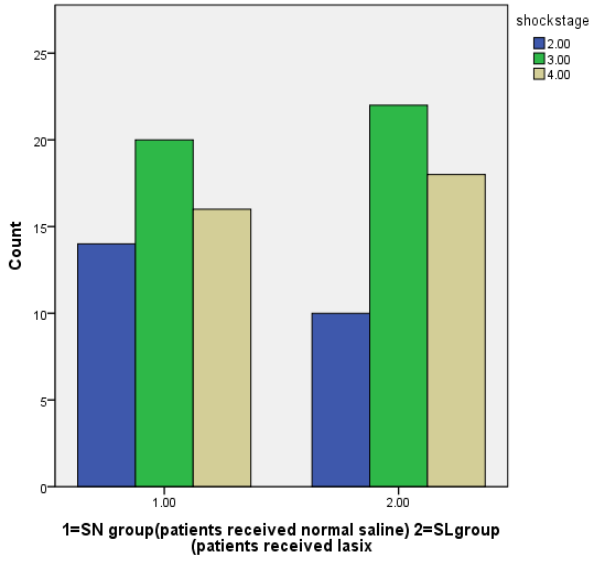
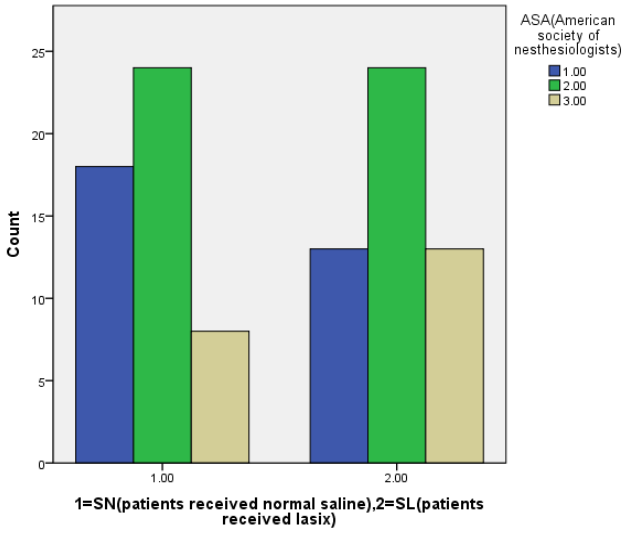


Figure (4): shocked patients received 2 ml normal saline group versus shocked patients received 2 ml Furosemide group in sense of shock stage, there is no significant statistical difference (p=0.216).



Figure(5): shocked patients received 2 ml normal saline versus shocked patients received 2 ml Furosemide in terms of ASA, there is no significant statistical difference (p=0.165).

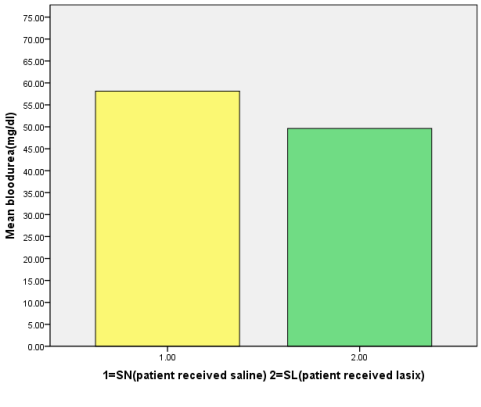


Figure (6): shocked patients received normal saline versus shocked patient received Furosemide in terms of blood urea, there is significant statistical difference (p=0.001).

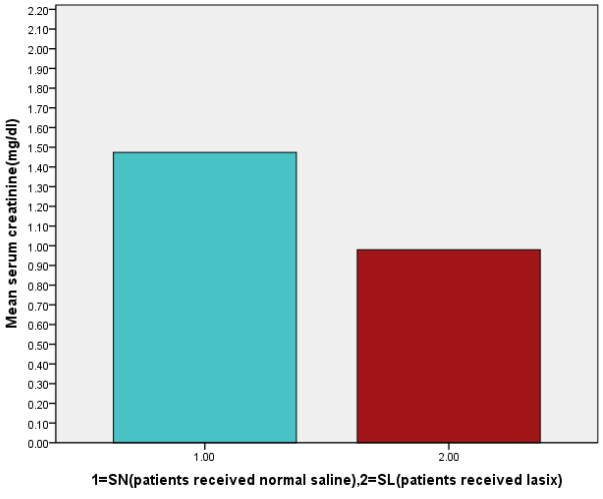


Figure (7): shocked patients received normal saline versus shocked patient received Furosemide in sense of serum creatinine, there is significant statistical difference (p=0.001).

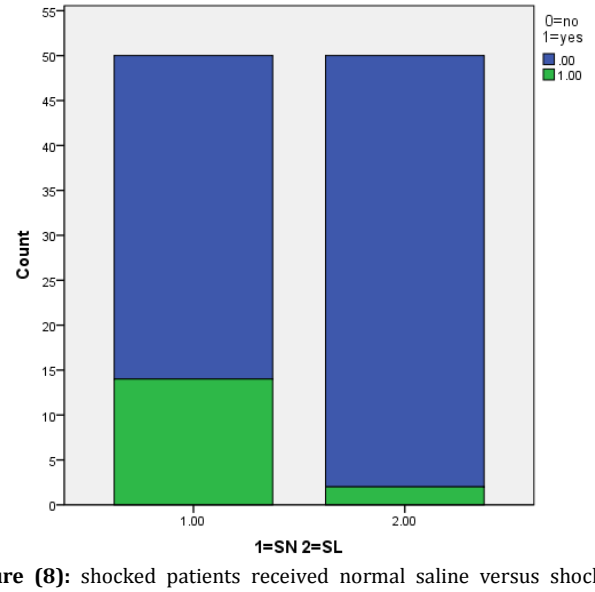


Figure (8): shocked patients received normal saline versus shocked patients received Furosemide in terms of ICU admission, there is significant statistical difference(p=0.001).

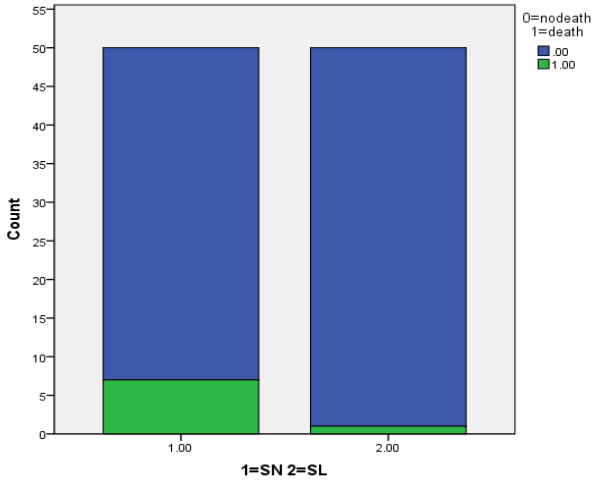
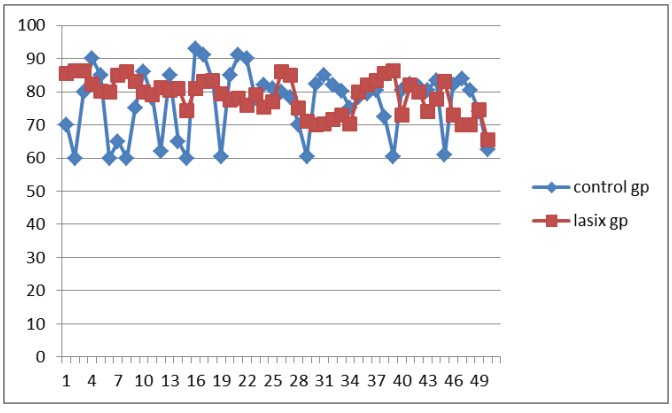
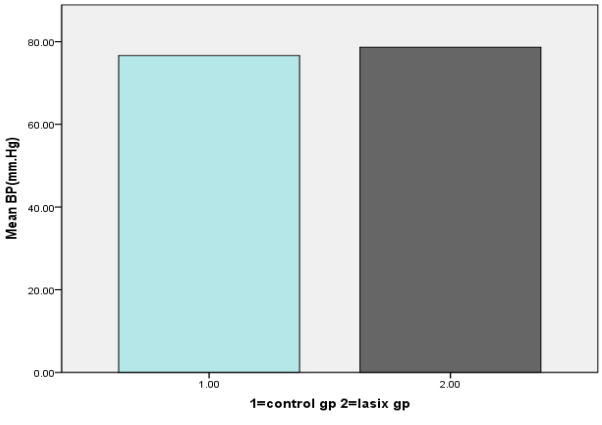


Figure (9): shocked patients received normal saline versus shocked patients received Furosemide in terms of mortality rate, there is significant statistical difference (p=0.013).



Figure(10): shocked patients received normal saline group versus shocked patients received furosemide group in term of mean blood pressure, there is no significant statistical difference(p=0.103).



Figure(10A): shocked patients received normal saline group versus shocked patients received furosemide group in term of mean blood pressure, there is no significant statistical difference(p=0.103).

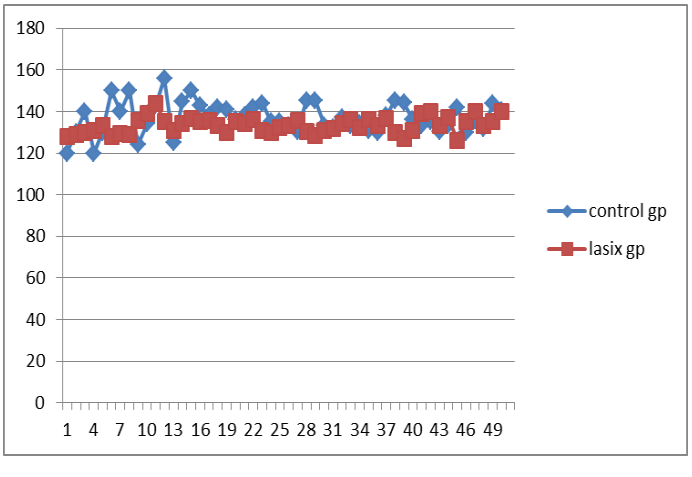


Figure (11): Shocked patients received normal saline group versus shocked patients received furosemide group in term of pulse rate,there is significant statistical diffrence(p=0001).

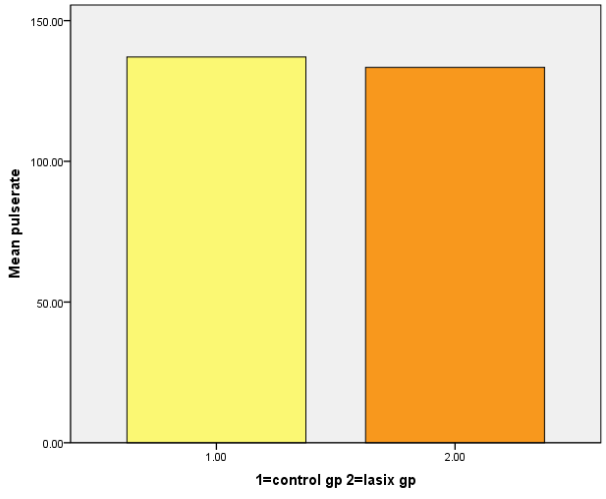
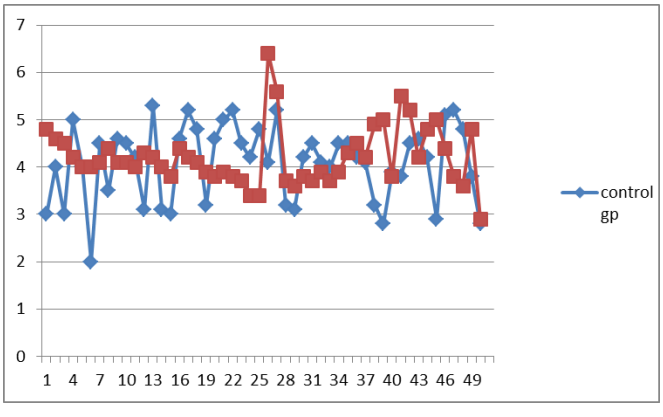
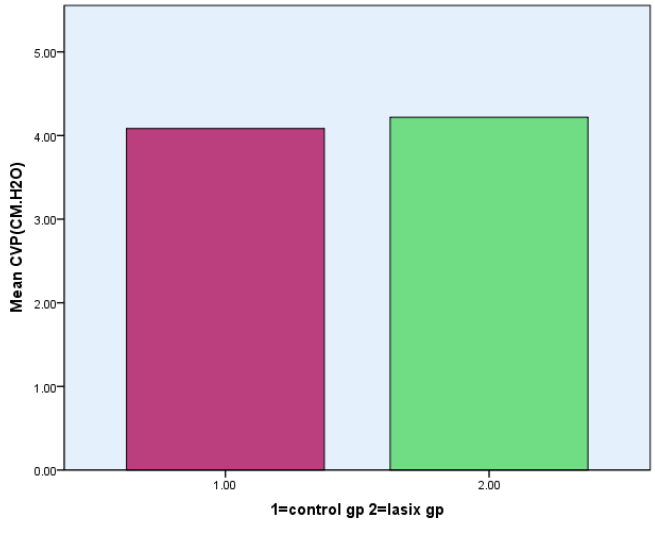


Figure (11A): Shocked patients received normal saline group versus shocked patients received furosemide group in term of pulse rate,there is significant statistical diffrence(p=0001).



Figure(12): Shocked patients received normal saline group versus shocked patients received furosemide group,in term of central venous pressure CVP,there is no significant statistical diffrence(p=0.176).



Figure(12A): Shocked patients received normal saline group versus shocked patients received furosemide group,in term of central venous pressure CVP,there is no significant statistical diffrence(p=0.176).

Discussion

Giving a large volume of fluid in hypovolemic shock is essential to optimize the fluid status but it is difficult to achieve because there is a strong and positive relation between volume overload and adverse outcome especially if the hypovolemic shocked patient has already sepsis [2,3] or acute lung injury ALI [4] or acute kidney injury (AKI)(previously called acute renal failure) [5].

Like any drug or protocol in medicine, furosemide when used to treat fluid overload and edema, it has its specific side effects and risk. Many studies have shown that Furosemide may cause oxidative stress injury and increase renal injury in patients who already has acute kidney injury [6, 7]. However other studies failed to show any incremental risk when using furosemide in patients with acute kidney injury (AKI) [8]. Moreover, some studies proved that furosemide was associated with an increased survival rate in AKI patients [9]. Despite these risks associated with Furosemide, Furosemide still used in more than 50% of patients in ICU [10].

As we mentioned before that the essential steps in the management of the hypovolemic hocked patient are to give crystalloid or colloid fluids to restore the hemodynamic state of the patient toward a normal state and improve the tissue perfusion, but this does not protect the vital organs like kidney, heart and the brain. So giving furosemide to the shocked patient after fluid resuscitation (positive fluid balance PFB) is a method to protect the kidney against acute kidney injury. Giving fluids to the shocked patient is usually associated with volume overload and this volume overload is usually associated with many detrimental effects and a worse outcome like acute kidney injury, acute lung injury, ventilator support, and prolonged ICU stays [11,12]. The extent and the duration of volume overload are associated with high morbidity and mortality rates. There are two methods to treat this volume overload either using diuretics or ultrafiltration.

In our study, the mortality rate in the study group (Furosemide group) was 2% versus 14% in the control group. This finding is similar to the finding of Yanfei Shen, Weimin Zhang, and Yong Shen. They did their trial 0n 7828 patients, all those patient were in shock and they were critical patients admitted to ICU and they were on vasopressor support, they gave loop diuretic to 1469 patient and they do not give any diuretic to 6359 patient and they found the mortality rate is less in the diuretic group(166/1469 versus 1171/6359) and p<0.001 [13]. They also found that giving diuretic to positive fluid balance patients was associated with a significantly reduced mortality rate(Odd ratio was 0.65 and p=0.001) but not in patients with negative fluid balance, this is similar to our finding where we gave Furosemide immediately after fluid resuscitation(patients with positive fluid balance).

Ghassan Bandak and his colleagues did a single-centered retrospective study on 939 patients whose median age was 68. All those patients were admitted to ICU and they were on vasopressor support. They divided the patients into two groups, the group received loop diuretic and the second group does not receive loop diuretic, they found the urine output increased in the diuretic group compared to the non-diuretic group (81ml/hr versus 42 ml/hr respectively, p<0.001)in the first 6 hours. They found also the incidence of acute kidney injury within 7 days after using diuretic were similar in both study and control group [86(15.6%) versus 83(19.6%), p=0,11]. The need for renal replacement therapy (RRT) was also similar between the two groups [34(8%) versus 37 (8.7%),p=0.69].[14]

Wang and his colleagues did his multicenter prospective trial on 2562 critical hemodynamically unstable patients; all those patients were admitted to RCU. 1172 patients develop acute kidney injury (AKI), while the rest do not. They found that the mean of fluid balance in the AKI group was 2.77 versus 0.93 in the non-AKI group with p<0.001 so they conclude that fluid overload is an independent risk factor in critically ill patients for AKI and fluid overload increase the severity of AKI with Odd ratio of 4.5 and p<0.001. They also found that the mortality rate is 25.7% in the AKI group while it is low (10.1%) in the non-AKI group. So they recommend treating this volume overload with loop diuretics or CRR [15].

Didier Payen and his colleagues did their observational multicenter study on 3147 patients, 1120 patients (36%) develop acute renal failure ARF

while the rest 2027 not, during their 60day staying in ICU. They found the 60-day mortality rate was 36% in the ARF group and 16% in the non-ARF group with p<0.001. Also, they found that oliguric patients who need renal replacement therapy (RRT) had a higher 60-day mortality rate than patients without oliguria or need for RRT(41%versus33% and52% versus32% respectively with p<0.001. They conclude that positive fluid balance was an important factor associated with an increased 60-day mortality rate and the outcome among patients treated with RRT was better when RRT started early in course of RCU staying [5].

Conclusion

Giving furosemide to a Critically ill shocked patient after initial fluid resuscitation (positive fluid balance) is associated with a decrease rate of RCU admission and a decrease in the mortality rate in the first 5 postoperative days.

Recommendation

In any shocked patients start fluid or blood resuscitation then give Furosemide to enhance diuresis in patients with positive fluid balance.

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Conflicting Interest
No conflict of interest.

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