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EFFECT OF ONLINE HEMODIAFILTRATION ON PATIENTS WITH SEPSIS AND ACUTE KIDNEY INJURY IN INTENSIVE CARE UNIT

By

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ABSTRACT

Background: Acute kidney injury is a common occurrence in critically ill patients, with incidence rates of occurrence varying from 5 to 60% and a trend towards higher rates (30 to 60%) when using the risk, injury, failure, loss of kidney function, end stage renal failure (RIFLE) or Acute Kidney Injury (AKI) Network (AKIN) classification.

Objective: To compare between effect of online hemodiafiltration and conventional hemodialysis in patients with sepsis and acute kidney injury in intensive care unit.

Patients and Methods: This study included forty (age and sex matched) patients with acute kidney injury (AKI) who were critically ill they were selected from the Nephrology Unit Ahmed Maher Teaching Hospital. The included patients were divided into two equal groups: Group (A) that included patients on online hemodiafiltration (OLHDF) and Group (B) that included patients on conventional hemodialysis.

Results: There was a statistically significant difference found between two groups after dialysis regarding HB, WBCs, platelet, Na and albumin. Also, there was high statistically significant difference between two groups regarding urea, creat, K and PCT, and there was no statistically significant difference between the two groups regarding CRP.

Conclusion: OL-HDF showed to be better than IHD-LI in many aspects but there was no statistically significant difference in mortality.

Keywords: Online Hemodiafiltration, Acute Kidney Injury, Intensive Care Unit.

INTRODUCTION

Acute Kidney injury occurs in a variety of settings, and has clinical manifestations ranging from a minimal elevation in serum creatinine levels to anuric renal failure. In fact, AKI exists along a continuum of disease: the acute decline in kidney function is often secondary to an injury that causes functional or structural changes in the kidneys. As the severity of the underlying renal injury increases, the risk of unfavorable outcome rises *(Zhang, 2015)*.

Sepsis is the body's response to infection. Sepsis is 'severe' when infection leads to organ dysfunction or failure. Septic shock is present when infection causes acute circulatory failure

that leads to persistent hypotension despite adequate fluid resuscitation. The sepsis syndrome is no longer seen just as a disorder of uncontrolled inflammation; it is regarded more as a syndrome reflecting loss of balance between pro-inflammatory and anti-inflammatory mediators resulting in organ damage and development of the multiple organ dysfunction syndrome with its associated high mortality *(Azkarate et al., 2015).*

Sepsis syndrome can occur with or without acute kidney injury (AKI; formerly known as acute renal failure (ARF)). Renal replacement therapy (RRT) is necessary in about 6% of critically ill patients, according to a large multinational, multicenter survey, and it is provided as supportive treatment to AKI patients, preventing additional disorders (hypervolemia, metabolic acidosis, progressive uremia, and hyperkalemia) *(Azkarate et al., 2015).*

Online hemodiafiltration (OL-HDF) is a mixed technique that combines a standard hemodialysis diffusive transport with a significant amount of convective transport, thus provides a greater clearance of medium and large molecular-size, which is difficult to remove by diffusion alone. This technique requires a biocompatible high flux and permeability membranes, as well as precise machines with ultrafiltration control and ultrapure dialysate fluid for replacement. There is a high economic impact in OL –HDF implementation, so it is necessary to know the real benefits for applying *(Darío et al., 2017).*

In Egypt, continuous renal replacement therapy (CRRT) is not widely available, so that patients are treated with SLED, IHD-LI or IHD-HI or intermittent OL-HDF and there are no comparative studies about benefits between the procedures so this study is developed in order to consolidate and choose the best procedure adapted to developing countries.

The aim of this study was to compare between effect of online hemodiafiltration and conventional hemodialysis in patients with sepsis and acute kidney injury in intensive care unit.

PATIENTS AND METHODS

This prospective study that was conducted on forty patients with age and sex matched with Acute Kidney Injury (AKI) and critically ill at ICU and Nephrology Units, Ahmed Maher Teaching Hospital, after taking the approval of the ethical committee of internal medicine department. Informed consent was taken from all patients included in the study.

Patients into 2 equal groups: Group (A) included patients with AKI on online hemodiafiltration (OLHDF), their ages ranged between 26 and 58 years with a mean of 44.85 ± 7.89 years. 14 of them were males and 6 were females. They received OL-HDF with mixed replacement (pre and post dilutional) therapy. **Group (B)** included patients with AKI on conventional hemodialysis, their ages ranged between 29 and 58 years with a mean of 44.15 ± 7.70 years. 13 of them were males and 7 were females.

Inclusion criteria: Patients aging16 years or more, patients presenting with a critical illness who developed acute kidney injury either at presentation or after admission and AKI as defined according to the AKIN criteria (AKIN-III).

Exclusion criteria: Age < 16 years, patients with chronic kidney disease including ESRD who are on renal replacement therapy (RRT) and patients who have malignant diseases.

All patients were subjected to the following: Full history taking from patients if possible or from relatives. Complete clinical examination. Basal laboratory work-up:(serum creatinine, Blood Urea, URR, S. Na, S. K, S. Albumin, Complete Blood Picture, C. Reactive protein S. Procalcitonin, Blood culture and sentivity test When indicated). Dialysis related clinical complications especially: Intradialytic Hypotension and arrhythmias. Mortality Rate of patients in this study. Intensive Care Unit (ICU) Stay of patients. Acute Physiology and Chronic Health Evaluation Score (APACHE II Score) The Quick sequential organ failure assessment score (qSOFA score).

Test for PCT (BRAHMS PCT-Q) was using immunochromatographic technique. A colored band appeared 30 minutes after application of 200 µL serum or plasma with the intensity of the band read against a reference card. The results were reported as < 0.5, 0.5 – 2.0, 2.0 –10 and >10 µg/L.

For serum samples, blood was collect in a tube without anticoagulant and was allowed to clot. Serum was separated from blood as soon as possible to avoid hemolysis. Only clear, non-hemolyzed specimens were used. Testing was performed immediately after the specimens have been collected. The blood was stored at 2ºC to 8ºC for up to three days if the tests cannot be performed immediately.

Ethics and patient consent: All procedures followed Al-Azhar University ethical committee regulations, and written consents were taken from patients or relatives.

Financial support: No financial support.

Statistical Analysis:

All data were subjected to revision and validation then description and analysis on IBM-compatible PC by using SPSS (Statistical Package for the Social Sciences) program version 22.0.0, Microsoft Office Excel 2007, and Graph Pad Prism 6. Descriptive statistics were performed for all studied parameters in the three studied groups and were presented in the form of mean, median, standard deviation (SD), range, and percentages. Analytical comparison between different groups was done by using student t test, Mean-Whitney U test. Chi-square test was used to component numbers. P value < 0.05 was considered significant.

RESULTS

The number of studied cases was 40 cases, including 28 males by 67.5% and 13 females by 32.5%, with an average age of 44.50 and a standard deviation of 7.70, and the lowest age of patients was 26 years and the oldest was 58 years **(Table 1)**.

Table (1): Distribution of the studied cases according to age, sex, cause and blood culture

Parameters	All Cases	No.= 40
Age (years)	Mean ± SD	44.50 ± 7.70
	Range	26 – 58
Sex	Female	13 (32.5%)
	Male	27 (67.5%)
Cause of AKI	Ischemic	5 (12.5%)
	Septic	27 (67.5%)
	Toxic	8 (20.0%)
Blood Culture	None detected	29 (72.5%)
	Gram Positive	11 (37.9%)
	Gram Negative	18 (62.1%)

There was no statistically significant difference found between two groups regarding HB, WBCs, platelet, urea, creat, URR, Na, K, albumin, PCT and CRP **(Table 2)**.

Table (2): Comparison between pre conventional hemodialysis group and pre online HDF group

Parameters	Groups	Conventional hemodialysis	Online HDF	P-value
		No.= 20	No.= 20	
HB (gm/dl)	Mean ± SD	10.22 ± 1.63	11.17 ± 1.64	0.074
	Range	7.8 – 13.4	9 – 15	
WBCs (10^3)	Mean ± SD	11.69 ± 3.97	13.81 ± 3.36	0.076
	Range	5.2 – 17.8	10.2 – 20	
Platelets (/microliter)	Mean ± SD	193.75 ± 68.84	235.60 ± 105.35	0.145
	Range	122 – 358	168 – 503	
Urea (mg/dl)	Mean ± SD	51.24 ± 10.83	53.64 ± 17.80	0.610
	Range	32.5 – 67	33 – 86.3	
Creat (mg/dl)	Mean ± SD	5.86 ± 1.63	6.71 ± 1.30	0.076
	Range	2.7 – 9.7	5.3 – 9	
URR	Mean ± SD	31.71 ± 16.56	38.35 ± 11.49	0.148
	Range	7.07 – 53.65	25.9 – 59.33	
$S.Na^+$ (mg/dl)	Mean ± SD	137.80 ± 1.62	138.75 ± 2.98	0.218
	Range	135 – 140.6	135.1 – 145	
$S.K^+$ (mg/dl)	Mean ± SD	7.42 ± 1.29	7.82 ± 0.96	0.266
	Range	5 – 9.7	6.4 – 9	
S.Albumin (g/dl)	Mean ± SD	3.40 ± 0.31	3.67 ± 0.56	0.070
	Range	3 – 3.9	2.9 – 4.5	
PCT (ng/ml)	Mean ± SD	0.53 ± 0.22	0.65 ± 0.24	0.095
	Range	0.1 – 0.9	0.2 – 1	
CRP (mg/dl)	Mean ± SD	9.57 ± 5.71	11.87 ± 7.52	0.284
	Range	2 – 20	2.3 – 25	

There was a statistically significant difference found between two groups regarding HB, WBCs, platelet, Na and albumin, urea, creat, K and PCT, and there was non-statistically significant difference found between two groups regarding CRP **(Table 3)**.

Table (3): Comparison between post conventional hemodialysis group and post online HDF group

Parameters \ Groups		Conventional hemodialysis No.= 20	Online hemodialysis No.= 20	P-value
HB (g/dl)	Mean ± SD	10.63 ± 0.92	11.45 ± 1.29	**0.025**
	Range	9 – 11.7	9 – 13.4	
Wbcs (10^3)	Mean ± SD	8.01 ± 2.37	9.45 ± 1.93	**0.042**
	Range	4.2 – 12	4.3 – 11	
Platelet (/microliter)	Mean ± SD	200.7 ± 69.1	245.60 ± 78.42	**0.049**
	Range	132 – 424	157 – 424	
Urea (mg/dl)	Mean ± SD	22.64 ± 4.69	42.29 ± 12.43	**0.000**
	Range	15.9 – 32.5	21 – 71	
Creat. (mg/dl)	Mean ± SD	6.22 ± 1.41	3.94 ± 0.4	**0.000**
	Range	3.5 – 9.5	3.5 – 4.7	
Na (mEq/L)	Mean ± SD	139.54 ± 4.37	136.86 ± 2.25	**0.019**
	Range	135 – 154	132.5 – 141.1	
K (mEq/L)	Mean ± SD	3.79 ± 0.7	5.28 ± 0.82	**0.000**
	Range	3 – 5.5	3.5 – 6.5	
Albumin (g/dl)	Mean ± SD	3.2 ± 0.27	3.42 ± 0.3	**0.025**
	Range	3 – 3.9	3 – 3.9	
PCT (ng/ml)	Mean ± SD	0.92 ± 0.20	0.38 ± 0.16	**0.000**
	Range	0.5 – 1.3	0.1 – 0.7	
CRP (mg/dl)	Mean ± SD	10.21 ± 5.28	13.07 ± 7.24	0.162
	Range	2 – 20	4 – 25	

There was a statistically significant difference found between two groups regarding intradialytic hypotension and intradialytic arrhythmia, and non-statistically significant difference for mortality, ICU stay APATCHE II Score and qSOFA Score **(Table 4)**.

Table (4): Comparison between Conventional hemodialysis group and online HDF group regarding intradialytic hypotension and intradialytic arrhythmia, mortality and ICU stay, APATCHE II Score and qSOFA Score

Parameters \ Groups		Conventional hemodialysis		Online HDF		P-value
		No.	%	No.	%	
Intradialytic hypotension	Negative	5	25.0%	12	60.0%	**0.025**
	Positive	15	75%	8	40.0%	
Intradialytic arrhythmia	Negative	4	20%	11	55.0%	**0.022**
	Positive	16	80%	9	45.0%	
Mortality	Negative	9	45.0%	11	55.0%	0.527
	Positive	11	55.0%	9	45.0%	
ICU stay	Prolonged	11	55.0%	8	40.0%	0.342
	Reduced	9	45.0%	12	60.0%	
APATCHE II Score	Mean ± SD	30.55 ± 4.09		29.89 ± 3.3		0.578
	Range	23.2 – 37.5		23.4 – 36.2		
qSOFA Score	Mean ± SD	0.3 ± 0.47		0.2 ± 0.41		0.478
	Range	0 – 1		0 – 1		

There was a statistically significant negative correlation between PCT (pre) and urea (pre), and between PCT (post) and creat (post) and CRP (post) **(Table 5)**.

Table (5): Correlations between PCT Pre and Post with age, HB, WBCs, platelet, urea, creat, URR, Na, K, albumin, APATCHE II score, qSOFA score and CRP in online hemodialysis group

Parameters \ Groups	Online hemodialysis (Pre)		Online hemodialysis (POST)	
	PCT		PCT	
	R	P-value	r	P-value
Age	-0.330	0.156	0.035	0.884
HB	0.295	0.206	-0.402	0.079
Wbcs	0.026	0.914	-0.043	0.858
Platelet	-0.194	0.412	-0.265	0.258
Urea	**-0.562**	**0.010**	0.248	0.291
Creat	0.270	0.250	**-0.467**	**0.038**
URR	-0.171	0.472	-0.011	0.963
Na	0.012	0.960	-0.086	0.718
K	-0.223	0.345	-0.117	0.623
Albumin	-0.318	0.172	-0.190	0.422
APATCHE II Score	0.292	0.212	-0.366	0.113
qSOFA Score	0.000	1.000	-0.243	0.303
CRP	0.115	0.630	**-0.637**	**0.003**

DISCUSSION

Acute kidney injury (AKI) is one of the most important complications during hospitalization, especially in critically ill patients. Recent data demonstrated that certain biomarkers including pro-inflammatory cytokines are associated with high morbidity and mortality *(Peerapornratana et al., 2019)*.

These biomarkers, most of which have middle molecular weight, and protein-bound uremic toxins are limitedly removed by diffusion mechanism in conventional hemodialysis *(Eloot et al., 2016)*.

Hemodiafiltration (HDF), a new modality that combines convective clearance with diffusion, could effectively enhance removal of middle molecule and protein-bound solutes. Therefore, HDF is increasingly used in several AKI settings such as septic AKI, rhabdomyolysis-associated AKI, myeloma cast nephropathy, and contrast-induced AKI *(Canaud et al., 2018)*.

Our study revealed no a statistically significant difference between the two groups regarding age, sex and blood culture. There was statistically significant difference found between two groups regarding intradialytic hypotension and intradialytic arrhythmia which comes in agree with *Masakane et al. (2017)* on comparing HDF and HD, serum ß2-m and albumin levels changed and this may be explained.

This was in contrary to *Jean et al. (2015)* in his study who don not confirm any hemodynamic advantage of HDF. These findings are not consistent with results from studies by *Schiffl et al. (2013)* who concluded that better preservation of RRF by high efficiency hemodiafiltration is not associated with left ventricular hypertrophy and *Locatelli et al. (2010)* who concluded that compared with conventional HD, convective therapies (HDF and HF) reduce ISH in long-term dialysis patients. Additionally, the ESHOL study reported fewer hypotensive episodes in the HDF group *(Maduell et al., 2013)*, especially when higher convective volumes were achieved, as reported by *Mora-Bravo et al. (2012)*.

Similarly, *Jean et al. (2015)* found no difference in blood pressure for HDF in association with intracellular or extracellular volume changes during sessions which supports our results. These findings not consistent with results from postdilution HDF *(Schiffl et al., 2013)* and predilution HDF studies *(Locatelli et al., 2010)*. Similarly, no difference in blood pressure was found for HDF in association with intracellular or extracellular volume changes during sessions *(Kumar et al., 2013)*. The favorable impact of HDF on hemodynamic stability is hypothesized to be due to higher sodium mass transfer. The cause of lower dialysis hypotension is avoiding critical blood volume reductions and/or improving cardiovascular compensatory mechanisms.

Our study showed that there was no statistically significant difference between two groups regarding mortality and ICU stay and also no statistically significant difference was found between two groups regarding APATCHE II Score and qSOFA Score. The explanation of these results could be explained by the limited number of cases, insufficient follow-up time, or failure to obtain a suitable

minimum convective volume, issues that should be explored in future studies.

Jimenez et al. (2017) showed that patients with RRT have high mortality (49.2%), similar to those reported in other studies where it reaches up to 70% *(Poukkanen et al., 2015).*

Prevalence in males and severity at admission to ICU are comparable to that reported in similar studies by *Kaukonen et al. (2014), Azkarate et al. (2015)* and *Rama et al. (2016).*

Like our study, *Jimenez et al. (2017)* revealed the severity grade at admission to ICU (APACHE, SOFA score) that showed no statistically significant differences between groups.

As regard to the laboratory data, our study revealed that there was a statistically significant difference found between the two groups after dialysis regarding HB, WBCs, platelet, Na and albumin. Also, there was a statistically significant difference between two groups regarding urea, creat, K and PCT, and there was no statistically significant difference found between the two groups regarding CRP.

Our study showed significant differences between HDF and conventional hemodialysis as regard albumin level. Online with this result, *Ok et al. (2013)* reported lower albumin levels in the low-efficiency HDF of their prospective study.

Movilli et al. (2011) reported the absence of an albumin level decrease during an HDF protocol. The lower serum albumin level observed during the HDF periods could be due to a dialysate albumin loss, as reported previously by *Combarnous et al. (2010)* who observed an albumin loss of 1000–6800 mg/session. *Ahrenholz et al. (2010)* reported a total albumin loss of 300–7000 mg/session, depending on the type of dialyzer used.

In contract, *Den Hoedt et al. (2014)* reported no difference in the rate of change in albumin between the HDF and low-flux HD. As serum albumin decreased mainly in patients with lower convection volume, the relationship between the change in albumin levels and the HDF technique itself remains unclear.

Den Hoedt et al. (2014) found that highly permeable membranes may increase albumin loss and lead to harmful consequences. However, they could not estimate accurately the extent of albumin loss through highly permeable dialysis membranes. This may be the result of improved dietary intake and potential explanation involving the removal of plasma substances that inhibit appetite.

Regarding the small molecule clearance, *Jean et al. (2015)* did not find differences between periods similar to *Movilli et al. (2011)* who also reported no advantage of HDF for urea and creatinine clearance. By contrast, *Movilli et al. (2011)* reported an increase in dialysis dose when using HDF vs. conventional hemodialysis, but higher blood flow rates in the HDF arm may have biased the results.

Pedrini et al. (2019), in a large observational study, confirm better control of anemia during hemodiafiltration which also supports our study.

Besides the modalities of CRRT, the CRRT dose utilized for sepsis-induced AKI is still unestablished. Prescribed and delivered doses of CRRT in AKI vary

widely. Two large, multicenter RCTs were conducted in critically ill patients with AKI to investigate the effects of RRT dose on survival benefit *(Kullaya et al., 2018)*.

In another RCT trial by *Premuzic et al. (2017)*, the randomized evaluation of normal versus augmented level (RENAL) of replacement therapy study of critically ill patients meeting the criteria for initiation RRT was included and randomly assigned to post-dilution CVVHDF with effluent rate of 40 or 25 mL/kg/hr with no statistically significant difference of 90-day mortality between high- and low-dose RRT groups.

Although the higher doses of CRRT are expected to provide more effective inflammatory cytokine removal in sepsis, subgroup analysis of patients with sepsis or organ failure revealed no significant differences in the mortality between the high- and low-intensity *(Kullaya et al., 2018)*.

Also, our study showed a statistically significant negative correlation between PCT and urea pre-dialysis and there was a statistically significant negative correlation between PCT and creatinine post-dialysis.

Regarding the study by *Chun et al. (2019)* correlation analyses showed a positive correlation between PCT and hsCRP, AKI and sepsis.

Nakamura et al. (2015) evaluated the performance of PCT levels in the diagnosis of sepsis in patients with and without renal failure, finding a negative correlation between the levels of PCT and renal function, and suggesting that the kidney could be one of the organs responsible for the elimination of PCT. However, this has not been confirmed by others. Although the molecular weight of PCT is 13,600 Da and therefore, it is ultra-filterable, it doesn't appear to accumulate in renal failure *(Herget et al., 2010* and *Steinbach et al., 2010)*.

CONCLUSION

OL-HDF showed to be better than IHD-LI in many aspects but there was no statistically significant difference in mortality.

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تأثير الإستصفاء الدموي مع الفلترة في مرضى الإعتلال الكلوي الحاد وتسمم الدم في الرعاية المركزة

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خلفيـــة البحـــث: الإعـــتلال الكلـــوى الحـــاد شـــائع الحـــدوث فـــي المرضـــى ذوي الحـــالات الحرجـــة، بمعـــدل يتـــراوح مـــن 5 إلـــى 60 ٪، ويـــزداد الـــى معـــدلات أعلـــى بنســـبة مـــن 30 إلـــى 60 ٪ عنـــد وجـــود عوامـــل خطـــورة، والإصـــابة، وقصـــور بوظائف الكلى، وصولا إلى مرحلة الفشل الكلوي المزمن.

الهـــدف مـــن البحـــث: مقارنـــة تـــأثير الإستصـــفاء الـــدموى عـــالى الكفـــاءة و الفلتـــرة بجلســـات الإستصـــفاء الـــدموى مـــنخفض الكفـــاءة (التقليـــدى) فـــى مرضـــى القصـــور الكلوى الحاد المصاحب للتسمم الدموى.

المرضـــي وطـــرق البحـــث: أجريـــت هـــذه الدراســـة بوحـــدتى الكلـــى و العنايـــة المركـــزة بمستشـــفى أحمـــد مـــاهر التعليمـــى واشـــتملت علـــى أربعـــين مريضـــا يعـــانون مـــن الإعـــتلال الكلـــوى الحـــاد المصـــاحب للتســـمم الـــدموى وتـــم تقســـيمهم إلـــى مجمـــوعتين متســـاويتين: المجموعـــة الأولـــى اشـــتملت مرضـــي تـــم عمـــل جلســـات الإستصـــفاء الـــدموى عبـــر مرشـــحات عاليـــة الكفـــاءة و التـــدفق مـــع الفلتـــرة. والمجموعـــة الثانيـــة اشـــتملت مرضـــي تـــم عمـــل جلســـات الإستصـــفاء الـــدموى عبـــر مرشحات منخفضة الكفاءة بدون تدفق (الغسيل الكلوى التقليدي).

نتـــائج البحـــث: لا يوجـــد فـــرق إحصـــائي مهـــم بـــين المجمـــوعتين فيمـــا يتعلـــق بالســـن والجـــنس ومزرعـــة الـــدم. والفـــرق الإحصـــائي الهـــام بـــين مجمـــوعتين فيمـــا يتعلـــق بـــنقص ضـــغط الـــدم بـــين الـــدم وعـــدم انتظـــام ضـــربات القلـــب. لا يوجـــد فـــرق مهـــم إحصـــائياً بـــين المجمـــوعتين فيمـــا يتعلـــق بالوفيـــات والإقامـــة فـــي وحـــدة العنايـــة المركـــزة. وكـــان هنـــاك فرقـــاً مهمـــاً إحصـــائياً بـــين مجمـــوعتين بعـــد غســـيل الكلـــى

فيما يتعلق بالهيموجلوبين وكرات الدم الحمراء والصفائح الدموية والصوديوم، وأيضاً كان هناك فرق كبير إحصائياً بين مجموعتين فيما يتعلق باليوريا والبوتاسيوم.

الاستنتاج: أظهر إستخدام المرشحات عالية التدفق نتائج أفضل من المرشحات التقليدية في العديد من الجوانب، ولكن لم يكن هناك فرقاً كبيراً إحصائيا في معدل الوفيات، مما يسمح لنا أن نوصي كخيار أول بإستخدام المرشحات عالية التدفق من العلاج المقترح للمرضى المصابين بأمراض خطيرة مع إصابات الكلى الحادة.

الكلمات الدالة: الاستصفاء الدموى عالي الكفاءة، القصور الكلوى الحاد، وحدة العناية المركزة.