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RESEARCH PAPER

Impacts of Gadolinium-Based MRI contrast Agent on Hematological and Biochemical Tests for the Human Volunteers.

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A B S T R A C T:
Magnetic resonance imaging (MRI) Gadolinium-Containing contrast agents are used in combination with MRI in some situations. The effects of gadolinium-based MRI contrast agent (MAGNEVIST® Gadopentetate Dimeglumine Injection Bayer Standard 469 mg/ml (0.5 mmol/ml) on some hematological and biochemical tests for human male volunteers have been investigated. The study consisted of nine healthy individuals of human male volunteers; they were injected with intravenous (IV) contrast without being exposed to MRI. The cases are divided into four subgroups based on how long and how many times of blood samples were withdrawn after the intravenous (IV) contrast injection (9, 25, and 40 minutes). Blood samples were examined for twenty-seven hematological and biochemical parameters. The results proved that; after 9 min of injection with IV contrast, the WBCs count, LYM, MID%, and ALT decreased by 6%,6%, 4%, and 5%, respectively, and the concentration of GRA% and ESR increased by 5%. 25min after injection, concentrations of PLT increased significantly ($P < 0.05$) by 4%, PCT %, LPCR %, MID, and ESR are increased non-significantly ($P > 0.05$) by 4%, 5%, 7%, and 26%, respectively. After 40min of injections; MID, and MID% increased by 11% and 12%, respectively, and AST decreased by 4%. The maximum rise in ESR was increased by 31%. There was no substantial variation with time can be seen in electrolytes; Sodium (Na^+), Potassium (K^+), and Chloride (Cl^-) under the effect of the intravenous contrast injection.

KEYWORDS: MRI; Contrast Materials; Hematological and Biochemical tests; Radiobiology.
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1. INTRODUCTION:

Magnetic resonance imaging (MRI) is a commonly used technology in clinical diagnostics that uses a static magnetic field (1.5–7T), Switching gradients of the magnetic field and radio-frequency (RF) electromagnetic radiation are used to produce images of the tissues and organs of interest (Uosef et al., 2020).

In some cases to improve the clarity of the images of the body's internal structures, MRI Gadolinium-Containing Contrast Agents that have magnetic properties are used in combination with magnetic resonance imaging (MRI), For example, visibility of inflammation, tumors, and blood vessels, and, for some organs, blood supply, and infectious diseases of the brain, spine, soft tissues and bones (Ferris and Goergen, 2016). According to international reports, over 40% of 1 billion global MRI scans are of gadolinium-based contrast agents (GBCAs), accounting for roughly 50 tons of Gadolinium (Gd) injected annually for clinical investigations (Marasini et al., 2020). Conditions

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that might mean a gadolinium injection would not be recommended (e.g. pregnancy, severe kidney disease, and previous allergic reaction). If you have any of these conditions, then you will not be given gadolinium (Ferris and Goergen, 2016).

Gadolinium is a ductile rare-earth element significantly paramagnetic above 20°C (68°F). These paramagnetic properties allow the solutions of chelated organic gadolinium complexes to be used as contrast agents for MRI (Uosef et al., 2020) Carr et al demonstrated the use of a gadolinium compound as a diagnostic intravascular MRI contrast agent for the first time in 1984 (Xiao et al., 2016). By 1988, gadopentetate dimeglumine (Magnevist®) was the first commercially available MRI contrast agent to be used clinically (Lohrke et al., 2016). Via electron-proton dipole interaction the contrast agents used in MRI are capable of changing the relaxation. When compared to other metal ions, Gd, a paramagnetic metal ion with seven unpaired electrons in the outermost shell and a large gyromagnetic moment (7.94 mB), is effective in reducing the T_1 relaxation time of hydrogen atoms, allowing quicker imaging with greater picture clarity (Marasini et al., 2020).

Adverse events of Gd chelates can be categorized into two groups: nonallergic reactions (e.g., fatigue, headache, taste perversion, arthralgia, flushed feeling, vomiting, or nausea) and idiosyncratic allergy-like reactions (e.g., diffuse erythema, hives, chest tightness, respiratory distress, and periorbital edema. Acute reactions to MRI CM are usually classified as mild, moderate, and severe. They are occurring at a rate between (0.07% and 2.4%., 0.004%–0.7%, and 0.001%–0.01%) respectively (Granata et al., 2016). The studies on rats showed that gadolinium accumulated in rat organs and tissues (Myrissa et al., 2017, Lohrke et al., 2017). In humans, the accumulation of gadolinium in the brain after the repeated administration of some kind of gadolinium-based MRI contrasts was especially strong in the Globus pallidus and the dentate nuclei (Ramalho et al., 2015, Stojanov et al., 2016, Murata et al., 2016, Moser et al., 2018, Kobayashi et al., 2021). They have reported gadolinium retention in the brain, especially high in the Globus Pallidus, of pediatric patients (Flood et al., 2017, Stanescu et al., 2020). The study identified gadolinium as the primary risk factor with the strongest association with nephrogenic systemic fibrosis (NSF) (Marckmann et al., 2006, Grobner, 2006, Abu-Alfa, 2011). In humans, there are reports of encephalopathy developing after the administration of a gadolinium-based MRI contrast (Hui and Mullins, 2009). There is also the accumulation of gadolinium in the bones reported (Rogosnitzky and Branch, 2016, Ramalho et al., 2016, Kobayashi et al., 2021). The present study is the first trial to evaluate the effects of medical contrast materials on some hematological and biochemical parameters for some volunteers undergoing MRI exams.

This study investigates the effects of medical contrast materials (MAGNEVIST® Gadopentetate Dimeglumine Injection Bayer Standard 469 mg/ml (0.5 mmol/ml) on some hematological and biochemical tests. The hematological tests (Complete Blood Count (CBC) and Erythrocyte Sedimentation Rate (ESR)) and biochemical tests (alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), Uric acid (Ua), Electrolyte (Sodium (Na+), (Potassium (K+), and Chloride (Cl-)) are carried out in this study.

2. MATERIALS AND METHODS

2.1. Materials and Equipment

volunteer participants consisted of nine healthy individuals male volunteers, and their ages of them ranged between (29 – 33) years old with their body mass index (BMI) ranging between (22.09 – 33.6) Kg / m^2 (Table 1)

Table (1): Age and BMI of individuals' male volunteers in the study

Case No.	Age (years)	BMI (kg/m^2)
1	32	28.34
2	29	24.14
3	30	22.09
4	32	33.6
5	33	22.64
6	33	22.3
7	29	24.5
8	32	32.72
9	32	28.4

2.2. Experimental Procedures

The contrast injection procedure was done in the Rania radiology center; about 5mL of blood was withdrawn from the vein of a volunteer's hand before (control) and after injection with IV contrast (cases) for various duration times (Table 2). The IV contrast was administered via cannula according to their weight (0.2mL/kg) in (70 ± 50 sec.). The blood samples were withdrawn from the volunteers after 9, 25, and 40 minutes of injection with IV contrast. And the cases were distributed to Subgroups A, B, C, and D as listed in (Table 2).

Table (2): Distribution of the cases regarded of withdrawal blood samples after the injection of IV contrast

Subgroup	Case No.	Status of blood withdrawal	
A	1 & 2	before IV contrast injection as a control for each subgroup	9 min after IV contrast injection
B	3 & 4		25 min after IV contrast injection
C	5 & 6		40 min after IV contrast injection
D	7,8 and 9		9, 25, and 40 min after IV contrast injection

2.3. Blood Samples Collections

Blood samples of the individuals were collected (5 mL of blood each time). 2 mL of blood was poured into the EDTA tube to prevent coagulation. Hematological parameters (CBC) were measured directly by the Swelab alfa hematology analyzer. 1.5 mL of blood samples were poured into the Westergren tube to measure the ESR rate during falling blood level for 1 hour (Abdulla et al., 2022), and the measurements were done in the lab of the dialysis center in Rania. On the other hand, 1.5 mL of blood was poured into Gel and Clot Activator tube to measure biochemical parameters and was left for 15 minutes up to be clotted, and it is inserted into a centrifuge till the serum was separated from the blood and the serum was poured into a plain test tube and it was kept in to box which the ice pack placed in under a temperature ($3\pm1\ C^0$) (Ismail et al., 2021) the serum samples analyzed after 3 hours in the lab of Rania teaching hospital to measure biochemical parameters using equipment of FUJIFILM DRI-CHEM NX500i analyzer.

2.3. Hematological parameters

The measured hematological parameters in each blood sample before and after injection intravenous medical contrast included; blood cells (WBC in count × 10^9/L), lymphocytes (LYM in %), Monocytes (MID in %), granulocytes (GRAN in %), lymphocytes (LYM in count ×10^9 /L), Monocytes (MID in count ×10^9/L) granulocytes (GRAN in count ×10^9 /L), red blood cells (RBC in count ×10^{12}/L), hemoglobin (HGB in g/dL), hematocrit (HCT in %), mean corpuscular volume (MCV in fL), mean corpuscular hemoglobin (MCH in pg), mean corpuscular hemoglobin concentration (MCHC in g/dL), red blood cell distribution width (RDW in %), red blood cell distribution width (RDWa in fL) platelet count (PLT in count ×10^9 /L), mean platelet volume (MPV in fL), plateletcrit (PCT IN %), and platelet larger cell ratio (LPCR in %), In addition, the Erythrocyte Sedimentation Rate (ESR).

2.4. Biochemical parameters

Seven Biochemical parameters were measured in each blood sample before and after injection with intravenous medical contrast such as; VI namely (Uric acid (Ua), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), Electrolytes (Sodium (Na^+), (Potassium (K^+), and Chloride (Cl^-)).

3. RESULTS AND DISCUSSION

The results of the measured (Average ratio ±SDV) hematological and biochemical parameters are listed in Table 3. Variations of the parameters with the duration time (time of remaining IV contrast materials in volunteers' blood: time after injection) were not homogenous due to the body mass index for each case and individual responses of the cases were different, and this agreement with the essential of hematological and biochemical responses (Abdulla et al., 2022).

The percentage of change of WBC counts and its indices in response to the time after intravenous contrast injection shown in (Figure 1), counts decreased after 9 min of IV contrast injection by 6%. Also, the lymphocytes decreased

at the same time by 6%. The effect of IV contrast material on MID% can be seen at 9 and 40 min after injection which declined by 4% at 9 min after injection and raised by 12% after 40 min of injection. The average ratio of MID increased dramatically at 25 min and 40 min after injection by 7%, and 11%, respectively. The average values of LYM%, GRAN, and GRA % after injection with IV contrast were non-considerable affected except the GRA% after 9min of injection increased by 5%

Table (3): The effect of contrast material on hematological and biochemical tests according to time

Parameters	Average ratio effects (Average ratio ± SDV)		
	9 min After Contrast injection / Before contrast injection	25 min After Contrast injection / Before contrast injection	40 min After Contrast injection / Before contrast injection
WBC (× 10^9/L)	0.94±0.07	1.01±0.08	0.98±0.03
LYM %	0.99±0.03	1.00±0.04	1.01±0.08
MID %	0.96±0.27	1.00±0.25	1.12±0.41
GRA %	1.05±0.13	1.00±0.05	1.00±0.10
LYM (× 10^9/L)	0.94±0.09	1.03±0.07	0.99±0.11
MID (× 10^9/L)	1.02±0.43	1.07±0.37	1.11±0.44
GRAN (× 10^9/L)	0.98±0.12	1.00±0.07	0.98±0.11
RBC (× 10^12/L)	0.99±0.03	0.98±0.02	1.00±0.05
HGB (g/dL)	0.98±0.02	0.99±0.02	0.99±0.05
HCT %	0.99±0.03	0.98±0.03	0.99±0.05
MCV (fL)	1.00±0.00	1.00±0.00	1.00±0.01
MCH (pg)	0.99±0.02	1.01±0.02	1.00±0.01
MCHC (g/dL)	0.99±0.02	1.01±0.02	1.00±0.01
RDW %	0.99±0.02	0.99±0.01	0.99±0.02
RDWa (fL)	1.00±0.02	1.00±0.03	0.99±0.02
PLT (× 10^9/L)	0.99±0.05	1.04±0.02	0.98±0.09
MPV (fL)	1.00±0.03	1.00±0.02	0.99±0.04
PCT %	0.99±0.08	1.04±0.03	0.97±0.08
LPCR %	1.02±0.14	1.05±0.13	0.97±0.15
ESR (mm/hrs.)	1.05±0.41	1.26±0.62	1.31±0.78
Uric acid (mg/dL)	0.98±0.03	0.99±0.03	1.01±0.04
AST (U/L)	1.03±0.10	1.03±0.11	0.96±0.10
ALT (U/L)	0.95±0.14	1.01±0.17	1.00±0.07
ALP (U/L)	0.97±0.04	0.98±0.06	0.98±0.03
Na^+ (mEq/L)	0.99±0.01	1.00±0.01	0.99±0.01
K^+ (mEq/L)	1.01±0.07	1.03±0.05	1.03±0.14
Cl^- (mEq/L)	1.00±0.01	1.00±0.02	1.00±0.03

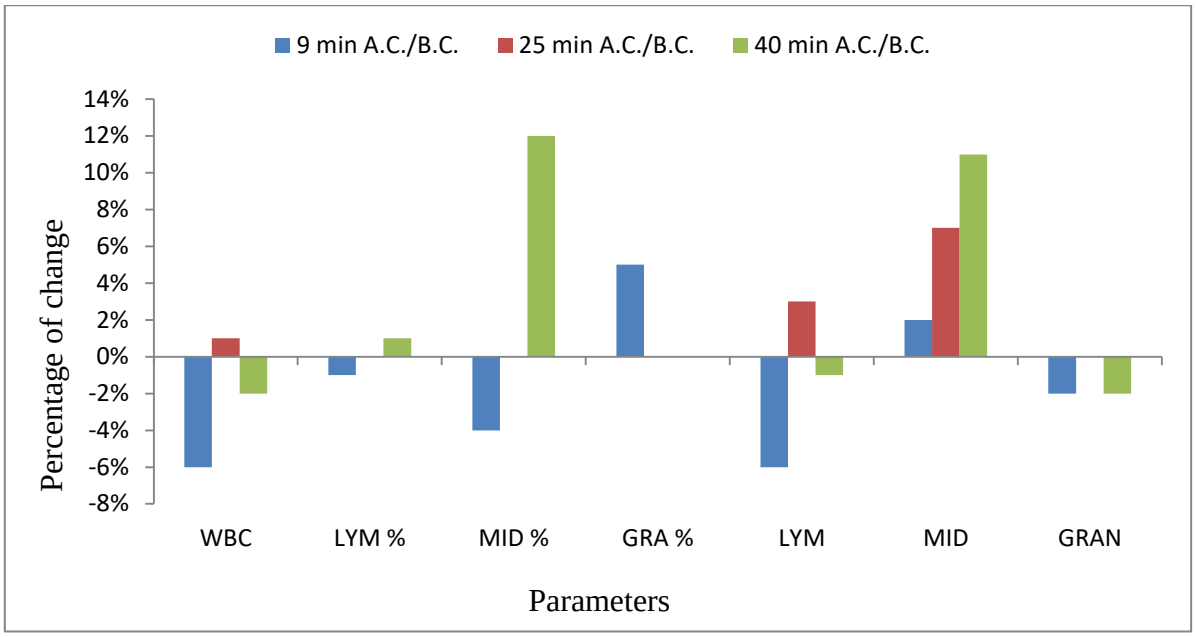

Figure 1: Percentage of change of (WBC) count and its indices in response to the time after contrast injection: A.C. and B.C are the after and before injection with IV contrast, respectively.

The percentage of change of RBC and its indices are displayed in (Figure 2), the IV contrast injection didn't have a considerable effect on RBC counts and its indices, there are non-considerable variations in RBC parameters, and all parameters are almost unchangeable according to the time after IV contrast injection due to the insensitive of RBC cells to the IV medical contrast materials.

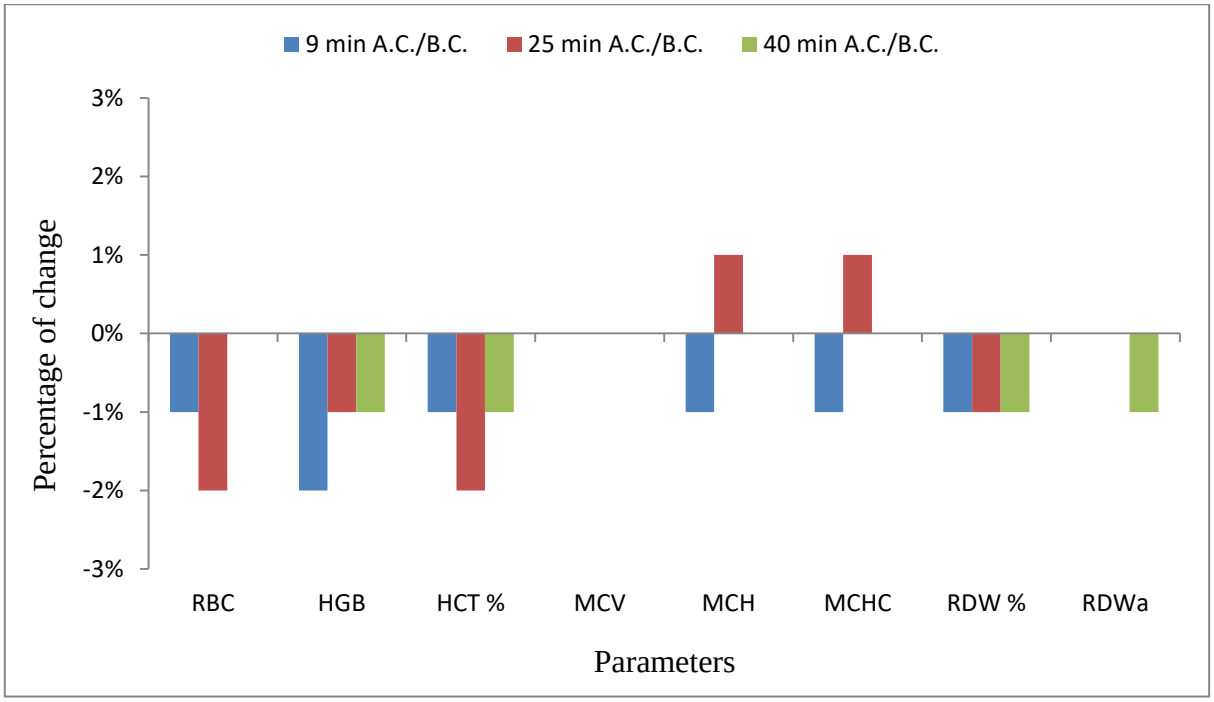

Figure 2: Percentage of change of RBC cell and indices in response to the time after contrast injection: A.C. and B.C are the after and before injection with IV contrast, respectively.

The percentage of change of PLT and its indices in response to time after IV contrast injection are displayed in (Figure 3). PLT cells were increased significantly ($P < 0.05$) by 4% due to the effect of contrast after 25 min of injection. After 25 min of injection PCT %, and LPCR %

increased by 4%, and 5%, respectively. The contrast injection didn't have a sizable effect except that described above.

The percentage of change of ESR in response to the time after IV contrast injection showed in (Figure 3). The effects of IV contrast on ESR increased dramatically as the time after injection increased, ESR average ratio increased by 5%, 26%, and 31% after 9, 25, and 40 min of injection respectively due to the impacts of IV contrast on the blood viscosity.

(Figure 5) shows the percentage of change of biochemical parameters in response to time after contrast injection. The average ratio of ALT, and AST varied and decreased by 5%, and 4% at 9min, and 40 min after IV contrast injection respectively. The average ratios of other parameters (Ua, ALP, Na^+, K^+, and Cl^-) were almost not affected by the IV contrast injection.

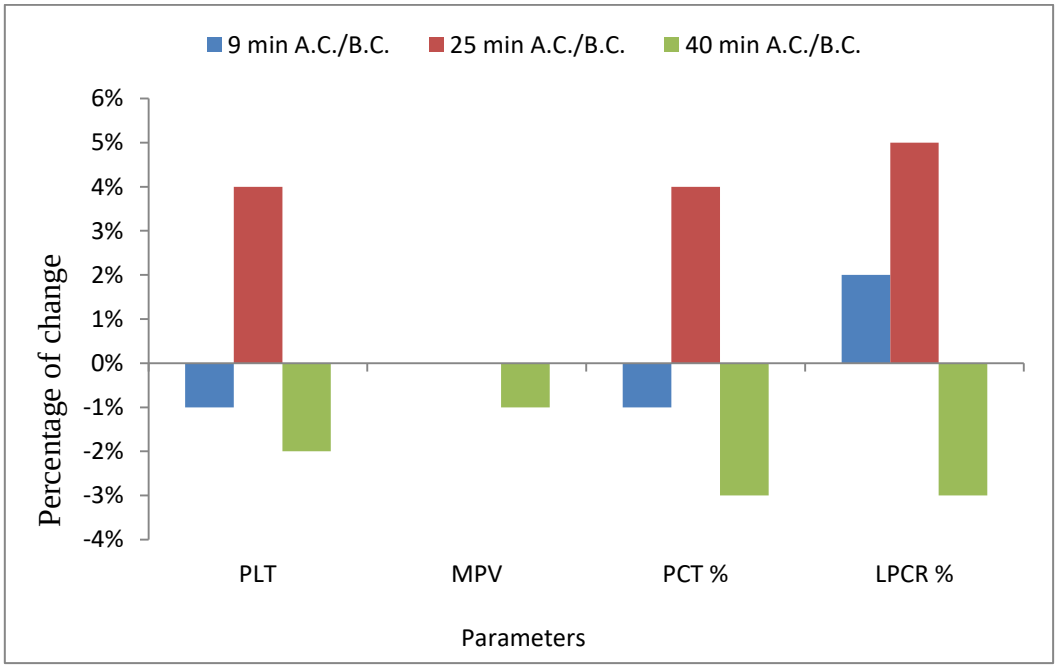

Figure 3: Percentage of change of PLT values and indices in response to the time after contrast injection. A.C. and B.C are the after and before injections with IV contrast, respectively.

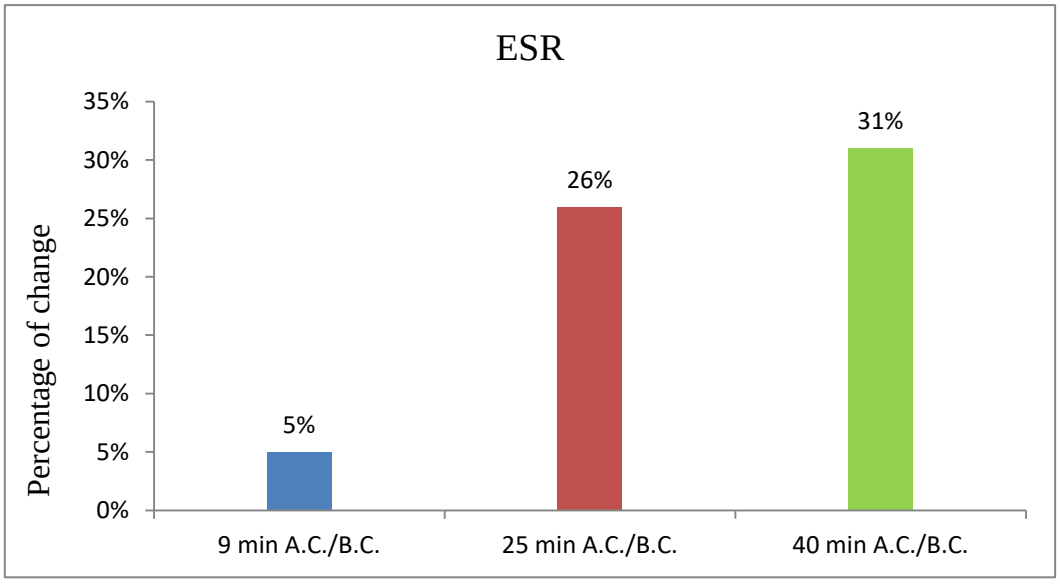

Figure 4: Percentage of change of ESR in response to the time after contrast injection. A.C. and B.C are the after and before injections with IV contrast, respectively.

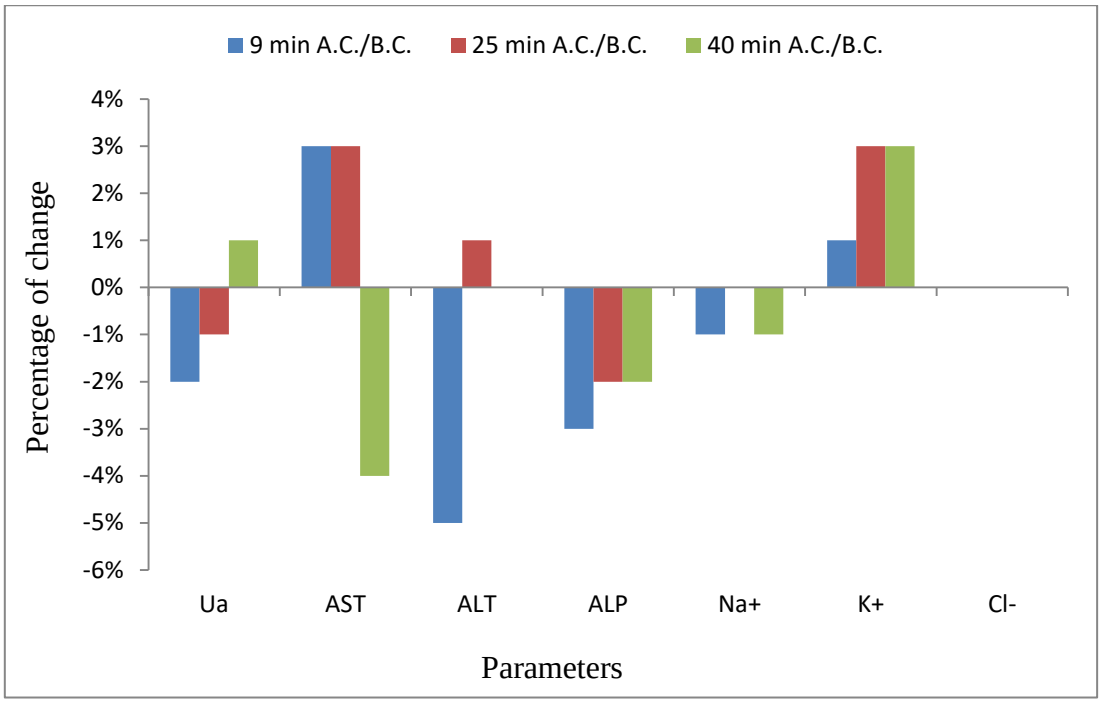

Figure 5: Percentage of change of biochemical parameters in response to time after contrast injection. A.C. and B.C are the after and before injections with IV contrast, respectively.

4. CONCLUSIONS

The impacts of the IV contrast injection on the hematological and biochemical parameters have been investigated for different periodic times (minutes). Time periodic after contrast injection has affected the hematological and biochemical parameters relativity. Increasing and decreasing the main parameters (GRA%, MID, MID%, PLT, LYM, WBC, PCT%, LPCR%, ESR, AST, and ALT) depended on the selected periodic time (after contrast injection) of 9, 25, and 40 minutes, The average ratios of other hematological and biochemical parameters except that described above were almost not affected by the IV contrast injection.

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Conflict of Interest (1)

The authors have not any conflicts interesting.

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