Comparison Between eGFR by Schwartz Formula with Measured GFR by Radionuclide Diethylenetriamine Pentaacetic Acid Scan (Tc99 DTPA scan), in Patients Undergoing Chemotherapy with Nephrotoxic Drugs

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Keywords. GFR, malignancy, chemotherapy, nephrotoxic

Introduction. Children with malignancy who are under treatment with nephrotoxic drugs are at risk of renal dysfunction. Due to increased life expectancy, evaluation of drug toxicity is now of higher importance than before. The aim of this study is to compare two methods of GFR measurement.
Methods. An analytical study on children with malignancy undergoing chemotherapy with nephrotoxic drugs (cisplatin, carboplatin, cyclophosphamide, ifosfamind, etoposide) during 2016 and 2017 in Mofid Children Hospital was done. Demographic information, anthropometric measurements, type of malignancy, type of chemotherapy medication and also lab tests including CBC and the biochemistry indices were recorded. The GFR of each patient was calculated using Schwartz formula and DTPA scanning. The rates were compared and the difference was analyzed statistically.
Results. According to Schwartz formula, 24% of patients needed dose adjustment, while based on DTPA scanning, this rate was 6%. Comparing these two measures by paired T-test, showed a significant statistical difference ($P < .05$). Schwartz formula had 25.5% more positive results of predicting the need for dose adjustment. The two measured GFRs for each person were evaluated in terms of compatibility and correlation based on Kappa statistical method, which were incompatible and had significant difference ($P < .05$).
Conclusion. Using evaluative methods including Schwartz formula cannot demonstrate renal dysfunctions reliability in patients taking nephrotoxic chemotherapy drugs. Eventually if the GFR measurement method overestimates patients with renal dysfunction, the patients will not be able to make adequate use of the therapeutic effects of chemotherapy with the appropriate dosage.

IJKD 2020;14:463-9
www.ijkd.org

Original Paper

INTRODUCTION

Children with malignancy under treatment with nephrotoxic chemotherapy are at risk of renal dysfunction, which its incidence, studied carefully in two cohort studies (2007 and 2010), has been 50 to 53% of patients.[1,2,3] Renal dysfunction will directly cause delay in drug excretion, increased drug level in blood (more than expected) and increased systemic toxicity.[3-5] There has been great progress in recovery and final outcome of chemotherapy

protocols recently. Many of patients with low life expectancy in the past will now return to their normal life.[1] Due to increased life expectancy, evaluation of drug toxicity, including nephrotoxic chemotherapy drugs in children with malignancy is now of greater importance than before, which might affect growth and development of children in long-time.[1] Chemotherapy drugs cause kidney dysfunction such as AKI, tubulointerstitial disease, endothelial injury, electrolyte imbalance and acid/base disorders.[4-6] They often have a limited therapeutic index, makes the decision-making about the protocol and dosage administration difficult.[6] The most common drugs used in children are cisplatin (CIS), ifosfamide (IFO), carboplatin, cyclophosphamide (CPM) and etoposide (VP16).[5] The renal complications of cisplatin are directly related to the dosage and are the result of apoptosis and cellular necrosis. Its nephrotoxicity is usually reversible. However, there is a risk of permanent damage that eventually causes tubular dysfunctions, which can cause oxidative stress, arterial damage, ischemia, and reduced GFR.[7]

Compared to Cisplatin, Carboplatin forms less and weaker binding with plasma proteins, and therefore has a longer final half-life. Carboplatin nephrotoxicity is linked to the dosage and often accompanied by hypokalemia, hypomagnesemia, and renal dysfunction together with increased level of urea and creatinine.[7,8] Cyclophosphamide nephrotoxicity complications include acute tubular necrosis (ATN) with less reported prevalence compared to hemorrhagic cystitis.[7] The most common manifestations of ifosfamide nephrotoxicity are proximal tubulopathy and diabetes insipidus (DI). Ifosfamide in high doses can cause tubular dysfunction and hemorrhagic cystitis in 20 to 40% of cases.[1,7,9] Etoposide is a semi-Synthetic chemotherapy drug. Within 1 to 3 days after administration, proteinuria and reduced GFR will occur.[7] Despite strategies used to reduce the nephrotoxicity of chemotherapy drugs includes adequate hydration and alkaline diuresis, nephrotoxicity is inevitable in some patients.[10] Evaluating renal function through measuring GFR is one the most important and practical methods which is necessary before starting treatment, during the treatment, in the intervals of chemotherapy cycles and in follow-up sessions.[1,5] Glomerular filtration Rate (GFR) is the most accurate index to evaluate renal function.[2] The type of chosen method of GFR measurement in children with malignancy who are under chemotherapy is the topic of discussion and studies. Measuring GFR based on serum creatinine level is the easiest and most practical method.[11] In this method "Schwartz formula" is applied. The formula is as follows:

GFR (mL/min/1.73m^2) = (K) (height in cm) / serum Creatinine (mg/dL)[11]

In this formula, height is a criterion of muscular mass. "K" in infants under one year of age with LBW and infants under one year and in young children is respectively 0.35, 0.45, and 0.55. This number for female and male patients in pubertal age is 0.55 and 0.7, respectively.[12,13]

Another method to evaluate GFR is using ^{99m}Tc-DTPA scan. Technetium 99 is an organic and soluble material. Considering that it also provides a renogram and a differential functional scheme of each kidney. This method needs no urine and blood collection.[11] We designed this research to study and compare two GFR calculation methods; Schwartz formula and ^{99m}Tc-DTPA scan; and to determine the appropriate method of GFR measurement in children treated with chemotherapy. Eventually if the GFR measurement method overestimates patients with renal dysfunction, the patients will not be able to make adequate use of the therapeutic effects of chemotherapy drugs with the appropriate dosage.

MATERIALS AND METHODS

This is an analytical study on children from one month to 14 years old with malignancy who were candidates for chemotherapy with nephrotoxic drugs (cisplatin, carboplatin, cyclophosphamide, ifosfamind, and etoposide) that were hospitalized in 2016 and 2017 in hematology-oncology ward of Mofid Children Hospital. They had no renal dysfunction prior to starting the course of chemotherapy. The exclusion criteria includes: untreated recent UTI, urolithiasis or any kind of obstructive uropathy (UPJO and etc.), diabetes, hypertension, any renal structural disease other than Wilms, chronic kidney disease, children undergoing dialysis, arterial or cardiac disease, shock or sepsis, decreased intra-arterial volume, ketosis, hyperbilirubinemia, and hyperglycemia. Finally, 52 children with different malignancies (leukemia, lymphoma, wilms, etc.) were chosen, 2 of which

were excluded (UPJO and chronic kidney disease). Fifty patients were entered in the study with the informed consent from their parents. Demographic information, anthropometric measurements, type of malignancy, type of chemotherapy medication and lab tests including CBC and the biochemistry results were recorded. Next, the GFR of each patient was calculated using Schwartz formula and DTPA scanning.

In the next step, the GFR measured through each method were compared and the difference was analyzed statistically. We studied the GFR based on each method and the necessity of dosage adjustment according to each method.

The link between dosage adjustment by each method and demographic data, underlying malignancy, abnormalities of lab tests were analyzed. All the tests (CBC and biochemistry) were carried out to the laboratory center of Mofid hospital. DTPA scanning with technetium 99 was performed in a nuclear scanning center. In order to calculate the GFR of each patient using Schwartz method, all of the patients' height was measured and registered by one person using one measuring equipment. Data was entered in SPSS software. Paired T-test, Kappa, and Chi-square tests were used to analyze the data.

RESULTS

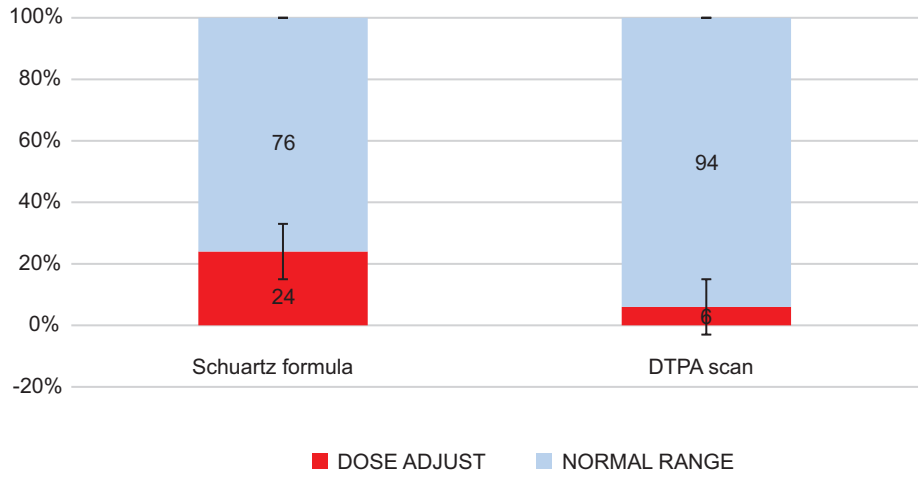
Fifty patients (60% male) with malignancy, candidate for chemotherapy with nephrotoxic drugs in the years 2016 and 2017 were entered in the study. The average age was 68 months (13 months to 11 years). The average weight of the patients was 19.8 kg. The average weight-for-age z-score was -1.3 in females and -1.2 in males. The average height of the patients was 108 cm. The average height-for-age z-score was -1.7 in female patients, and -2.3 in male patients. According to the initial diagnosis, the cases included 68% ALL, 12% lymphoma (B-cell, T-cell, Pre B-cell), 14% Wilms' tumor and 6% other malignancies (urethral sarcoma,AML). The type of nephrotoxic chemotherapy drug in the order of frequency was Cyclophosphamide 46%, ifosfamide 16%, etoposide 14%, carboplatin 14%, and cisplatin 10%.

Results of laboratory tests:

- 40% leukopenia and 4% leukocytosis
- 22% neutropenia
- 50% anemia according to normal ranges for their age
- 30% thrombocytopenia and 4% thrombocytosis
- 2% hyponatremia and 2% hypernatremia
- 34% hypokalemia
- 26% hypophosphatemia
- 6% Hypouricemia

The average GFR by Schwartz method was 74.22 and by DTPA scanning was 92.26. According to Schwartz formula, 24% of patients needed dosage adjustment, while based on DTPA scanning, this number was reduced to 6% (Figure). Comparing these two measures by paired T-test, showed a significant statistical difference (P value $\leq .05$). According to statistical analysis, Schwartz formula had a 25.5% more need for dosage adjustment.

The two measured GFR methods for each person were evaluated in terms of compatibility and correlation based on Kappa statistical method, which



Adjustment in Patients Based on the GFR Measurement by 2 Methods of Schwartz and DTPA scan

were incompatible and had statistical difference ($P \leq .05$). Leukocytosis in patients who needed dosage adjustment based on Schwartz method was higher than the patients with normal GFR. Chi-square method showed a significant statistical difference in terms of leukocytosis ($P \leq 0.05$).

The chi-square test demonstrated no significant statistical relation between the need for adjustment in Schwartz method and the type of underlying malignancy. According to the GFR measured by DTPA scan, 42.9% of the patients with Wilms' tumor needed dosage adjustment. In other types of underlying malignancy, there was no need for changing the dosage of nephrotoxic drugs according to this method. Chi-square statistical test showed a significant statistical relation ($P \leq .05$). According to chi-square test, there was no significant statistical link between the type of chemotherapy drug and the need for adjustment based on Schwartz formula, neither did DTPA scan.

It needs to be pointed out that gender, age and other demographic data of the patients had no statistical impact on the adjustment in any of the GFR measurement methods.

DISCUSSION

Using Schwartz formula is obviously very simple and handy in practice. There is no need for repeated blood sampling and 24-hour urine collection. Reliability of this method needs to be taken into consideration, since it is both laboratory and operator dependent. Height measurement especially in young children is difficult because they tend not to cooperate. In acute lymphoblastic leukemia and other patients with malignancy there is growth hormone deficiency;[14] considering the fact, height deficit of these children is inevitable, affecting GFR measurement formulas including Schwartz method.[15,16] Using creatinine level is another factor, which can reduce the accuracy of this calculation in children under chemotherapy. Many factors are involved, such as: normal level of creatinine in the initial stages of glomerular and tubular dysfunction[2,6,8]; change in creatinine level in patients after chemotherapy due to decreased intravascular volume because of complications such as polyuria, nausea and vomiting and not receiving enough liquid as a result of anorexia[3,16]; changes in creatinine level in patients on chemotherapy in acute stages during treatment due to excessive fluid therapy which is prescribed in order to prevent complications such as tumor lysis syndrome[17]; inaccurate measurement of serum creatinine level because of cachexia and reduced muscle mass of the children under chemotherapy[18]; false increase in the measurement of creatinine level as a result of taking specific drugs such as hydroxyurea[18,19]; height is used as a factor of muscle mass in Schwartz formula in children but considering inevitability of growth hormone disturbances and growth deficiency, GFR measurements will be affected using constant number of K compatible with the patient's muscle mass using Juffe method for creatinine measurement showed higher levels than the actual level, most probably in cases of extremely elevated creatinine.[20] In a study by Ghanesharbaf *et al.* in 2017 with the purpose of evaluating appropriate methods for diagnosis and prevention of chemotherapy nephrotoxicity, the reliability and characteristics of different GFR measurement methods were evaluated. Based on the results of this study, GFR has to be measured and compared before, during and after finishing the courses of chemotherapy. In the Results of this article, GFR measurement using Schwartz formula, despite being used on a routine basis in chemotherapy patients, is known to be unreliable and the estimated GFR is higher than the real measurement.[5] In the study by Interiano *et al.* in 2017 for evaluating long-term renal dysfunction in Wilms patients under chemotherapy, the GFR was measured by Schwartz formula and DTPA scan and then compared with each other. In their study, the average GFR measured by Schwartz formula was higher than the average GFR measured by DTPA scan. Despite the fact that the results of the two above mentioned GFR measurement methods were different in these patients, the statistical results and discussion of the study indicates that Schwartz formula is adequate for evaluation of GFR in these patients, and the difference in GFR in the two methods has not been statistically significant.[21] The number of samples in Interiano's study has been fewer than those used in our study. Their study was carried out only on bilateral Wilms' tumor patients and other malignancies such as lymphoma and leukemia were not studied. Based on the results of our study, Wilms' tumor has had a significant impact on GFR measurement by DTPA scan. The GFR has been lower and drug

adjustments were higher as a result. The results of this study are not statistically compatible with ours, as the difference has been significant in our study based on statistical studies.

In the study by Salek *et al.* in 2015 comparison of GFR measurement by DTPA scan with that of Schwartz formula before chemotherapy was done. In this study, the average GFR measured by Schwartz formula was significantly higher than that of DTPA. Statistical analysis in this study indicates a significant difference in the GFR measurement by DTPA scan and other GFR measurement methods.[22] In the study by Bernhardt *et al.* in 2015, a retrospective review was carried out with the purpose of determining the diagnostic accuracy of the three methods of Schwartz formula, Counahan-Barratt equation, and modified Schwartz formula in measuring the GFR of children with cancer. The result of this study showed that none of the three formulas were able to measure the accurate GFR in these children. The average difference of the GFR measured by modified Schwartz and the correct value of GFR was the lowest. For the original Schwartz formula, variables of age and history of chemotherapy drugs were the predictive factors of error in GFR measurement.[23] It is obvious that the results of this study were the same with those of ours and overestimated the GFR measured by Schwartz formula.

Inou *et al.* carried out a study in 2014 with the purpose of studying GFR measurement methods based on creatinine in patients under chemotherapy. In this study, based on statistical analysis, the more muscle mass patients had lost during the course of chemotherapy that resulted in the lower 24-hour creatinine level, the more overestimation was occurred in GFR measured by Schwartz formula, and in fact the difference with the real GFR was higher.[24] The Results and Discussion of this article suggest that none of the above-mentioned methods can be suitable for evaluation of renal function in patients under chemotherapy. This study is compatible with ours; however, it introduces no better method to predict and evaluate the renal function of patients with higher accuracy. The study by Gibson *et al.* in 2013 was a retrospective review with the purpose of early diagnosis of renal dysfunction by DTPA scan in patients whose measured GFR by Schwartz formula was in normal range. In this study, first the GFR was measured using Schwartz formula in patients. If it was normal, DTPA scan was performed, so DTPA scan was not performed for patients with abnormal GFR measured by Schwartz formula.[25] This study contradicts ours in that respect. In our study the average measured GFR using Schwartz formula was lower than that of DTPA, and DTPA scan was performed for all patients including those with normal and reduced GFR.

In the study by Dias *et al.* in 2013, the purpose was to evaluate GFR indirectly using MDRD and CKD-EPI and determining its link with the results of DTPA scan. The results indicate that GFR evaluation formula had shown GFR underestimation compared to nuclear method. This study recognize using serum creatinine for GFR measurement at the bedside was not a suitable method, especially in patients in whom renal dysfunction was probable and chemotherapy dosage adjustment seemed to be necessary.[26] The statistical results of this study were compatible with those of ours. In the study carried out by Hartlev *et al.* in 2012[27] with the purpose of evaluating the renal function of patients with malignancy during the course of chemotherapy, GFR measurement was done through calculation of Cr EDTA plasma clearance and compared with the GFR measured by Cr EDTA plasma clearance. According to the Conclusion of this study, plasma creatinine level is not an accurate and suitable method to evaluate patients' renal function, especially in patients under chemotherapy, which is similar to our conclusion. In this study, EDTA is suggested as the best method for evaluating GFR in patients with critical conditions such as patients with malignancy.[27] Based on the results of our study and the mentioned studies above, except for that of Interian *et al.*, using GFR measurement methods including Schwartz formula cannot demonstrate renal dysfunctions reliably. Eventually if the GFR measurement method overestimates patients with renal dysfunction, the patients will not be able to make adequate use of the therapeutic effects of chemotherapy with the appropriate dosage. Practically and clinically, there are more interfering factors. Patients undergoing chemotherapy, due to opportunistic bacterial and fungal infections, are often under treatment with nephrotoxic antibiotics including aminoglycosides, vancomycin and amphotericin B. Moreover, administration of antalgic medications such as

NSAIDs, and also anti-acids such as proton-pump inhibitors (PPI) and other medications such as allopurinol for hyperuricemia during the courses of chemotherapy is inevitable. Some of these patients receive radiotherapy or undergo various radiological studies using radioactive iodine, all of which aggravates reduced renal function.[28] Some of underlying malignancies directly result in reduced renal function such as Wilms and kidney parenchymal infiltration and glomerulopathy such as leukemia and lymphoma.[16] Among the lab data, the only parameter, which made a significant statistical difference, was leukocytosis, which was higher in patients in need of dosage adjustment by Schwartz method. So that leukocytosis can be a predicting factor in overestimation of GFR by Schwartz formula.

All the above factors are suggested to study in the future in order to evaluate their accurate effects on different GFR measurement methods.

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Received June 2020
Revised August 2020
Accepted September 2020