Comparison of Rapid Hydration and Standard Hydration Prior to Ifosfamide Administration in Pediatric Patients: A Safety and Efficacy Study

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OBJECTIVES Adequate hydration status prior to chemotherapy initiation prevents nephrotoxicity in patients receiving potentially nephrotoxic regimens. The purpose of this study was to evaluate the time to initiation of ifosfamide administration between patients receiving standard 6-hour pre-hydration versus 1-hour rapid pre-hydration.

METHODS A retrospective study was conducted to determine the primary endpoint of time to ifosfamide administration. Patients 1 to 21 years of age who received ifosfamide with standard 6-hour pre-hydration (125 mL/m²/hr for 6 hours) between September 2017 and January 2018 or 1-hour rapid pre-hydration (750 mL/m²/hr for 1 hour) between September 2018 and March 2019 were included. Secondary endpoints included the incidence of hemorrhagic cystitis, incidence of acute kidney injury (AKI), urine specific gravity, amount of time that ifosfamide was delayed from the originally scheduled administration time, the number of times ifosfamide was delayed greater than 4 hours from the originally scheduled administration time, and length of stay.

RESULTS A total of 128 patients were included; 68 patients received standard 6-hour pre-hydration and 60 patients received 1-hour rapid pre-hydration prior to ifosfamide administration. Time to ifosfamide administration was reduced from an average of 9.3 hours to 2.4 hours ($p < 0.0001$). There was no incidence of hemorrhagic cystitis or AKI in either group.

CONCLUSIONS The 1-hour rapid pre-hydration protocol significantly reduced the time to ifosfamide administration without an increase in adverse effects.

ABBREVIATIONS AKI, acute kidney injury; ULN, upper limit of normal; UOP, urine output; SCr, serum creatinine

KEYWORDS chemotherapy; hydration; ifosfamide; nephrotoxicity

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Introduction

Rapid pre-hydration protocols prior to administration of nephrotoxic chemotherapy agents have generated interest over the past several years. Many chemotherapy regimens require patients to meet a urine specific gravity measurement of 1.010 or less prior to the initiation of nephrotoxic chemotherapy agents to ensure adequate hydration status and to minimize nephrotoxicity. The standard 6-hour pre-hydration protocol (125 mL/m²/hr for 6 hours) requires patients to meet a urine specific gravity measurement of 1.010 or less before chemotherapy initiation. If the urine specific gravity measurement is not met, hydration is continued, and urine specific gravity measurements are taken every hour until the patient meets parameters before chemotherapy may be administered. The 1-hour rapid pre-hydration protocol (750 mL/m²/hr over 1 hour) does not require patients to meet specific urine

requirements. Chemotherapy is initiated immediately after completion of pre-hydration. One-hour rapid pre-hydration (750 mL/m²/hr over 1 hour) may provide a safe alternative to minimize time from admission to chemotherapy initiation and prevent chemotherapy administration delays.^{1–4} A few studies^{1–5} have shown that 1-hour rapid pre-hydration decreases length of stay and minimizes the need for chemotherapy administration to be handed-off to multiple nursing shifts while also resulting in no observed increase in the incidence of nephrotoxicity.

In September 2018, our institution changed the pre-hydration protocol prior to ifosfamide infusion from a standard 6-hour pre-hydration of intravenous fluid to a 1-hour rapid pre-hydration (750 mL/m²/hr over 1 hour) of normal saline. The goals were to reduce the time to ifosfamide administration, minimize delays, and reduce the need to check specific gravity measurements. One-hour rapid pre-hydration with other nephrotoxic

Figure. Inclusion and exclusion of patients.

chemotherapy agents, such as cisplatin, cyclophosphamide, and methotrexate, has not been implemented.

At our institution, chemotherapy orders are pre-entered and scheduled 48 hours to 1 week prior to the patient's arrival by the pharmacist. Each order is verified by 2 pharmacists before being compounded. Per our institution policy, any chemotherapy administration that deviates greater than 4 hours from the scheduled time must be deleted from the computer system, retimed, re-entered, and verified by 2 pharmacists to minimize nursing retiming of chemotherapy and associated errors. This process is time consuming and may introduce computer entry-related errors. Reasons for delay in chemotherapy administration typically include patients not meeting urine specific gravity measurement requirements (applicable only to 6-hour pre-hydration), patients arriving late for appointments, nursing responsibilities, and shift changes, during which no chemotherapy would be initiated as a result of the higher chance of distraction-induced errors associated with this time period. While most delays are not greater than 4 hours, there are instances in which chemotherapy needs to be re-entered because of significant delays in chemotherapy administration.

The purpose of this study was to evaluate the time to initiation of ifosfamide administration between patients receiving standard 6-hour pre-hydration (125 mL/m²/hr over 6 hours) versus 1-hour rapid pre-hydration (750 mL/m²/hr over 1 hour). In addition, we evaluated the incidence of hemorrhagic cystitis, incidence of acute kidney injury (AKI), urine specific gravity, amount of time that ifosfamide was delayed from the originally scheduled administration time, the number of times

ifosfamide was delayed greater than 4 hours from the originally scheduled administration time, and length of stay.

Materials and Methods

Study Design and Patients. A retrospective chart review was conducted to determine the primary endpoint of time to ifosfamide administration. Secondary endpoints included the incidence of hemorrhagic cystitis, incidence of AKI, urine specific gravity measurements, amount of time that ifosfamide was delayed from the originally scheduled administration time, the number of times ifosfamide was delayed greater than 4 hours, and length of stay. Patients diagnosed with either rhabdomyosarcoma or Ewing's sarcoma were included if they were 1 to 21 years of age, had been admitted to the pediatric hematology/oncology unit, received ifosfamide (6–9 g/m²/cycle), and received either standard 6-hour pre-hydration from September 2017 through January 2018 or 1-hour rapid pre-hydration from September 2018 through January 2019. Patients were excluded if they had a history of hemorrhagic cystitis or cardiac impairment, had existing renal insufficiency, or were receiving other nephrotoxic chemotherapy agents (Figure).

Definitions. Acute kidney injury was defined by the National Cancer Institute Common Terminology Criteria for Adverse Events in 2017.⁶ Acute kidney injury was established by both AKI and decreased urine output (UOP). Grade 1 AKI was defined as a serum creatinine (SCr) greater than the upper limit of normal (ULN) to 1.5 times ULN. Grade 2 AKI was defined as a SCr greater

Table 1. Baseline Demographics

Variables	Standard 6-Hr Hydration (n = 68)	Rapid Hydration (n = 60)
Age, yr, mean (range)	9.7 (2–21)	11.3 (1–21)
Male, n (%)	39 (57)	34 (57)

than 1.5 to 3 times the baseline or SCr greater than 1.5 to 3 times ULN. Grade 3 AKI was defined as SCr greater than 3 times baseline or greater than 3.0 to 6.0 times ULN. Grade 4 AKI was defined as SCr greater than 6 times ULN. Grade 3 decreased UOP was defined as UOP less than 0.5 mL/kg/hr for 24 hours for infants and UOP less than 500 mL/1.73m² body surface area per day for children. Grade 4 decreased UOP was defined as no UOP for more than 12 hours.

Non-infectious cystitis was also defined using the National Cancer Institute Common Terminology Criteria for Adverse Events. Grade 1 non-infectious cystitis was defined as microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; or new onset of incontinence. Grade 2 was defined as moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia, or incontinence; urinary catheter placement or bladder irrigation indicated; or limits to instrumental activities of daily living. Grade 3 non-infectious cystitis was defined as gross hematuria, transfusion, IV medications, or hospitalization indicated or elective invasive intervention indicated. Grade 4 non-infectious cystitis was defined as life-threatening consequences or urgent invasive intervention indicated.

Data Collection. Patients who received ifosfamide during the periods of September 2017 through January 2018 and September 2018 through January 2019 were retrospectively reviewed using an electronic medical record. Data collection of patients' demographic and clinical data included the following: age, sex, type of hydration, time of start of hydration, time of start of ifosfamide, renal function (SCr at baseline and at end of hospitalization, UOP at baseline, completion of pre-hydration, completion of ifosfamide infusion), urine specific gravity measurements, presence of hemorrhagic cystitis, and total length of stay.

Statistical Analysis. A sample size of 120 patients (60 patients per group) was determined to achieve 90% power to show a significant difference in the time from start of hydration to chemotherapy initiation.

A Mann-Whitney *U*-test was used to assess continuous data, and a Fisher's exact test was used for nominal data. A *p* value of less than 0.05 was determined to be significant.

Results

Patient Characteristics. A total of 128 patients were included in the study; 68 patients received standard 6-hour pre-hydration and 60 patients received 1-hour

rapid pre-hydration prior to ifosfamide administration. Twelve patients were excluded: 11 patients because of age and 1 patient who received concomitant high-dose methotrexate. Baseline characteristics are presented in Table 1. The mean age of patients was 9.7 years in the standard 6-hour pre-hydration and 11.3 years in the 1-hour rapid pre-hydration group. Fifty-seven percent of the population was male in the standard 6-hour pre-hydration group, and 57% were male in the 1-hour rapid pre-hydration group (Table 1). Patients with rhabdomyosarcoma and Ewing's sarcoma are included with ifosfamide doses ranging from 6 to 9 g/m² per cycle. Time to ifosfamide administration was, on average, 9.3 hours in the standard 6-hour pre-hydration group and 2.3 hours in the 1-hour rapid pre-hydration group (*p* < 0.001) (Table 2).

Rapid Hydration. The amount of time that ifosfamide was delayed from the originally scheduled administration time was 3.3 hours in the standard 6-hour pre-hydration group and 1.3 hours in the 1-hour rapid pre-hydration group (*p* < 0.001). Urine specific gravity measurements were statistically different between the groups, with an average of 1.007 in the standard 6-hour pre-hydration group and an average of 1.009 in the 1-hour rapid pre-hydration group (*p* = 0.004). The 1-hour rapid pre-hydration arm had fewer ifosfamide administration delays that were greater than 4 hours from the originally scheduled administration time (i.e., 15 delays in the standard 6-hour pre-hydration group and 1 delay in the 1-hour rapid pre-hydration group; *p* = 0.002). Length of stay was 74.4 ± 31 hours in the standard hydration group and 71.4 ± 30.7 hours in the rapid hydration group (*p* = 0.609).

Adverse Events. There was no incidence of hemorrhagic cystitis or AKI recorded in either group. This study was not powered to detect a difference, since the reported incidence is between 10% and 20%.

Discussion

The 1-hour rapid pre-hydration protocol significantly reduced the time to ifosfamide administration without an observed increase in adverse effects. This prevented chemotherapy from being significantly delayed and allowed the patient to receive chemotherapy sooner. While urine specific gravity measurements were statistically different between the groups, this finding is not clinically relevant since both groups had urine specific gravity measures of less than 1.010.

Our study demonstrated findings similar to those of

Table 2. Results (Mean $\pm$ SD)

Variables	Standard 6-Hr Hydration (n = 68)	Rapid Hydration (n = 60)	p value
Time to ifosfamide administration, hr	9.3 $\pm$ 5.3	2.3 $\pm$ 1.5	< 0.001
Delay of chemotherapy, hr	3.3 $\pm$ 5.2	1.3 $\pm$ 1.5	< 0.001
Incidence of hemorrhagic cystitis, n (%)	0 (0)	0 (0)	
Incidence of AKI, n (%)	0 (0)	0 (0)	
Urine specific gravity measurements	1.007 $\pm$ 0.003	1.009 $\pm$ 0.007	< 0.001
Number of chemotherapy administration delays > 4 hr, n (%)	15 (21.7)	1 (1.7)	0.002
Length of stay, hr	74.4 $\pm$ 31	71.4 $\pm$ 30.7	0.609

other studies that evaluated the 1-hour rapid pre-hydration protocol. Meredith et al⁴ evaluated the implementation of the 1-hour rapid pre-hydration protocol prior to high-dose methotrexate, cyclophosphamide (>500 mg/m²), ifosfamide, and cisplatin infusions. The study evaluated 116 pre-chemotherapy hydration events in pediatric patients, both in the inpatient and ambulatory settings. The 1-hour rapid pre-hydration protocol was found to reduce time from admission to discharge by 26.9 hours ($p = 0.005$) and resulted in more first chemotherapy administrations occurring prior to nursing shift change on the day of admission ($p = 0.002$).⁴ The authors reported that more fluid boluses were required to achieve the urine specific gravity targets in the 1-hour rapid pre-hydration group than in the standard pre-hydration group (32.5% vs 10.2%; $p = 0.009$). Two adverse events in each group related to the hydration received were also noted. Adverse events included hypertension, hypokalemia, and fluid overload/weight gain requiring furosemide.⁴

Ouchi et al⁵ evaluated 30 patients who received short or continuous hydration in chemotherapy regimens containing intermediate- to high-dose cisplatin (≥ 60 mg/m²/cycle). The authors concluded that the short hydration regimen was as safe as the continuous hydration regimen, as there was no difference in AKI between the groups. However, the authors observed that 3 patients in the continuous hydration group and 1 patient in the short hydration group had Grade 2 or higher AKI. One patient in the continuous hydration group discontinued therapy because of nephrotoxicity.⁵

These 2 studies demonstrated that the 1-hour rapid pre-hydration protocol is both safe and effective, and in neither of the studies were any adverse drug reactions observed. While our study was only powered to evaluate the effectiveness of the 1-hour rapid pre-hydration protocol prior to ifosfamide administration, previous studies have demonstrated that 1-hour rapid pre-hydration is both safe and effective in the administration of ifosfamide, cisplatin, cyclophosphamide, and methotrexate.

The strengths of this study include the use of historical controls and adequate patient sample size to detect

a statistically significant finding. Limitations of the study include the retrospective nature of the study and the fact that this study was not powered to evaluate the safety of the 1-hour rapid pre-hydration protocol. In addition, underlying cancer diagnosis and exact doses of ifosfamide were not collected and specifically analyzed. However, all patients had a diagnosis of rhabdomyosarcoma or Ewing's sarcoma and received 6 to 9 g/m² per cycle of ifosfamide. In order to detect a difference in the incidence of hemorrhagic cystitis or AKI, a large prospective trial will need to be conducted.

Conclusions

In spite of the limitations, our study demonstrated that the implementation of a 1-hour rapid pre-hydration protocol decreases time to ifosfamide administration. In the future, our institution plans on evaluating the use of 1-hour rapid pre-hydration protocol prior to use of other nephrotoxic chemotherapy agents. Length of stay was not significantly different because of the required length of stay (usually 4–7 days) for full administration of multiple doses of chemotherapy.

Benefits of rapid pre-hydration include the elimination of urine specific gravity measurements, shorter time to chemotherapy administration, and less nursing time. In addition, the 1-hour pre-hydration protocol is more reliable in predicting the start of chemotherapy and minimizes the need to retime and manipulate chemotherapy orders. More studies with large patient populations are needed to adequately assess the safety of this protocol.

ARTICLE INFORMATION

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the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and has been approved by the appropriate committees at our institution. Given the nature of this study, the institution review board/ethics committee did not require HIPAA Waiver of Authorization, Waiver of Assent, and Waiver of Parental Permission under Exempted criterion.

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