Efficacy of Intralipid infusion in reducing amphotericin-B-associated nephrotoxicity in head and neck invasive fungal infection: A randomized, controlled trial

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Introduction

Amphotericin B, an antifungal agent used to treat systemic fungal infections, is associated with multiple adverse effects, including renal toxicity. This drug can even cause persistent impairment of renal function, which may lead to a significant increase in morbidity and mortality.

Various measures have been undertaken to reduce this adverse effect and to improve the outcomes of patients with invasive fungal infections. These measures include the infusion of intravenous fluids before the infusion of therapeutic agents and the administration of simultaneous diuretics and oral sodium chloride. One of the more important steps in this regard was the introduction of lipid-associated formulations of amphotericin B. These drug formulations have shown the same clinical effectiveness as their original form while causing less renal toxicity. However, they do impose a 10- to 60-fold increase in treatment costs.

The administration of amphotericin B deoxycholate (ABD) with a simultaneous or near-simultaneous fat emulsion (Intralipid) infusion has been proposed as an alternative. It has been shown that this treatment regimen can decrease toxicity by 18.4%. However, the instability of ABD in Intralipid solution can be an issue, since it has been shown that amphotericin can precipitate in Intralipid solution. Theoretically, this can lead to a higher risk of pulmonary embolism.

In this article, we describe our study of Intralipid administered shortly after ABD as a means of decreasing renal toxicity.

Patients and methods

We conducted a randomized, controlled trial of Intralipid infusion shortly after the infusion of ABD to evaluate its effects on reducing ABD-associated nephrotoxicity.

Patients. We enrolled patients with head and neck invasive fungal infections who required intravenous ABD therapy. Patients were recruited from Amir-Alam Hospital and Imam Khomeini Hospital, both of which are affiliated with the Tehran University of Medical Sciences, over a 2-year period. In these patients, fungal disease had been suspected clinically and confirmed by pathologic and microbiologic analysis.

Our exclusion criteria included the presence of pathologic hyperlipidemia, severe hepatic failure or diagnosed cirrhosis, a basal serum creatinine level of greater than 2 mg/dl or more, pregnancy, pancreatitis, and a history of severe anaphylaxis to lipid serums, soya, egg, or ABD. Also, we excluded patients who were receiving less than 7 days of ABD therapy.
Our initial enrollment consisted of 39 patients. Of these, we excluded 8 for various reasons: a baseline creatinine level greater than 2 mg/dl (n = 4), fewer than 7 days of ABD treatment (n = 3), and the presence of cryptogenic cirrhosis (n = 1).

The remaining 31 patients were randomized into two groups: an intervention group (n = 16) and a control group (n = 15). The intervention group was made up of 7 men and 9 women, aged 21 to 77 years (mean: 56), and the control group consisted of 8 men and 7 women, aged 21 to 76 years (mean: 52). There were no statistically significant differences between the two groups in demographic or clinical variables (table 1).

### Table 1. Selected baseline characteristics in the intervention and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>ABD plus Intralipid (n = 16)</th>
<th>ABD alone (control) (n = 15)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean ± SD (range)</td>
<td>55.9 ± 17.5 (21 to 77)</td>
<td>52.2 ± 13.9 (21 to 76)</td>
<td>0.52</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Male</td>
<td>7 (43.8)</td>
<td>8 (53.3)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9 (56.3)</td>
<td>7 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Underlying pathology, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (93.8)</td>
<td>14 (93.3)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (56.3)</td>
<td>9 (60.0)</td>
<td>0.72</td>
</tr>
<tr>
<td>Hematologic disease</td>
<td>1 (6.3)</td>
<td>2 (13.3)</td>
<td>0.60</td>
</tr>
<tr>
<td>Serum creatinine level mg/dl, mean ± SD (range)</td>
<td>1.31 ± 0.38 (0.8 to 1.9)</td>
<td>1.27 ± 0.34 (0.8 to 1.9)</td>
<td>0.73</td>
</tr>
<tr>
<td>Serum potassium level, mEq/L, mean ± SD (range)</td>
<td>4.22 ± 0.38 (3.5 to 4.7)</td>
<td>4.19 ± 0.53 (3.0 to 5.1)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

**Intervention.** All patients received 1 mg/kg/day of ABD in dextrose 5%. In addition, the patients in the intervention arm received Intralipid 10%, which was started as soon as possible within 1 hour after the infusion of ABD.

**Evaluation.** All patients underwent a daily clinical evaluation, which included measurements of serum urea and creatinine levels. Possible Intralipid complications were evaluated in the intervention group by checking each patient's complete blood count, lipid profile, and liver enzyme level every 2 weeks.

**Outcomes.** Response to treatment and improvement were based on signs and symptoms and/or resolution of pathologic and microbiologic evidence of disease.

The primary nephrotoxicity outcome was defined as a minimum of 50% increase in the baseline serum creatinine level to a minimum of 2 mg/dl. Secondary outcomes included the number of patients who stopped taking ABD due to an increase in their creatinine level above 3.5 mg/dl, maximum serum creatinine levels, the time interval between ABD administration and renal toxicity, the time interval between ABD administration and treatment cessation due to a creatinine level higher than 3.5 mg/dl, the creatinine level on day 3 of treatment, and the difference between the baseline creatinine level and the final level measured before study's end. Also, daily creatinine levels during the first 2 weeks of treatment were analyzed to better determine the effects of the two therapeutic regimens on renal toxicity. The incidence of hypokalemia was also compared.
Statistical analysis. Statistical analysis was performed with the Statistical Package for the Social Sciences software (v. 18). An alpha error level of <0.05 was set as significant. For comparison of qualitative measures, the chi-square test and the Fisher exact test were used. The Student $t$ test was used for normally distributed quantitative measures and the Mann-Whitney $U$ test for non-normal measures. Daily progression of creatinine levels was analyzed by the repeated measures ANOVA test.

Ethical considerations. This study protocol was approved by the ethics committee of the Tehran University of Medical Sciences.

Results

Nephrotoxicity occurred in 15 intervention group patients and 14 controls (93.8 and 93.3%, respectively; $p = 0.74$) (table 2). There was no significant difference between the two groups in maximum creatinine levels ($p = 0.40$) (figure 1) or in any other nephrotoxicity measures (table 2). Likewise, there was no statistically significant difference in the daily progression of creatinine levels during the first 2 weeks of treatment ($p = 0.62$) (figure 2).

Figure 1. Chart shows the maximum creatinine levels in the control group (left) and the intervention group. The curved line indicates the normal distribution. The difference between the two groups was not statistically significant ($p = 0.40$).

Figure 2. Graph shows the mean daily creatinine levels during the first 2 weeks of treatment in the intervention and control groups. The difference between the two groups was not statistically significant ($p = 0.62$).
Table 2. Outcomes measures in the intervention and control groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>ABD plus Intralipid (n = 16)</th>
<th>ABD alone (control) (n = 15)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxicity, n (%)</td>
<td>15 (93.8)</td>
<td>14 (93.3)</td>
<td>0.74</td>
</tr>
<tr>
<td>Interruption, n (%)</td>
<td>5 (31.3)</td>
<td>4 (26.7)</td>
<td>0.55</td>
</tr>
<tr>
<td>Maximum serum creatinine level, mg/dl, mean ± SD (range)</td>
<td>3.07 ± 0.66 (1.9 to 3.9)</td>
<td>2.87 ± 0.67 (1.6 to 3.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>Interval between the initiation of therapy and the onset of nephrotoxicity, days, median (range)</td>
<td>7 (2 to 38)</td>
<td>9 (4 to 30)</td>
<td>0.20</td>
</tr>
<tr>
<td>Serum creatinine level on last day, mg/dl, mean ± SD (range)</td>
<td>2.74 ± 0.90 (1.4 to 3.9)</td>
<td>2.34 ± 0.94 (1.4 to 3.9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Difference between first and last creatinine level, mg/dl, mean ± SD (range)</td>
<td>1.42 ± 0.80 (0.1 to 2.7)</td>
<td>1.07 ± 0.84 (0.1 to 2.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>Interval between the initiation of therapy and the onset of interruption, days, median (range)</td>
<td>10 (7 to 38)</td>
<td>16.5 (13 to 27)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Hypokalemia was seen in 8 patients in the intervention group and 10 patients in the control group (50.0 and 66.7%, respectively; \( p = 0.47 \)).

Discussion
Renal toxicity is an important limiting factor in long-term ABD administration. In most cases, it necessitates a decrease in the dose or even complete cessation. In our study, we found no statistically significant difference between the group that took ABD alone and the group that took ABD plus Intralipid.

Our review of 9 recent clinical trials found that nephrotoxicity was decreased by combined ABD and Intralipid treatment in 5,4-8 no change was seen in 3,3,9,10 and toxicity increased in 1,11 This diversity of results might be attributable to study sizes, differences in the definition of nephrotoxicity, or other factors.

ABD stability in Intralipid is controversial. In some similar studies, the infusion solution was prepared by mixing ABD with Intralipid. There is no consensus regarding how to make such a mixture. Although some have proposed that the two agents can be mixed by simply shaking the container, standardization of this method is difficult.2 Egito et al proposed that this preparation problem might be another reason for variations in study results.12 They showed that with a special mechanical shaker, ABD can be transferred to a lipid missile. A commercially manufactured mixture of ABD and Intralipid is available in India at a low price.13

It has been shown that if ABD and Intralipid are infused simultaneously, ABD can precipitate in Intralipid and the size and number of the undissolved particles in this solution are similar to those of ABD infused with dextrose 5% solution.3 Although these particles can be removed by filters, filtration can also decrease the drug's efficacy.

Considering all of these issues, it appears that separate administrations of ABD and Intralipid—either simultaneously or with a short delay between infusions—can overcome some of these problems. To the best of our knowledge, no other study has looked at Intralipid and ABD administered separately. Even so, this technique did not decrease renal toxicity in our study.

While the incidence of hypokalemia was lower in our intervention group than in our control group, the difference was not statistically significant. Among the previous studies of ABD alone and ABD with Intralipid, the incidence of hypokalemia was analyzed in 5,3,6,9-11 No difference was seen in 3 of these studies,6,9,11 while hypokalemia was less common in the ABD/Intralipid group in the other 2,3,10 However, in 1 of the latter 2 studies, the ABD/Intralipid group received a lower dose of diuretics than did the ABD-only group.10 Therefore, it seems that our findings are congruent with most of these other studies, even though our intervention group was treated with a different method of infusion (i.e., separate infusions). Differences in the incidence of hypokalemia in other studies might be attributable to inconsistencies among study patients and methods.

Research aimed at reducing ABD toxicity and improving treatment response in patients with fungal infections should be a priority. It is reasonable to conduct multicenter studies with a large number of patients and a more homogeneous study population in an effort to standardize the mixture method of ABD and Intralipid and to define the appropriate dosage. It is also appropriate to study the administration of ABD and Intralipid separately.

In conclusion, our study found that the administration of Intralipid a short time after infusion of ABD had no effect on reducing nephrotoxicity or hypokalemia.

References


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Ear Nose Throat J. 2017 February;96(2):E18