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Research Article

Efficacy of Prophylactic Oral Levofloxacin to Prevent Infection during Intensive Chemotherapy of Haematological Malignancy in Children

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Abstract

Patients undergoing cytotoxic chemotherapy for hematologic malignancy are at high risk for drug induced myelosuppression leading to neutropenia, which increases the susceptibility to infection, subsequent morbidity and mortality. Febrile neutropenia, with its potential to cause death, remains the most important dose limiting toxicity of anti-cancer treatment, influencing the quality of life and the clinical outcomes. A number of different antibiotic prophylaxis has been tried over several decades in order to prevent the chemotherapy related infections, but most of these studies were done in adults, and very few in children. This study was carried out in children to see the efficacy of prophylactic oral levofloxacin in reducing the bacterial infection which occurs during the cycles of intensive chemotherapy given to bring down the hematologic malignancy into remission.

Forty three children of 1 - 15 years with either acute lymphoblastic leukemia (ALL) or non-Hodgkin lymphoma (NHL) were enrolled, and were given levofloxacin prophylaxis during a total of 61 courses of chemotherapy. Another 77 chemotherapy courses of 44 ALL or NHL children, from the previous 6 months hospital records of the same department, were analyzed as historical control. In the study group, infection or fever rate was 47.54%, and in the control group, it was 79.22%. Risk reduction for infection was 31.68% (Relative Risk of 0.60, P-value < 0.001). In the ALL (acute lymphoblastic leukemia) group, during the Induction phase of chemotherapy, infection rate with prophylaxis and without prophylaxis were 60% and 78% respectively. During Early Intensification it was 46% and 81%, and during High Dose Methotrexate it was 30.77% and 76.47% respectively. This was also true for NHL (non-Hodgkin lymphoma) (75% vs. 90%). There was no systemic side effect due to Levofloxacin noted in the study group children, except one child developed back pain and skin striation, which later considered to be due to steroid. Compliance was very good.

Thus, it can be concluded from here, that Levofloxacin prophylaxis in children with ALL or NHL during the intensive chemotherapy is effective and well tolerated. Large scale study necessary to come up with solid recommendation.

Keywords: *Intensive Chemotherapy; Febrile Neutropenia; Antibiotic Prophylaxis; Levofloxacin; ALL (Acute Lymphoblastic Leukaemia); NHL (Non-Hodgkin Lymphoma)*

Abbreviations

ALL: Acute Lymphoblastic Leukaemia; NHL: Non-Hodgkin Lymphoma

Introduction

Infection remains the most important dose limiting toxicity of anti-cancer treatment, impacting on the quality of life and clinical outcome, with the potential to cause death. The relationship between neutropenia and infection was first recognized in the 1960s [1]. Prompt

administration of empiric antibiotics, before laboratory confirmation of infection, was determined to be crucial in patients with febrile neutropenia due to the rapid progression of infection in these patients. Since then the outcomes of febrile neutropenia have improved gradually [2].

Epidemiological studies demonstrate a high prevalence of sepsis among children with cancer. Haematological malignancy itself make the children somewhat immunosuppressed, and moreover the aggressive myeloablative therapy make them more prone to develop sepsis, when compared to solid tumors. Children on intensive chemotherapy protocols have a six times greater chance of developing sepsis than more conservative protocols [3]. Moreover, the septic episode increases the duration of hospital stay, often needs dose reduction or alteration of the chemotherapy regime, which negatively affect the outcome.

Prompt institution of empiric treatment has improved the outcome but comes with added treatment cost [2]. In a developing country like Bangladesh, where it is already difficult for the poor families to bears the cost of the lengthy treatment of Acute Leukaemia or lymphoma, each episode of febrile neutropenia, is truly an economic burden to them. Thus, this current study was started with intention to find a suitable antibiotic prophylaxis which can help to prevent this infection. Acute Lymphoblastic Leukaemia (ALL) and non-Hodgkin Lymphoma (NHL) was chosen as these two disorder are related to each other, and together constitute almost one third of childhood cancer.

Patients and Methods

This was a prospective clinical trial done in 1 to 15 years old children with acute lymphoblastic leukaemia or non-Hodgkin's lymphoma, who were admitted for chemotherapy between April 2010 and September 2010 in department of Pediatric Haematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU). This is the only dedicated Paediatric Haematology and Oncology Center in Bangladesh. Diagnosis was done by history and clinical exam and confirmed by peripheral blood film and bone marrow study (for ALL) or biopsy and histopathology (for NHL). Immuno-phenotyping by flow-cytometry was done, where needed. Other investigations were done according to department's policy, like ultrasonogram of abdomen, chest X-ray, serum LDH and serum uric acid were done.

Children who were going to start Induction Chemotherapy or any subsequent Intensive Phase Chemotherapy, were enrolled, provided having no fever or other signs of infection before starting the chemotherapy, and not already receiving any antibiotic. Children, outside this age range, or not meeting the above criteria, were excluded. Children received regular oral Co-trimoxazole during the chemotherapy, and this was not considered as exclusion criteria. The study was clearly explained to the parents by the author, and written consent was taken from them, and when applicable, from the patients. All consecutive cases meeting the inclusion criteria were enrolled, and there were 43 children in the study group. Some children were enrolled for more than one once, if their subsequent cycle fell into the study period.

Antibiotic prophylaxis was not practiced during chemotherapy in the department before this study. Children of same age range, having same diagnosis, who were treated in this department during the previous six months with same protocol, were taken as historical control. Hospital records of all the admitted cases from October 2009 to March 2010 were scrutinized thoroughly. Those who were admitted for receiving intensive chemotherapy phases, were not having fever or other signs of infection at the beginning of chemotherapy and were not receiving any antibiotic (except co-trimoxazole), were taken as control.

Ethical Statement

Proper approval was taken from the ethical review committee of the university (BSMMU) before enrollment of the first patient. The study was done as part of fulfilling the requirements of thesis for MD Pediatric Hematology Oncology course.

Procedure

After enrollment, each study patient was started on prophylactic oral levofloxacin, at a dose of 10 mg/kg body weight/day, as single daily dose from the same day of starting chemotherapy. For patients who receive intensive chemotherapy, full blood count, serum trans-

aminase and serum urea and electrolyte were done a minimum of thrice weekly, according to department's rule. Neutrophil count starts to fall by about 7 - 8 days of starting chemotherapy, frequently goes below 500/L, and starts to recover by day 14. Levofloxacin was, thus, continued for 14 days or until the rising absolute neutrophil count (ANC) reached > 500/L, whichever took longer.

Clinical course of the patients were followed up meticulously, regarding development of fever or any other sign of infection, during their hospital stay and up until next admission. Fever was defined as temperature more than or equal to 38.3°C at any time or more than or equal to 38.0°C for at least 1h, or measured twice within 12h. Cases where fever or infection developed in spite of giving prophylaxis, were managed with empirical antibiotic according to department's protocol, which complies with international standards. Levofloxacin was stopped when clinical condition of the patient necessitated the initiation of empirical broad spectrum intravenous antibiotic. Depending on the condition of the patient, chemotherapy was also stopped temporarily, when necessary. Before starting empiric antibiotic, blood culture, urine culture and microscopy, serum electrolyte and SGPT were sent as part of septic screening. Chest X-ray was also done. Stool culture and microscopy, and other investigations were done, according to patient's clinical condition.

All the relevant data was recorded. Notes were kept regarding signs and symptoms on first day of illness, appearance of new signs or symptoms, days needed for the fever to subside, days needed to recover clinically, antibiotics used, either oral or injectable, levofloxacin continued or not, and anti-virals or antifungals needed or not. The delay in chemotherapy schedule in days, or any re-arrangement made in the schedule was noted. For detection of intolerance to levofloxacin, parents were advised to report unusual nausea or vomiting, appearance of rash or joint pain in their children, while they were on Levofloxacin, or within one month of stopping it.

For the control group, hospital admission records of each qualifying cases were analyzed. It was looked into, whether the courses were uneventful, or whether there was any chemotherapy interruption due to fever or infection which prolonged the time of their scheduled hospital stay. It was then checked whether their subsequent admission was for scheduled chemotherapy or for treating fever or infection.

Treatment (Cases and Controls)

Children with ALL were treated with UK-ALL protocol (MRC-11). Those with non-Hodgkin lymphoma were treated with French lymphoma protocol (for B-cell NHL- LMB-89, for T-cell NHL- BFM- 90). At the onset of fever or infection, each case was assessed individually. Where risk was low, Levofloxacin was continued, supplemented by oral co-amoxiclav and/or metronidazole and acyclovir. Where risk was high, intravenous broad spectrum antibiotic was started and Levofloxacin was discontinued. Patients of control group were also treated with same chemotherapy protocol. They were managed in the same way at the occurrence of fever or infection, except only that they were not receiving any antibiotic prophylaxis.

Outcome Variables

1. Total number of days without fever or other infection when ANC is < 1000
2. For detection of severity of infection
    a. Fever
    b. Oral ulcer
    c. Pharyngeal inflammation
    d. Necrotic skin lesion
    e. Cellulitis or Septic Focus
    f. Diarrhoea
    g. Dehydration
    h. Cough, Chest infection
    i. Treatment as inpatient

3. Any feature of side effect of levofloxacin:
    a. Vomiting
    b. Rash
    c. Joint pain

4. Withholding therapy due to infection

Statistical analysis

Data were compiled manually and statistical analysis was done both manually and rechecked by using the statistical package SPSS-version 17 for windows. Confidence Interval was set at 95% and power of the test 70%. Categorical data were described by their frequencies and proportions. Relative risks were calculated and Pearson Chi square test were done. Continuous variables were compared with Z-test. P-values were determined and $P < 0.05$ was considered as significant and $P < 0.01$ as highly significant.

Results

A total of 43 children, (ALL 40 and NHL 3 patients) in their 61 phases of chemotherapy, fulfilled the inclusion criteria, and were enrolled in the study. After careful scrutiny, 77 chemotherapy cycles of 44 children from the previous six months hospital admission qualified to serve as control. Majority of the ALL children were between 2 - 5 years (52.5% in study group, 51.28% in control group), and in NHL this was between 10 - 15 years (66.6% in study group, 60% in control group) (Table 1). In study group, there 23 male (53.48%) and 20 female (46.73%). In the control group, there were 34 male (77.27%) and 10 female (22.73%).

Age Group	ALL - Study Group	ALL - Control Group[1]	NHL - Study Group	NHL - Control Group
< 2 years	1 (2.5%)	0	0	01 (20%)
2 - 5 years	21 (52.5%)	20 (51.28%)	0	0
5 - 10 years	14 (35%)	12 (30.76%)	01 (33.33%)	01 (20%)
10 - 15 years	04 (10%)	06 (15.38%)	02 (66.66%)	03 (60%)
Total	40	38	03	05

Table 1: *Age Distribution of the Children in Study and Control Group.*
1. Age of 1 patient could not be found anywhere in the file.
ALL: Acute Lymphoblastic Leukaemia; NHL: Non-Hodgkin Lymphoma.

The number of fever/infection episode despite prophylaxis was in 29 cycles of chemotherapy (29/61, 47.54%). Of these 29 cycles, 26 were from total 57 ALL cycle intervened (26/57, 45.61%), and other 3 were from the 4 NHL cycles (3/4, 75%). In the control group, total 61 episodes of infection was noted in the 77 chemotherapy cycles analyzed (79.22%). Of these, 52 episode were from ALL chemotherapy phases (52/67, 77.61%) and other 9 was from NHL chemotherapy cycles (9/10, 90.00%). In total, Levofloxacin reduced the infection rate in the study group by 31.68% (Table 2).

Disease	Number of Cycles Intervened	Number of Infection episode	Number of Cycles analyzed	Number of Infection episodes
	Study group		Control group	
ALL	57	26/57 (45.61%)	67	52/67 (77.61%)
NHL	04	03/04 (75.00 %)	10	09/10 (90.00%)
Total	61	29/61 (47.54 %)	77	61/77 (79.22 %)

Table 2: *Total number of infection in ALL and NHL (Study and Control Group).*
ALL: Acute Lymphoblastic Leukaemia; NHL: Non-Hodgkin Lymphoma.

Occurrence of infection in various phases of the ALL cycles in study and control group are shown in table 3. Absolute risk reduction was seen in all the phases of therapy when compared to control group (Figure 1), except in in Late Intensification. In ALL cases, during induction it was decreased by 18.26%, during Early Intensification by 35.10%, during High Dose Methotrexate by 45.70%. Relative risk (RR) was calculated for each phase of chemotherapy cycle in both study and control group, and it was < 1 in all the phases of chemotherapy, except in late intensification. In Pearson χ^2 test, at 1 degree of freedom χ^2 value was calculated and then p-value was determined (Table 4). Overall difference in infection between study and control group is found highly significant (P < 0.001). Phase wise, EI had a p-value of less than 0.05 and high dose MTX had < 0.001.

Phase of Therapy	Number of Cycles Intervened (n = 57)	Number of infection (n = 26)	Total cycles analyzed (n = 67)	Total episodes of infections (n = 52)
	Study group		Control group	
Remission Induction	15	9/15 (60.00 %)	23	18/23 (78.26%)
Early intensification	13	6/13 (46.15 %)	16	13/16 (81.25%)
Re-Induction[1]	---	---	03	02/03 (66.67%)
High dose MTX	26	8/26 (30.77 %)	17	13/17 (76.47%)
Late intensification	3	3/3 (100.00%)	08	06/08 (75.00%)
Total	57	26/57 (45.61%)	67	52/67 (77.61%)

Table 3: *Phase-wise episodes of infection in ALL chemotherapy cycles (Study and Control Group).*

1. No patient in the study group needed re-induction.

ALL: Acute Lymphoblastic Leukaemia; NHL: Non-Hodgkin Lymphoma.

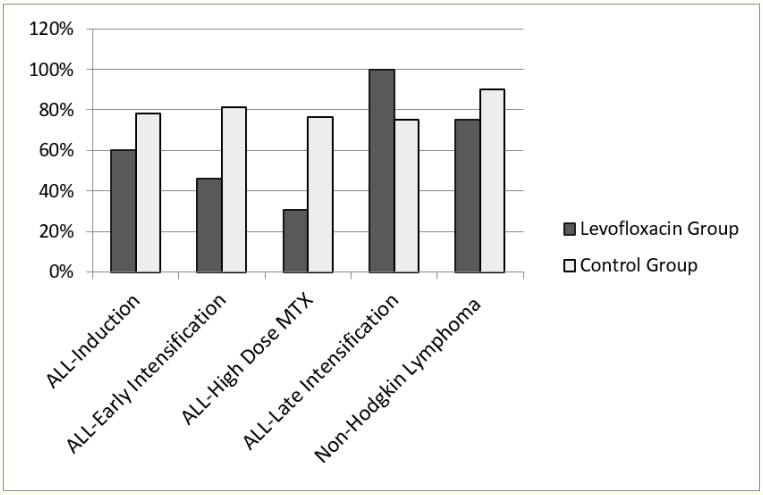

Figure 1: *Comparison of infection rate in the study and control group.*

ALL: Acute Lymphoblastic Leukaemia; MTX: Methotrexate.

(There was no case of re-induction in the study group, so it was not compared).*

Phase of Chemotherapy	Number of Episodes of Infection (%)		Relative Risk	P- value (at 1 degree of freedom and 95% CI)
	Study Group	Control Group		
ALL: Remission Induction	9/15 (60%)	18/23 (78.26%)	0.766	> 0.05
ALL: Early Intensification	6/13 (46.15%)	13/16 (81.25%)	0.586	< 0.05
ALL- High-dose MTX	8/26 (30.77%)	13/17 (76.47%)	0.402	< 0.001
ALL- Late Intensification	3/3 (100%)	6/8 (75%)	1.33	> 0.05
NHL	3/4 (75%)	9/10 (90%)	0.833	> 0.05
Total	29/61 (47.54%)	61/77 (79.22)	0.60	< 0.001

Table 4: *Relative risk and P-Value: Comparison between study and control group.*
ALL: Acute Lymphoblastic Leukaemia; NHL: Non-Hodgkin Lymphoma.

Analysis of the infection cases showed, 28 out of 29 (96.55%) episodes in study group improved comparatively earlier (Mean duration of illness 7.25d, range 2 - 15d, SD 3.816). In the control group 54 out of 61 showed improvement (mean duration 9.96d, range 3 - 22d, SD 5.047). Applying Z-test for comparing the mean, the value was 2.72, corresponding to a P value of 0.007. In the control group, one patient developed septicemia and severe renal toxicity after HD-MTX and took discharge on risk bond after 17 days of illness. Another patient developed fever, few days after starting the Induction phase. After 26 days she was taken abroad for the remaining treatment. In the study group, one patient (1/43, 2.33%) expired after 17 days of suffering from illness, and in the control group, 04 patients (4/44, 9.09%). This did not show statistical significance (RR 0.256, P > 0.05). All these were ALL cases and were receiving Remission Induction. Proportionately more infection episodes in the study group (11/29, 37.93%) were treated with oral antibiotic compared to Control Group (1/61, 1.64%), and for IV antibiotic it was opposite (62.07% vs 98.36%). Though the difference was not statistically significant, it is noteworthy that compared to study group, more episodes in control group needed antiviral (5/29, 17.24% vs 14/61, 22.95%) and antifungal therapy (1/29, 3.45% vs 3/61, 4.92%).

No patient in the study group developed any excessive nausea, vomiting, or any joint problems other than only one boy, 15 years, who developed musculoskeletal pain associated with profuse striation all over his body (1/61, 1.64%). It probably was steroid induced. His serum calcium level was found to be low, and pain diminished after giving calcium supplementation. In all the children, compliance was very good. In five cycles (5 out of 61 i.e. 8.20%) levofloxacin was stopped after 7 days of starting, which was identified later to be a miscommunication regarding when to stop.

Discussion

This was an intervention study using historical data as control. Similar study design was used in a pilot study done during 1997 to 2000 showing similar rate reduction in infectious episodes using prophylaxis [4]. Previous studies done on this topic, were in adults, mostly large multi-centric randomized clinical trials, carried out over a longer period of time, using treatment vs. no treatment or treatment vs. placebo model, or meta-analysis [5,6]. This was the first study done in children in Bangladesh, in the tertiary level children oncology center, with a small sample size. Both ALL and NHL children (1 - 15 years) were included in the study to increase the number of enrolment. Randomization was not done because it would further decrease the number of patient in each group. Ethical issues arose when giving treatment to one group and giving placebo or no treatment to another group, knowing the benefit of using prophylaxis from few studies which have been done abroad. Time and manpower were also limited. Considering all these factors, historical data of the same department was used as control. Phase restriction was not done for same reason.

Age distribution of ALL and NHL in the study and control group are almost similar to the international findings [7]. Our commonest ALL age group was 2 - 5 years, and for NHL it was 10 - 15 years. In one of few epidemiological data found in Bangladesh regarding age distribution of ALL and NHL showed similar result [8].

In this study 43 children in their total 61 courses of chemotherapy cycle, were given Levofloxacin prophylaxis to prevent infection during the ensuing period of neutropenia. Infection occurred in 32 cycles (32/61, 47.54%). In the control group infection rate was 79.22% (61/77). It showed an absolute risk reduction of infection of about 32% with a P-value < 0.001. In most of the published reports, e.g. in the meta-analysis by Gafter-Gvili and the reports of the two big trials done in adults, GIMEMA and SIGNIFICANT, all showed effectiveness of the levofloxacin (sometimes other fluoroquinolones) in reducing incidence of infection during chemotherapy induced neutropenia [9-11].

In this study levofloxacin was found to be effective in every stages of chemotherapy except the late intensification (LI) of ALL. As number of patient that could be enrolled in the study during that period, who were receiving LI was very small, this lack of effectiveness might not have been there if larger number of samples were included. However, further study is necessary to clarify it. In all other phases, infection was less in study group. Infection was statistically significant during Early Intensification ($P < 0.05$) and High Dose-MTX therapy ($P < 0.001$). Similar result is seen in review done by Leibovici in 2006 [12].

Before 2000, there was little enough data in the literature addressing the role of antibiotic prophylaxis in immunosuppressed children. Cruciani., *et al.* has compared trimethoprim/ sulfamethoxazole to norfloxacin in 44 neutropenic children and showed no significant difference in gram-negative or gram-positive bacterial infections [5]. Mullen., *et al.* in 2000 in a retrospective analysis, showed a reduction in bacteremia from 58 to 30% in transplant patients, although there was no reduction in febrile neutropenic episodes [13]. Despite favorable findings in relation to infection prevention, guidelines before and around 2002 - 2003, kept on advising against the use of prophylactic antibiotics [14]. Their main concern was based on lack of improvement in mortality and threat of developing antibiotic resistance. This argument is no longer valid. Antibiotic prophylaxis reduces mortality, and low numbers of treated patients are required to prevent 1 death [12]. In our study there was one death among the 43 patients treated (2.33%) in the study group and four deaths in the control group out of 44 patient treated (9.09%). This gives a relative risk of 0.256 which is significant. All these patients were in their induction of remission of ALL. Similar result was seen in SIGNIFICANT trial of solid tumors and lymphoma published by Cullen., *et al.* in 2005 [11].

Second concern was about emergence of bacterial resistance. The growing concern regarding emerging drug resistant bacteria was mostly before 2003 or 2005. Many reports have documented the emergence of bacteria resistant to fluoroquinolone. It was for this reason that the infectious diseases society of America used to advocate against routine prophylaxis [4]. Against this, one has to evaluate the potential benefit in a well selected group of patients who are at high risk of bacteremia, increased morbidity and even death from sepsis. There are no quantitative data indicating the extent to which prophylaxis if harmful for the patients. Studies have been done evaluating the potential benefit in well selected group of patients. The ethics of withholding a clearly effective antibiotic drug from current patients to reserve it for future patients are far from clear [12]. This study was not designed to show the effect levofloxacin on gut flora. The high rate of infection in our patient population (79.22% overall in the control group and 47.54% in the study group) suggests that the benefit of an effective prophylactic antibiotic regimen, outweighs the disadvantages.

There is now convincing evidence that antibiotic prophylaxis reduces the incidence of FN and mortality in patients receiving cytotoxic chemotherapy for acute leukemia and for patients with solid tumors and lymphoma receiving high-dose chemotherapy [15]. As mentioned in the Prevention and Treatment of Cancer-Related Infections, Version 2.2016, guideline published by National Comprehensive Cancer Network, neutropenia is a recognized major risk factor for developing infection in cancer patients receiving chemotherapy. And improved strategies of anticipation, prevention, and management of these have improved outcome over time. They recommended prophylactic fluoroquinolones for high-risk and intermediate-risk groups, which largely comprise patients receiving high-dose chemotherapy and those with hematological malignancy in which the anticipated duration of neutropenia is longer than 7 days [16].

Even until recent time, when clinical practice guideline for adult patients with cancer related immunosuppression is out there [17], there is no clear consensus about pediatric patients in similar situation [18]. There was always some hesitancy to use fluoroquinolones,

including levofloxacin, in children largely because studies in juvenile laboratory animals suggest there may be an increased risk of fluoroquinolone-associated cartilage lesions. But in the study in 2007 on 2523 children, author found levofloxacin to be well tolerated during and for 1 month after therapy as evidenced by similar incidence and character of adverse events compared with non-fluoroquinolone antibiotics [19]. In our study also, no bone or joint related side effects were noted in either group, except mild pain in one patient which probably was due to steroid [20-23]. More placebo-controlled, randomized, clinical trials are necessary in pediatric population for generalization of the result.

Limitations

The study design was aimed at recruiting as much patients possible over a short period of time. The sample size was small and control group was from the previous hospital records due to time limitations. For this reason some of the patients who served as control, were again taken up in the study group in their later chemotherapy phases. This might have had some effect.

For time limitation, children with acute lymphoblastic leukemia in different phases of their chemotherapy and children with non-Hodgkin lymphoma were included in the study. To make the comparison more justified, this should better be avoided. Also it may bring up the issues which may be specific for any particular phase of treatment.

Conclusions

This study observed that prophylactic oral levofloxacin during intensive chemotherapy in children with ALL or NHL was effective in reducing the rate of infection by more than 30% (47.54% vs. 79.22%, P-value < 0.001). Levofloxacin was well tolerated and cost effective. The decreased rate of infection related complications with the use of prophylaxis can counterbalance the potential threats of levofloxacin. Thus, levofloxacin can be considered as prophylaxis in patients with ALL and those who receive high dose chemotherapy for NHL, from the commencement of chemotherapy until resolution of neutropenia.

Further randomized, placebo-controlled trials are necessary to identify which patients are more likely to be benefitted from prophylaxis.

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Conflict of Interest

There was no external funding or university grant. The study was completed solely by the investigator. There was no conflict of interest.

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